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REVIEW

XTP8, a key player in pan-cancer

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Abstract

XTP8/DEPDC1B has been found overexpressed in oral cancer, non-small cell lung cancer (NSCLC), prostate cancer, soft-tissue sarcomas, malignant melanoma, and neuroblastoma. In some cancer types, high XTP8/DEPDC1B levels have been associated with shorter survival and metastatic progression. XTP8/DEPDC1B is an effector of the proto-oncogene kinase Raf-1 and promotes a variety of tumorigenic process including cell survival, proliferation, anchorage-independent growth, migration, and invasion. In NSCLC, the regulation of migration and invasion by XTP8/DEPDC1B is mediated by the Wnt/β-catenin pathway. Despite being catalytically inactive, XTP8/DEPDC1B has been shown to indirectly suppress RhoA activity, although the mechanism is not completely understood. In neuroblastoma cells overexpressing N-myc protein, the expression of XTP8/DEPDC1B is regulated by the long non-coding RNA lncNB1, which is one of highest overexpressed transcripts in these tumors. LncNB1 promotes XTP8/DEPDC1B expression, which in turn induces ERK protein phosphorylation and N-myc protein stabilization. Silence of IncNB1 expression in mice reduces the expression of XTP8/DEPDC1B, which results in tumor regression. XTP8/DEPDC1B expression was found to promote metastatic phenotypes in chordoma through UBE2T-mediated ubiquitination of BIRC5 and in hepatocellular carcinoma (HCC) through interactions with CDK1. The study on the function and mechanism of XTP8/DEPDC1B protein will pave the way for invention of new drugs and therapeutics.

Introduction

Hepatitis B virus (HBV) is the major etiological factor for hepatocellular carcinoma (HCC) development in China and most part of the world. But the tumorigenicity process caused by HBV remained unclear. In order to explore the hepatocellular mechanism, Cheng et al conducted suppression subtraction hybridization (SSH) and microarray assay to define the target gene tans-activated by HBx protein. In the primary analysis, a new coding sequence has been recognized

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as the target of HBx protein, and named as XTP1 (X protein-transactivated protein 1). In further analysis, an even longer coding sequence has been confirmed as the target of HBx protein, and named as XTP8 (X protein-transactivated protein 8). Later on, it is found that XTP1 only represents part of the 3'-terminal of XTP8 coding sequence, so XTP1 and XTP8 have been recognized as the same gene, and renamed as XTP8, lately DEPDC1B, or BRCC3 by others (Boudreau et al., 2007), for there is a DEP (Dishevelled, Egl-1, Pleckstrin) domain in the protein sequences and Rho-GAP-like domains containing predominately membrane-associated protein (Han et al., 2019). DEPDC1B gene was discovered by mRNA expression profiling of human breast cancer cells (Boudreau et al., 2007). This protein aliases with different names as XTP1, XTP8, DEPDC1B, BRCC3, but in this review we designated this gene/protein as XTP8, otherwise indicated.

XTP8/DEPDC1B gene is located on chromosome 5 (5q12.1) and encodes a protein containing two conserved domains DEP and RhoGAP. On the one hand, the DEP domain enables proteins to interact with G protein-coupled receptors and negatively charged membrane phospholipids. On the other hand, the RhoGAP domain is responsible for Rho GTPase signal transduction. XTP8/DEPDC1B can interact with a variety of signal molecules, from splicing regulators to transmembrane proteins. The expression of XTP8/DEPDC1B is positively regulated by p63 and there is a p63-binding site at the 27 kb from the initiation of transcription of XTP8/DEPDC1B genomic DNA. Moreover, Pitx2 can inhibit the expression of GTPase activating protein XTP8/DEPDC1B at the transcriptional level. Besides, XTP8/DEPDC1B is required for the coordination of deadhesion events and cell cycle processes in mitosis. Furthermore, XTP8/DEPDC1B promotes the growth, invasion, and anchoring-independent growth of oral cancer cells through the interaction between Rac1 and ERK protein. Different levels of XTP8/DEPDC1B may affect the prognosis of patients with prostate cancer through the regulation of autophagy. Although the role of XTP8/DEPDC1B in the progression of various types of cancers have been understood, whether XTP8/DEPDC1B could affect bladder cancer remains to be elucidated (Lai et al., 2020).

DEPDC1B Promotes Disassembly of Focal Adhesion, De-adhesion, and Cell Entry into Mitosis

Earlier, Boudreau et al investigated the XTP8/DEPDC1B mRNA and protein expression throughout the cell cycle. Human breast cancer cells MDA-MB-231 were enriched in G1 phase by treatment with aphidicolin, followed by incubation in aphidicolin-free medium for various times. XTP8/DEPDC1B mRNA and protein levels were elevated in G2/M phase (Boudreau et al., 2007). Similar results were observed in MDA-MB-435 melanoma cells. High expression of XTP8/DEPDC1B during the G2/M phase has been shown to promote progression of cells into mitosis via disassembly of focal adhesions leading to detachment of cells (i.e., de-adhesion), referred to as a XTP8/DEPDC1B-mediated de-adhesion mitotic checkpoint (Marchesi et al., 2014). Mechanistically, cell de-adhesion, a requisite for mitotic entry, is achieved by XTP8/DEPDC1B accumulation during G2 phase, XTP8/DEPDC1B-mediated inhibition of the small GTPase RhoA via competitive interaction of XTP8/DEPDC1B to protein tyrosine phosphatase receptor type F (PTPRF), and preventing GEF-H1-mediated activation of RhoA (DEPDC1B-RhoA-PTPRF axis). XTP8/DEPDC1B silencing has been associated with delayed mitotic entry and delayed activation of mitosis promoting factors. XTP8/DEPDC1B amino acid sequence shows a CDK1 binding motif (S110). Whether XTP8/DEPDC1B influences CDK1 activity is unknown. In a recent report, under reduced growth factor signaling conditions, XTP8/DEPDC1B seems to promote focal adhesion disassembly by the membrane lipid phosphatidylinositol 3,4-bisphosphate (PtdIns(3,4)P2)-dependent inactivation of RhoA. In this scenario, a synergism between XTP8/DEPDC1B and protein kinase N2 (PKN2) results in synthesis of the PtdIns(3,4)P2 by class II PI3K-C2β, and PtdIns(3,4)P2, in turn, inactivates RhoA through recruitment of the ARAP3 GAP (Posor et al., 2022). XTP8/DEPDC1B high expression in the G2/M phase is critical to inactivation of RhoA, disassembly of focal adhesions, and cell de-adhesion, thereby leading cell entry into mitosis.

Tumor microenvironment (TME) became an important topic in the cancer research. Jing et al conducted a study on expression-based analyses indicating a central role for hypoxia in driving tumor plasticity through microenvironment remodeling and chromosomal instability. XTP8/DEPDC1B and HMMR that have known roles in both TME remodeling as well as chromosomal instability (CIN) associated functions (Jing et al., 2018).

SNP, Breakpoints and Chromosomal Rearrangement of XTP8 Genomic DNA

Cryptorchidism is a hereditary anomaly characterized by the incomplete descent of one or both testicles to the scrotum. One of the challenges of this anomaly is that the retained testicle maintains its endocrine function. As a consequence, cryptorchid animals produce hormone-tainted meat in comparison to castrated animals and are likely to be more aggressive. Cryptorchidism can lead to reduced animal welfare outcomes and cause economic losses. Identifying

genetic markers for cryptorchidism is an essential step toward mitigating these negative outcomes and may facilitate genome manipulation to reduce the occurrence of cryptorchidism. Attempts to identify such markers have used genome-wide association studies (GWAS). Using whole-exome sequencing, da Silva et al identified single nucleotide polymorphisms (SNPs) in the coding regions of cryptorchid pigs and to characterize functional pathways concerning these SNPs. DNA was extracted and sequenced from 5 healthy and 5 cryptorchid animals from the Landrace breed. GATK was used to identify polymorphisms (SNPs and InDels), which were annotated using the VEP tool. A total of 63 SNPs were identified across the genes including XTP8/DEPDC1B. These data suggest the involvement of new SNPs and genes in developing cryptorchidism in pigs (da Silva et al., 2023). In a study to identify and characterize genomic regions that differ between Groningen White Headed (GWH) breed and other cattle, and in particular to identify candidate genes associated with coat color and/or eye-protective phenotypes, on BTA20 (10.9–20 Mb), the region with the most significant SNPs contains the XTP8/DEPDC1B gene at position 18.5–18.6 Mb, which is associated with the hyperproliferation of abnormal melanocyte cells (Gonzalez-Prendes et al., 2022).

XTP8/DEPDC1B is in the list of 20 SNP consecutive genomic windows found to be associated with bias in teat (TS) in young (parities 1 and 2) Canadian Angus cows (Devani et al., 2021). Molecular alterations critical to development of cancer include mutations, copy number alterations (amplifications and deletions) as well as genomic rearrangements resulting in gene fusions. Massively parallel next generation sequencing, which enables the discovery of such changes, uses considerable quantities of genomic DNA, a serious limitation in ever smaller clinical samples. However, a commonly available microarray platforms such as array comparative genomic hybridization (array CGH) allows the characterization of gene copy number at a single gene resolution using much smaller amounts of genomic DNA. Przybytkowski et al explored the use of ultra-dense array CGH analysis for the discovery of micro-copy number alterations and gene fusions in the cancer genome. Those copy number alterations (CNAs) were DNA copy number gains (USP6, NAALADL2, BCAS4, DEPDC1B/ELOVL7, BCAS3). Four of these genes (DEPDC1B, ELOVL7, BCAS3 and BCAS4) involved regions of micro-copy number alterations. The one intra-chromosomal translocation involving the XTP8/DEPDC1B and ELOVL7 genes was detected as an increase in DNA copy number involving both adjacent genes, but breaking each of them within the gene. The XTP8/DEPDC1B gene amplification is also involved in the development of cancer (Przybytkowski et al., 2011).

Pseudohypoparathyroidism (PHP) is a series of diseases related to pathological changes and neurocognitive and endocrine abnormalities, mainly due to the GNAS mutation on chromosome 20q13.2, which weakens receptor-mediated hormone signal transduction. Fei et al also found copy number variations (CNVs) in patients with PHP, implying XTP8/DEPDC1B may be involved in the pathogenesis of PHP (Fei et al., 2023).

Breakpoints existed in the genome affect function of genome. Chen et al found a PDE4D-DEPDC1B breakpoint, indicating there is breakpoint(s) in the XTP8/DEPDC1B exon sequences. Long-read sequencing has demonstrated great potential for characterizing all types of structural variations (SVs). However, existing algorithms have insufficient sensitivity and precision. To address these limitations, Chen et al present DeBreak, a computational method for comprehensive and accurate SV discovery. Based on alignment results, DeBreak employs a density-based approach for clustering SV candidates together with a local de novo assembly approach for reconstructing long insertions. A partial order alignment algorithm ensures precise SV breakpoints with single base-pair resolution, and a κ-means clustering method can report multi-allele SV events. DeBreak outperforms existing tools on both simulated and real long-read sequencing data from both PacBio and Nanopore platforms. An important application of DeBreak is analyzing cancer genomes for potentially tumor-driving SVs. DeBreak can also be used for supplementing whole-genome assembly-based SV discovery. By this analysis five additional gene fusions, such as WDR82-PBRM1, PDE4D- XTP8/DEPDC1B, CPNE1-PHF20, CSE1L-KCNB1, and CSNK2A1-NCOA3 were defined (Chen et al., 2023).

Besides, the homologous recombination defectiveness (HRDness) group suffered genomic instability and epigenomic alterations, including ATM mutation, POLD4 and NBN copy number gain, XTP8/DEPDC1B and H2AFX loss, UBR5 hypomethylation, and FANCE hypermethylation, which were enriched in homologous recombination repair (HRR) genes (Li et al., 2021). Hampton et al identified the expressed DEPDC1B-ELOVL2 chimeric mRNA transcript which is formed by a 5q12.1 intra-chromosomal inversion in two breast cancer cell lines (Hampton et al., 2011). Sakarya et al also found gene fusion between XTP8/DEPDC1B and ELOVL7 in breast cancer tissues (Sakarya et al., 2012).

XTP8 Protein Structure and Phosphorylation at Ser110

Full-length XTP8/DEPDC1B open reading frame codes for a ~60 kDa (529 amino acids) predominately membrane-associated protein (Boudreau et al., 2007). GEPIA2 tool was used to generate the isoform structure of two protein coding variants of XTP8/DEPDC1B, DEPDC1B-001 (529 amino

acids), and DEPDC1B-002 (467 amino acids). Both isoforms contain a DEP domain (amino acids 24–108) and a Rho-GAP-like domain (amino acids 201–393). The Rho-GAP family of GTPase activating proteins have important implications in cancer progression (Kreider-Letterman et al., 2022; Schaefer et al., 2022). XTP8/DEPDC1B Rho-GAP domain lacks the arginine finger residue critical for its Rho GTPase activity. However, it may bind to a target Rho protein and influence activity of cognate Rho GTPase (Amin et al., 2016). The Scansite search showed potential interactions of XTP8/DEPDC1B with the p85 regulatory subunit of membrane lipid kinase PI3K (at P111 and P116) and DNA double-strand break repair enzyme DNA protein kinase (DNA-PK) (at S139 and S448). Additional predicted binding motifs present are for CRK SH2 at Y104, CDK1 at S110, and aurora kinase A/B at S160. If validated, any one or more these interactions are likely to shed new insights into XTP8/DEPDC1B-mediated mechanisms of tumor progression and therapy response.

XTP8/DEPDC1B is overexpressed in multiple cancers and is associated with cell cycle progression. Chen et al have investigated the expression, localization, phosphorylation and function of XTP8/DEPDC1B during mitosis (Chen et al., 2017). XTP8/DEPDC1B has two isoforms (isoform a and isoform b), and both of them are increased in mitosis and degraded once cells exit mitosis. DEPDC1a is localized to the centrosome in metaphase, whereas XTP8/DEPDC1B is localized to the entire cell cortex during mitosis. DEPDC1a, but not XTP8/DEPDC1B, was required for the integrity of centrosome and organization of the bipolar spindle. Mass spectrometry and biochemical analyses revealed phosphorylation of DEPDC1 at Ser110. The phosphorylation of Ser110 is essential for localization of DEPDC1a to the centrosome. Consistently, non-phosphorylation mutants of DEPDC1a did not rescue disruption of centrosome organization by depletion of endogenous DEPDC1. The results show a novel role for DEPDC1 in maintaining centrosome integrity during mitosis for the accurate distribution of chromosomes.

DEPDC1B is a Positive Upstream Effector of pERK

XTP8/DEPDC1B is an upstream positive effector of pERK. The MAPK canonical signaling pathway (RAS-CRAF/Raf-1-MEK-ERK) is activated in a majority of cancers, and CRAF/Raf1 and MEK have been extensively investigated as promising druggable targets (Karoulia et al., 2017). Raf-1-induced transcriptional changes are dependent, in part, on phosphorylation and activation of ERK. However, regulation of pERK via Raf-1 transcriptome is unclear. Earlier report indicated that siRNA knockdown of Raf-1 in MDA-MB-231 cells resulted in decreased expression of DEPDC1 and pERK; and siRNA knockdown of XTP8/DEPDC1B in MDA-MB-231 cells was associated with decrease in pERK expression (Boudreau et al., 2007). Boudreau et al have also demonstrated that transient or stable expression of myc-tagged XTP8/DEPDC1B in COS-1, HEK293T, and MCF-7 cells led to increased pERK levels compared to vector control. In addition to the enhanced basal levels of pERK, XTP8/DEPDC1B expression also seems to correlate with IGF1-stimulated expression of pERK. In this context, these data shows that siRNA knockdown of XTP8/DEPDC1B is associated with reduced IGF1-induced pERK expression in MCF-7 breast cancer cells. XTP8/DEPDC1B expression has also been correlated with enhanced pERK expression in neuroblastoma cells (Liu et al., 2019). Together these data suggest that XTP8/DEPDC1B, a component of Raf-1 transcriptome, is a positive upstream effector of both the constitutive and ligand-stimulated pERK expression.

DEPDC1B Binding with p85 Subunit of PI3K and Correlates with Downregulation of p85 Tyrosine Phosphorylation and pAKT1 Expression

As mentioned above, XTP8/DEPDC1B amino acid sequence shows putative binding motifs of the p85 subunit of PI3K at P111 and P116. Here Bouchi et al have verified this interaction by reciprocal co-immunoprecipitation using whole cell lysates from HEK293T cells transfected with myc- XTP8/DEPDC1B. Interestingly, the interaction was found to be reduced in response to insulin. In addition, insulin-stimulated tyrosine phosphorylation of p85 was negated in cells expressing myc-XTP8/DEPDC1B as compared to vector control. XTP8/DEPDC1B appears to also bind to insulin receptor β (IRβ), and this binding was also decreased in the presence of insulin. However, in contrast to p85, insulin-stimulated tyrosine phosphorylation of IRβ was unaffected in XTP8/DEPDC1B overexpressing HEK293T cells (Bouchi et al., 2014). Transient transfection experiments using the N-terminus deletion construct (DEPDC1B-NT) or the C-terminus deletion construct (DEPDC1B-CT) of myc-DEPDC1B and co-immunoprecipitation showed that N-terminus of XTP8/DEPDC1B containing the p85 binding motifs and not the C-terminus of myc-DEPDC1B interacts with p85, IRS-1, and insulin receptor. These data demonstrate direct and constitutive interaction between XTP8/DEPDC1B and the p85 subunit of PI3K and suggest that XTP8/DEPDC1B may also associate with IRS1 and IRβ. Bouchi et al conclude that the N-terminal portion of XTP8/DEPDC1B contains at least one bona fide p85 binding motif required for its binding to the p85 subunit of PI3K.

Insulin binding to the insulin receptor tyrosine kinase (IR) induces autophosphorylation of the receptor and activation of the IR-IRS1-PI3K pathway. Activated class I PI3K phosphorylates PtdIns-4,5P2 to PtdIns-3,4,5P3. PtdIns-3,4,5P3 interacts with the Pleckstrin homology domain of AKT1 (PKBα), recruiting AKT1 to the membrane where it is phosphorylated at T308 and S473 by PDK1 and mTORC2, respectively (Fujii et al., 2021). Myc-DEPDC1B expression in HEK293T cells correlated with a substantial reduction of insulin-induced pAKT (S473) level compared to vector control. Conversely, siRNA knockdown of endogenous XTP8/DEPDC1B was associated with relatively higher levels of insulin-stimulated pAKT versus scrambled siRNA control. To verify that XTP8/DEPDC1B-mediated negative regulation of pAKT1 indeed occurs downstream of PI3K, HEK293T cells were treated with wortmannin, a PI3K-specific inhibitor, prior to insulin stimulation. Insulin stimulated pAKT(S743) levels were significantly inhibited within 30 min of insulin treatment in myc-DEPDC1B transfected cells as compared to control vector and completely inhibited in the presence of wortmannin in both the myc-DEPDC1B transfected cells and control vector transfectants versus no wortmannin control counterparts. Furthermore, using a combination of the immunoprecipitation and immunoblotting assays, overexpression of XTP8/DEPDC1B was found to suppress insulin-induced phosphorylation of AKT1 (S473). XTP8/DEPDC1B overexpression in HEK293T cells also attenuated the cell viability in insulin-treated cells. Insulin receptor substrates (IRS1, IRS2) are known positive scaffolding adaptors linking the insulin and IGF1 receptors to activation of PI3K/AKT. XTP8/DEPDC1B appears to function as a newly discovered negative adaptor in this pathway, further exposing AKT1 as a targetable vulnerability in cancer cells. Previously, pAKT1-mediated inhibition of invasion and migration has been reported (Chugh et al., 2021). In MCF-10A cells, knockdown of AKT1 was shown to enhance ERK activation and cell migration in response to IGFI or EGF (Chugh et al., 2021). Other reports suggest cell context-dependent cross-regulation of AKT1 and ERK signaling pathways. Specifically, activated AKT1-mediated phosphorylation of cRAF/ Raf-1 (S259) has been shown to inhibit Raf-1 activity (Longmire et al., 2012; Liang et al., 2013). It remains to be determined whether modulation of XTP8/DEPDC1B influences Raf-1 activity and the outcome of Raf-1/MEK-targeted therapies. Nonetheless, it is concluded that XTP8/DEPDC1B is central to cross-regulation of the AKT1 and ERK pathways.

DEPDC1B is Implicated in Other Protein–protein Interactions and Tumor Progression

Several other cell context-dependent mechanisms of XTP8/DEPDC1B mediated oncogenesis, angiogenesis, and metastasis have been reported. For instance, while XTP8/DEPDC1B expression had no effect on RHOA-GTP/RAC1-GTP levels or Wnt/β-catenin signaling in melanoma cells, activation of SOX10-DEPDC1B-SCUBE3 axis was found to promote melanoma angiogenesis and metastasis (Driehuis et al., 2020). XTP8/DEPDC1B was identified as a direct downstream target of transcription factor SOX10 and shown to interact with ubiquitin ligase CDC16, thereby preventing degradation of SCUBE3, a member of the SCUBE family of secreted glycoproteins. In contrast, XTP8/DEPDC1B seems to enhance cell migration and invasion in non-small cell lung carcinoma through activation of Wnt/β-catenin signaling (Bartfeld et al., 2017). In a predicted 3D model of XTP8/DEPDC1B, amino acid residues interacting with Rac-1 have been identified, and XTP8/DEPDC1B has been shown to promote cell migration and invasion through the Rac1/PAK1-LIMK1-Cofilin1 signaling pathway in pancreatic cancer cells (Jabs et al., 2017; Nagle et al., 2018). In prostate cancer cells, XTP8/DEPDC1B was shown to bind to Rac1, activating the Rac1-PAK1 signaling pathway and inducing epithelial-mesenchymal transition (Costales-Carrera et al., 2020). STRING protein–protein interaction network analysis shows a number of predicted XTP8/DEPDC1B interacting proteins. These are Rho GTPase activating protein 11a (ARHGAP11A), mitotic checkpoint serine/threonine (BUB1), CDK1, centrosomal protein of 55 kDa (CEP55), disk large-associated protein 5 (DLGAP5), hyaluronan-mediated motility receptor (HMMR), kinesin-like protein-15 (KIF15), kinesin-like protein-2C (KIF2C), LMBR1 domain-containing protein-2 (LMBRD2), and exportin-7 (XPO7). Many of these interactions, if validated, are likely to expand the repertoire of XTP8/DEPDC1B-centric networks implicated in regulation of tumor progression and therapy response. High expression of XTP8/DEPDC1B has been demonstrated in several cancer types (Bartfeld et al., 2017; Jabs et al., 2017; Driehuis et al., 2019; Costales-Carrera et al., 2020; Driehuis et al., 2020). Moreover, a survey of publicly available datasets showed significantly high XTP8/DEPDC1B expression in breast, lung, and pancreatic carcinoma and melanoma compared to matched benign specimens. Furthermore, high XTP8/DEPDC1B expression has been correlated with decreased probability of survival in patients with breast cancer, lung cancer, pancreatic adenocarcinoma, and renal cell carcinoma. Thus, XTP8/DEPDC1B is a viable target in a clinical setting.

XTP8/DEPDC1B was expressed in proliferating murine and human myoblasts, with expression then decreasing markedly during myogenic differentiation. SiRNA-mediated knockdown of XTP8/DEPDC1B reduced myoblast proliferation and induced entry into myogenic differentiation, with deregulation of key cell cycle regulators (cyclins, CDK, CDKi). XTP8/

DEPDC1B and β-catenin co-knockdown was unable to rescue proliferation in myoblasts, suggesting that XTP8/DEPDC1B functions independently of canonical Wnt signaling during myogenesis. XTP8/DEPDC1B can also suppress RHOA activity in some cell types, but XTP8/DEPDC1B and RHOA co-knockdown actually had an additive effect by both further reducing proliferation and enhancing myogenic differentiation. XTP8/DEPDC1B was expressed in human Rh30 rhabdomyosarcoma cells, where XTP8/DEPDC1B or RHOA knockdown promoted myogenic differentiation, but without influencing proliferation (Figeac et al., 2020).

Up-stream Regulators for XTP8 Gene/protein

Earlier, Liu et al and others have reported that XTP8/DEPDC1B is a downstream effector of Raf-1 and long noncoding RNA lncNB1 (Liu et al., 2019). lncRNA lncNB1 directly binds to the ribosomal protein RPL35 and promotes the translation of tumorigenic mRNAs such as E2F1, leading to transcriptional activation of E2F1 target genes such as XTP8/DEPDC1B, N-myc protein phosphorylation at serine 62 and stabilization and neuroblastoma tumorigenesis (Shen et al., 2021).

Homeobox genes of the Hox class are required for proper patterning of elements in the developing skeleton (McIntyre et al., 2007). They also play a role in the regulation of cartilage differentiation prior to overt bone formation (Kappen et al., 2004). Misexpression and overexpression studies suggested that Hox genes affect the size of cartilage condensations and chondrocyte proliferation. Kruger et al demonstrated a role for Hoxc8 in cell cycle regulation in primary chondrocytes. Transgenic mice with overexpression of Hoxc8 and Hoxd4 under control of the Hoxc8 promoter exhibit profound cartilage defects, predominately in the ribs and vertebral column, and the severity of defects is dependent on transgene dosage. The abnormal cartilage is characterized by an accumulation of proliferating chondrocytes and reduced cartilage maturation. The cartilage of the ribs in transgenic mice remains weak and is structurally insufficient, resulting in pulmonary failure and death shortly after birth. Thus, Hox genes are important regulators of chondrocyte proliferation and maturation. XTP8/DEPDC1B expression level was found significantly increased (1.51-fold) in chondrocytes of Hoxd4(-/-) mice. This result has been confirmed in the study of differentially expressed genes in Hoxd4-transgenic chondrocytes (Kruger et al., 2010). In the list of top 20 upregulated genes in immortalized mesenchymal stem cells, XTP8/DEPDC1B expression level increased 12.26-fold compared with primary mesenchymal stem cells, but no increase in p53 knockdown-mesenchymal stem cells, indicating p53 is the key regulator for XTP8/DEPDC1B gene expression regulation (Liu et al., 2013).

Mutant p53 (mtp53) promotes chemotherapy resistance through multiple mechanisms, including disabling proapoptotic proteins and regulating gene expression. Comparison of genome wide analysis of mtp53 binding revealed that the ETS-binding site motif (EBS) is prevalent within predicted mtp53-binding sites. Do et al demonstrate that mtp53 regulates gene expression through EBS in promoters and that ETS2 mediates the interaction with this motif. Importantly, Do et al also identified TDP2, a 59-tyrosyl DNA phosphodiesterase involved in the repair of DNA damage caused by etoposide, as a transcriptional target of mtp53. It is demonstrated that suppression of TDP2 sensitizes mtp53-expressing cells to etoposide and that mtp53 and TDP2 are frequently overexpressed in human lung cancer; thus, the analysis identifies a potentially ‘‘druggable’’ component of mtp53’s gain-of-function activity. It is also observed that other genes such as WRAP53, THADA, XTP8/DEPDC1B, and GOLGA1 also had reduced transcript levels following mtp53/ETS2 knockdown and had either no change or an increase in levels after ETS1 knockdown.

In the assess of changes in miRNA expression upon mycobacterium tuberculosis infection and mapped expression quantitative trait loci (eQTL) in dendritic cells from a panel of healthy individuals, it is found that miR-eQTL SNPs for miR-582-5p were associated with the expression of XTP8/DEPDC1B in cis and PNMAL1 in trans, the latter gene being a predicted target of miR-582-5p, in HapMap samples (Siddle et al., 2014). The XTP8/DEPDC1B expression is also related to the gastrointestinal disease and organismal injury and abnormalities caused by COVID-19 infection (Lipman et al., 2022).

In a study to identify novel renal tubular biomarkers that may influence the diagnosis and treatment of focal segmental glomerulosclerosis (FSGS) based on immune infiltration, 79 genes were found downregulated expression (44.1%) and 100 genes upregulated expression (55.9%) among 179 differential expression genes (DEGs), in the FSGS samples. XTP8/DEPDC1B was found in the list of the downregulated expression genes. The results indicated XTP8/DEPDC1B is a renal tubular gene biomarker in focal segmental glomerulosclerosis (Bai et al., 2022).

Ozone pollution is associated with adverse effects on respiratory health in adults and children but its effects on the neonatal lung remain unknown. Gabehart et al conducted a study to define the effect of acute ozone exposure on the neonatal lung and to profile the transcriptome response. Transcriptome analysis indicated that 455 genes were down-regulated and 166 genes were up-regulated by at least 1.5-fold at 6 h post-ozone exposure. At 24 h, 543 genes were down-

regulated and 323 genes were up-regulated in the lungs of ozone-exposed, compared to filtered air-exposed, newborn mice. Among them, XTP8/DEPDC1B gene expression has been found decreased (−1.80-fold), indicating XTP8/DEPDC1B was related to the lung response to acute ozone exposure.

Lung squamous cell carcinoma (lung SCC) is a common type of lung cancer, but its mechanism of pathogenesis is unclear. Zhang et al identified key transcription factors associated with lung SCC. Zhang et al found XTP8/DEPDC1B expression increased (4.727546-fold). Transcription factors NFATC2 and ELF5 are the potential regulators for the expression of XTP8/DEPDC1B in lung SCC tissues.

Pitx2 is a bicoid-related homeobox transcription factor implicated in regulating left-right patterning and organogenesis. Wu et al demonstrated that Pitx2 is a transcriptional repressor of XTP8/DEPDC1B. The first intron of the human and mouse XTP8/DEPDC1B genes contains multiple consensus DNA-binding sites for Pitx2. Chromatin immunoprecipitation assays revealed that Pitx2, along with histone deacetylase 1, was recruited to the first intron of XTP8/DEPDC1B. In contrast, RNAi-mediated depletion of Pitx2 not only enhanced the acetylation of histone H4 in the first intron of XTP8/DEPDC1B, but also increased the protein level of XTP8/DEPDC1B. Luciferase reporter assays also showed that Pitx2 could repress the transcriptional activity mediated by the first intron of human XTP8/DEPDC1B. The GAP domain of XTP8/DEPDC1B interacted with nucleotide-bound forms of RAC1 in vitro. In addition, exogenous expression of XTP8/DEPDC1B suppressed RAC1 activation and interfered with actin polymerization induced by the guanine nucleotide exchange factor TRIO. Moreover, XTP8/DEPDC1B interacted with various signaling molecules such as U2AF2, ERH, and SALM. Pitx2-mediated repression of XTP8/DEPDC1B expression contributes to the regulation of multiple molecular pathways, such as Rho GTPase signaling (Wu et al., 2015).

In total, one fourth of familial breast cancer (BC) is attributed to germline mutations of the BRCA1 and BRCA2 genes, while the rest of the cases are included in the BRCAX group. BC is also known to affect men, with a worldwide incidence of 1%. Epigenetic alterations, including DNA methylation, have been rarely studied in male breast cancer (MBC) on a genomewide level. Abeni et al examined the global DNA methylation profiles of patients with BC to identify differences between familial female breast cancer (FBC) and MBC, and according to BRCA1, BRCA2 or BRCAX mutation status. The comparison between FBC and MBC revealed 2,846 significant differentially methylated regions corresponding to 2,486 annotated genes including XTP8/DEPDC1B gene. The results may provide useful insights into the epigenomic subtyping of BC and shed light on a possible novel molecular mechanism underlying BC carcinogenesis (Abeni et al., 2021).

Radiation is also a factor to reduce XTP8/DEPDC1B gene expression. In a study on lymphoid organs of a non-human primate model after total-body irradiation (TBI), XTP8/DEPDC1B was found repressed -7.25-fold, -17.74-fold in monkey after irradiated at dosages 2 and 5 Gy[a] (Caudell et al., 2019).

Down-stream Regulators for XTP8 Gene/protein

A gap exists in the mechanistic understanding of how genetic and environmental risk factors converge at the molecular level to result in the emergence of autism symptoms. It is need to compare blood-based gene expression signatures in identical twins concordant and discordant for autism spectrum condition (ASC) to differentiate genetic and environmentally driven transcription differences, and establish convergent evidence for biological mechanisms involved in ASC. In an analysis, genome-wide gene expression data were generated using RNA-seq on whole blood samples taken from 16 pairs of monozygotic (MZ) twins and seven twin pair members (39 individuals in total), who had been assessed for ASC and autism traits at age 12. In the discordant twin analysis, three genes showed evidence for DE at FDR < 10%: IGHG4, EVI2A and SNORD15B. In the case-control analysis, four DE genes were identified at FDR<10% including IGHG4, PRR13P5, XTP8/DEPDC1B, and ZNF501. It has been found enrichment for DE of genes curated in the SFARI human gene database. Pathways showing evidence of enrichment included those related to immune cell signaling and immune response, transcriptional control and cell cycle/proliferation. Integrative methylomic and transcriptomic analysis identified a number of genes showing suggestive evidence for cis dysregulation. XTP8/DEPDC1B was the second ranked coding gene in the case-control analysis. While it has not previously been associated with ASC, variants in XTP8/DEPDC1B have been associated with intelligence and general cognitive ability in two recent large-scale GWAS studies. The evidence taken together suggests that XTP8/DEPDC1B could be an interesting and potentially relevant signal for further follow up study (Saffari et al., 2019).

Wang et al found that XTP8/DEPDC1B regulates the progression of human chordoma through UBE2T-mediated ubiquitination of BIRC5. Chordoma is a rare bone malignancy with a high rate of local recurrence and distant metastasis. Although XTP8/DEPDC1B is implicated in a variety of malignancies, its relationship with chordoma is unclear. The malignant behaviors of XTP8/DEPDC1B knockdown chordoma cells was significantly inhibited, which was

characterized by reduced proliferation, enhanced apoptosis, and hindered migration. Consistently, decreased expression of XTP8/DEPDC1B suppressed tumor growth in xenograft mice. Mechanically, XTP8/DEPDC1B affected the ubiquitination of baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) through ubiquitin-conjugating enzyme E2T (UBE2T). Simultaneous downregulation of BIRC5 and XTP8/DEPDC1B may exacerbate the inhibitory effects of chordoma. Moreover, BIRC5 overexpression reduced the inhibitory effects of XTP8/DEPDC1B knockdown in chordoma cells. XTP8/DEPDC1B regulates the progression of human chordoma through UBE2T-mediated ubiquitination of BIRC5, suggesting that it may be a promising candidate target with potential therapeutic value (Wang et al., 2021).

The pathogenesis of neuropathic pain (NP) is characterized by an increased responsiveness of nociceptive neurons in the nervous system. However, the molecular mechanisms underpinning the NP still remain elusive. Recent data suggest that long non-coding RNAs (lncRNAs) regulate expression of NP-associated genes. Zhou et al analyzed lncRNAs and mRNA profiles in the spinal cord of rats by RNA sequencing during the progression of NP in a spared nerve injury (SNI) model. The results revealed the profiles of lncRNAs and mRNAs in the rat spinal cord under an NP condition including decreased XTP8/DEPDC1B mRNA with $\log_2$ (fold change) (-1.02939). These lncRNAs and mRNAs may represent new therapeutic targets for the treatment of NP (Zhou et al., 2017).

Regulation of XTP8 by Non-coding Elements

Non-coding elements including mirRs, LncRNAs, ceRNAs and circRNAs also are involved in the expression regulation of XTP8/DEPDC1B expression in both normal and malignant cells and tissues. LncRNAs regulate gene expression through modulating chromatin architecture, gene transcription, precursor messenger RNA splicing, mRNA transport, and post-translational modification. Importantly, aberrant lncRNA expression leads to cell proliferation, differentiation block, resistance to apoptosis, chromosome instability, cancer cell migration and invasion, tumor initiation and progression. It is found that LncNB1 up-regulates XTP8/DEPDC1B gene and E2F1 protein expression. Affymetrix microarray differential gene expression analysis revealed that knocking down lncNB1 modulated the expression of a number of target genes, among which XTP8/DEPDC1B was a potentially important candidate gene as it is known to induce ERK protein phosphorylation and phosphorylated ERK is known to enhance N-myc protein stability. RT-PCR and immunoblot analyses confirmed that lncNB1 siRNAs consistently reduced XTP8/DEPDC1B mRNA and protein as well as E2F1 protein, but did not show a consistent effect on E2F1 mRNA. RT-PCR and immunoblot analyses confirmed that treatment with doxycycline consistently reduced lncNB1 and XTP8/DEPDC1B mRNA as well as XTP8/DEPDC1B and E2F1 protein but not E2F1 mRNA expression in doxycycline-inducible lncNB1 shRNA cells. Taken together, the data demonstrate that lncNB1 up-regulates XTP8/DEPDC1B gene expression and increases E2F1 protein expression (Liu et al., 2019). And then it is confirmed that LncNB1 up-regulates N-myc protein expression through XTP8/DEPDC1B. XTP8/DEPDC1B is known to induce ERK protein phosphorylation. Transfection with lncNB1 siRNAs did not alter N-myc mRNA expression, but considerably reduced XTP8/DEPDC1B protein expression, ERK protein phosphorylation, N-myc protein phosphorylation at S62 and expression in BE(2)-C, Kelly, and CHP134 cells. Consistent with these data, transfection with XTP8/DEPDC1B siRNAs reduced XTP8/DEPDC1B but not N-myc mRNA expression, and reduced XTP8/DEPDC1B protein expression, ERK protein phosphorylation, N-myc protein phosphorylation at S62 and expression in the three neuroblastoma cell lines. In addition, transfection with a lncNB1 or XTP8/DEPDC1B over-expression construct in BE(2)-C and Kelly cells up-regulated XTP8/DEPDC1B protein expression, ERK protein phosphorylation as well as N-myc protein expression. Immunoblot analysis showed that forced XTP8/DEPDC1B over-expression largely reversed lncNB1 shRNA mediated ERK protein dephosphorylation, N-myc protein dephosphorylation at S62, and N-myc protein reduction. The pulse chase assays showed that N-myc protein half-life was reduced by approximately 50% by lncNB1 siRNA or XTP8/DEPDC1B siRNA, and was increased by approximately 39% by the lncNB1 expression construct. While MG-132 did not increase XTP8/DEPDC1B protein expression in cells transfected with lncNB1 siRNA or XTP8/DEPDC1B siRNA, which ablated XTP8/DEPDC1B mRNA, MG-132 dramatically up-regulated N-myc protein expression in cells transfected with lncNB1 siRNA or XTP8/DEPDC1B siRNA. The data demonstrate that lncNB1 and XTP8/DEPDC1B are required for N-myc protein stability. Only knocking down RPL35 significantly down-regulated XTP8/DEPDC1B, N-myc, and E2F1 protein expression. The data demonstrate that lncNB1 increases E2F1 protein expression by binding to the ribosomal protein RPL35, leading to E2F1 protein synthesis and XTP8/DEPDC1B gene transcription. XTP8/DEPDC1B, E2F1, and RPL35 are also required for neuroblastoma cell proliferation and/or survival. In addition, in human neuroblastoma tissues, lncNB1, E2F1, or RPL35 RNA expression positively correlates with XTP8/DEPDC1B RNA expression, and high levels of lncNB1, E2F1, RPL35, or XTP8/DEPDC1B expression predict poorer patient outcome. Thus, the data demonstrate that lncNB1, its binding

protein RPL35 and their target protein E2F1 and target gene XTP8/DEPDC1B induce neuroblastoma cell proliferation and survival. As high levels of lncNB1, RPL35, E2F1, and XTP8/DEPDC1B expression in tumor tissues correlate with poor prognosis in neuroblastoma patients, these findings identify lncNB1, RPL35, and XTP8/DEPDC1B as important co-factors for N-myc-driven oncogenesis and provide therapeutic targets for neuroblastoma (Liu et al., 2019). Specifically, RPL35 protein bound lncNB1 and E2F1 mRNA and facilitated E2F1 mRNA translation into protein, leading to increased XTP8/DEPDC1B gene transcription. The GTPase-activating protein XTP8/DEPDC1B also promotes ERK protein phosphorylation, leading to MYCN protein phosphorylation and stabilization. RPL35 thereby up-regulates E2F1 and MYCN oncoprotein expression and induces neuroblastoma cell proliferation.

Prostate cancer (PCa) represents the most prevalent type of cancer among men (Sung et al. 2021). PCa is mostly indolent at first and can later develop into aggressive disease (Attard et al. 2016). Therefore, an in-depth understanding of PCa pathogenesis is necessary to improve the early diagnosis of PCa. Published studies suggest that circular RNAs (circRNAs) are vital regulators in the development of human diseases, including tumorigenesis (Kristensen et al. 2018). CircRNA is a type of non-coding RNA (ncRNA) that undergoes back splicing from precursor mRNA (Hua et al. 2019). Recent studies have revealed the widespread and valued functions of circRNA molecules in PCa. For example, circRNA-102004 was highly expressed in PCa tissues, and it functioned as an oncogene by promoting PCa cell migration, invasion, and proliferation (Si-Tu et al. 2019). Circ_0005276, deriving from X-linked inhibitor of apoptosis protein (XIAP), was reported to contribute to PCa progression (Feng et al. 2019). Nonetheless, the role and mechanism of circ_0005276 in PCa is not completely understood. CircRNA may function as miRNA sponge to sequester miRNA expression (Witkos et al. 2018). Therefore, the study of circRNA-targeted miRNAs is constructive to explore the functional mechanisms of circRNAs. The advance of bioinformatics makes it easier to predict circRNA-targeted miRNAs (Jiang and Ye, 2019).

To clarify the mechanism of circ_0005276 action in PCa, Li et al characterized miRNAs targeted by circ_0005276 and obtained miR-128-3p. MiR-128-3p, as a tumor suppressor in PCa, has been previously reported (Khan et al. 2010). XTP8/DEPDC1B was widely reported to be an oncogene in various cancers, including PCa (Bai et al. 2017). The miR-128-3p depleted XTP8/DEPDC1B expression by binding to XTP8/DEPDC1B 3'-untranslated region (3'-UTR), suggesting that XTP8/DEPDC1B might be involved in PCa progression via miR-128-3p-mediated manner. Li et al investigated the function of circ_0005276 in PCa cells in vitro and in nude mice in vivo, and determined the crosstalk between miR-128-3p and circ_0005276 or XTP8/DEPDC1B, thus providing a new mechanism regarding circ_0005276 function in PCa.

Circular RNAs (circRNAs) are a new type of extensive non-coding RNAs that regulate the activation and progression of different human diseases, including cancer. The expression profile of RNAs in 8 lung squamous cell carcinoma (LUSC) tissues, and 9 healthy lung tissues were assayed using RNA sequencing (RNA-seq) techniques. The data showed that circPVT1 was upregulated in LUSC tissues, serum, and cell lines. LUSC patients with higher circPVT1 expression exhibited shorter survival rates. The in vivo and in vitro data revealed that circPVT1 promotes the proliferation of LUSC cells. Additionally, mechanistic analysis showed that HuR regulated circPVT1. On the other hand, circPVT1 acted as a competing endogenous RNA (ceRNA) of miR-30d and miR-30e in alleviating the suppressive influences of miR-30d and miR-30e on its target cyclin F (CCNF). Out of the 20 genes, CCNF and XTP8/DEPDC1B were consistently down-regulated after inhibition circPVT1 expression, indicating XTP8/DEPDC1B might be a downstream target of circPVT1 (Shi et al., 2021).

By using a microarray, Song et al analyzed the temporal changes of mRNA and microRNA expression in primary mouse hepatocytes after Sho-saiko-to (SST) treatment. In this study, Song et al found that SST regulates temporal XTP8/DEPDC1B gene expression by way of microRNAs such as miR-495-3p and miR-142-5p (Song et al., 2014).

MicroRNAs (miRNAs), which mostly cause target gene silencing via transcriptional repression and degradation of target mRNAs, regulate a plethora of cellular activities, such as cell growth, differentiation, development, and apoptosis. In the case of skin keratinocytes, the role of miRNA in epidermal barrier integrity has been identified. Based on the impact of key genetic and environmental factors on the integrity and maintenance of skin barrier, the association of miRNAs within epidermal cell differentiation and proliferation, cell–cell adhesion, and skin lipids is reviewed. The critical role of miRNAs in the epidermal barrier extends the use of miRNAs for control of relevant skin diseases such as atopic dermatitis, ichthyoses, and psoriasis via miRNA-based technologies. Most of the relevant miRNAs have been associated with keratinocyte differentiation and proliferation. Few studies have investigated the association of miRNAs with structural proteins of corneocytes and cornified envelopes, cell–cell adhesion, and skin lipids. Further studies investigating the association between regulatory and structural components of epidermal barrier and miRNAs are needed to elucidate the role of miRNAs in epidermal barrier integrity and their clinical implications. Downregulated miR-26a-5p is also involved in barrier function of patients with atopic dermatitis

by targeting XTP8/DEPDC1B, DEPDC1, hyaluronan synthase 3 (HAS3), nicotinamide phosphoribosyltransferase (NAMPT), and a disintegrin and metalloproteinase domain 19 (ADAM19), which mediate cell differentiation, cell proliferation, and anti-apoptosis (Lee AY, 2020).

Previous study revealed that the miR-199 family (miR-199a-5p/-3p and miR-199b-5p/-3p) acts as tumor-suppressive miRNAs in head and neck squamous cell carcinoma (HNSCC). Furthermore, recent studies have indicated that the passenger strands of miRNAs are involved in cancer pathogenesis. Tanaka et al try to identify cancer-promoting genes commonly regulated by miR-199-5p and miR-199-3p in HNSCC cells. In silico analysis and luciferase reporter assay identified paxillin (PXN) as a direct target of both miR-199-5p and miR-199-3p in HNSCC cells. Analysis of the cancer genome atlas (TCGA) database showed that expression of PXN significantly predicted a worse prognosis (5-year overall survival rate). Analysis revealed that a total of 12 genes (ABCA1, ADRBK2, ANKRD52, XTP8/DEPDC1B, FXR1, ITGA3, KLF12, NLK, PCDH17, PDE7A, PXN, and SLC24A2) are regulated by miR-199-5p and miR-199-3p in HNSCC cells. The expression levels of the putative targets (68 genes) of miR-199-5p and miR-199-3p were evaluated using the TCGA database (TCGA-HNSC). Among these genes, the expression levels of 12 genes (ABCA1, ADRBK2, ANKRD52, XTP8/DEPDC1B, FXR1, ITGA3, KLF12, NLK, PCDH17, PDE7A, PXN, and SLC24A2) were significantly upregulated in HNSCC tissues compared with normal tissues. Among these 12 genes, XTP8/DEPDC1B had a negative correlation with the miR-199 family in cancer tissues according to Spearman's rank test. PXN expression was identified as an independent factor predicting patient survival according to multivariate Cox regression analyses. Overexpression of PXN was detected in HNSCC clinical specimens by immunostaining. Functional assays in HNSCC cells showed that knockdown of PXN expression attenuated cancer cell migration and invasion, suggesting that aberrant expression of PXN contributed to HNSCC cell aggressiveness. The miRNA-based approach will provide new insights into the molecular pathogenesis of HNSCC. In a study to identify miRNAs able to predict the outcomes in breast cancer patients after neoadjuvant chemotherapy (NAC), XTP8/DEPDC1B was confirmed as the target for miR-199-3a (Fuso et al., 2021). In an integrative analysis of the gastric cancer long noncoding RNAassociated competing endogenous RNA network, Jiang et al found 3 potential miR27a3p, miR107, miR449c5p for XTP8/DEPDC1B regulation (Jiang et al., 2021). miR-888-5p also could be a regulator for XTP8/DEPDC1B (Sidiropoulos et al., 2014).

One of the hallmarks of cancer is sustained angiogenesis. Favorable results have been reported in some breast cancer (BC) patients receiving antiangiogenic therapy with bevacizumab (Bev) in combination with chemotherapy, and further knowledge on how Bev can be optimally combined with conventional treatment to increase efficacy is strongly needed. MiRNA expression profiling was performed on biopsies from each time point. Altogether, 241 biopsies were analyzed with the aim of identifying miRNA-based biomarkers of response to therapy. In this research, miR-4465 was found to correlate genes with both predicted target scores and significant regulation in bevacizumab-responding patients such as XTP8/DEPDC1B (0.49-fold), indicating miR4465-XTP8/DEPDC1B axis is involved in development and chemotherapy of breast cancer (Lindholm et al., 2019).

Li et al investigated the functions of circ_0005276 in prostate cancer (PCa) and provide a novel mechanism for circ_0005276 action. The expression of circ_0005276, microRNA-128-3p (miR-128-3p) and XTP8/DEPDC1B was detected by quantitative real-time PCR. The potential binding relationship between miR128-3p and circ_0005276 or XTP8/DEPDC1B was ascertained by dual-luciferase reporter assay and RIP assay. Mouse models were used to verify the role of circ_0005276 in vivo. The upregulation of circ_0005276 was determined in PCa tissues and cells. Circ_0005276 knockdown inhibited proliferation, migration, invasion and angiogenesis in PCa cells, and circ_0005276 knockdown also blocks tumor growth in vivo. Mechanism analysis discovered that miR-128-3p was a target of circ_0005276, and miR-128-3p inhibition recovered circ_0005276 knockdown-inhibited proliferation, migration, invasion and angiogenesis. In addition, XTP8/DEPDC1B was a target of miR128-3p, and miR-128-3p restoration-inhibited proliferation, migration, invasion and angiogenesis were rescued by XTP8/DEPDC1B overexpression. Circ_0005276 might promote the development of PCa by activating the expression of XTP8/DEPDC1B via targeting miR-128-3p.

Maccani et al analyzed and compared the microRNA expression patterns of high, low, and non-producing recombinant CHO cell lines expressing two structurally different model proteins in order to identify microRNAs that are involved in heterologous protein synthesis and secretion and thus might be promising targets for cell engineering to increase productivity. The results and the comparison to published data suggest that the reaction of CHO cells to the heterologous protein expression is strongly product- and/or clone-specific, and XTP8/DEPDC1B specific miR-19a-3p also involved in this regulation (Maccani et al., 2014).

Lung cancer poses severe threats to human health. It is indispensable to discover more druggable molecular targets. Zhu et al identified a novel dysregulated long non-coding RNA (lncRNA), LINC00669, in lung adenocarcinoma (LUAD) by analyzing the TCGA and GEO databases. Pan-cancer

analysis indicated significantly upregulated LINC00669 across 33 cancer types. GSEA revealed a tight association of LINC00669 with the cell cycle. Zhu et al next attempted to improve the prognostic accuracy of this lncRNA by establishing a risk signature in reliance on cell cycle genes associated with LINC00669. The resulting risk score combined with LINC00669 and stage showed an AUC of 0.746. The risk score significantly stratified LUAD patients into low- and high-risk subgroups, independently predicting prognosis. Its performance was verified by nomogram (C-index = 0.736) and decision curve analysis. Gene set variation analysis disclosed the two groups' molecular characteristics. Zhu et al also evaluated the tumor immune microenvironment by dissecting 28 infiltrated immune cells, 47 immune checkpoint gene expressions, and immunophenoscore within the two subgroups. Furthermore, the risk signature could predict sensitivity to immune checkpoint inhibitors and other anticancer therapies. Eventually, in vitro and in vivo experiments were conducted to validate LINC00669's function using qRT-PCR, CCK8, flow cytometry, Western blot, and immunofluorescence staining. The gain- and loss-of-function study substantiated LINC00669's oncogenic effects, which stimulated non-small cell lung cancer cell proliferation but reduced apoptosis via activating the Wnt/β-catenin pathway. Its oncogenic potentials were validated in the xenograft mouse model. Overall, it was identified a novel oncogenic large intergenic non-coding RNA (lincRNA), LINC00669. The resulting signature may facilitate predicting prognosis and therapy responses in LUAD (Zhu et al., 2023). Liu et al also found that lncRNA LINC02525, which acts as a modifier of ribosomal proteins, can function as an oncogene by interacting with the ribosomal protein RPL35 to activate the translation of E2F1 and subsequently enhance the transcription of the GTPaseactivating protein XTP8/DEPDC1B to regulate the biological activity of neuroblastoma cells (Liu et al., 2019).

Tyrosine kinase inhibitors (TKIs) that target epidermal growth factor receptor (EGFR) mutations are commonly administered to EGFR-positive lung cancer patients. However, resistance to EGFR-TKIs (mostly gefitinib and erlotinib) is presently a significant problem. Limited studies have focused on an EGFR-TKI resistance-related gene signature (ERS) in lung adenocarcinoma (LUAD). Gefitinib and erlotinib resistance-related genes were obtained through the differential analyses of three Gene Expression Omnibus (GEO) datasets. These genes were investigated further in LUAD patients from The Cancer Genome Atlas (TCGA). Patients in the TCGA-LUAD cohort were split into two groups: one for training and one for testing. The training cohort was used to build the ERS, and the testing cohort was used to test it. GO and KEGG analyses were explored for the enriched pathways between the high-risk and low-risk groups. Various software, mainly CIBERSORT and ssGSEA, were used for immune infiltration profiles. Somatic mutation and drug sensitivity analyses were also explored. An ERS based on five genes (FGD3, PCDH7, XTP8/DEPDC1B, SATB2, and S100P) was constructed and validated using the TCGA-LUAD cohort, resulting in the significant stratification of LUAD patients into high-risk and low-risk groups. Multivariable Cox analyses confirmed that ERS had an independent prognostic value in LUAD. The pathway enrichment analyses showed that most of the genes that were different between the two risk groups were related to the immune system. Further immune infiltration results revealed that a lower immune infiltration score was observed in high-risk patients, and that various leukocytes were significantly related to the ERS. Importantly, samples from the high-risk group showed lower levels of PD-1, PD-L1, and CTLA-4, which are important biomarkers for immunotherapy responses. Patients in the high-risk group also had more gene mutation changes and were more sensitive to chemotherapy drugs like docetaxel and sorafenib. The ERS was also validated in the GSE30219, GSE11969 and GSE72094, and showed a favorable prognostic value for LUAD patients. The ERS established was able to predict a poor prognosis for LUAD patients and had great potential for predicting drug responses. Fu et al also construction of prognostic predictive signature for LUAD, and found five genes XTP8/DEPDC1B, TPSB2, GJB3, RHOV, CPS1 could be used as predictor of LUAD prognosis. Among them, XTP8/DEPDC1B has been defined as the most valuable parameter in the prognostic signature (Fu et al., 2022).

Competing endogenous RNAs (ceRNAs) have become an emerging topic in cancer research due to their role in gene regulatory networks. To date, traditional ceRNA bioinformatic studies have investigated microRNAs as the only factor regulating gene expression. Growing evidence suggests that genomic (e.g., copy number alteration [CNA]), transcriptomic (e.g., transcription factors [TFs]), and epigenomic (e.g., DNA methylation [DM]) factors can influence ceRNA regulatory networks. Herein, it is used the Least absolute shrinkage and selection operator regression, a machine learning approach, to integrate DM, CNA, and TFs data with RNA expression to infer ceRNA networks in cancer risk. The gene‐regulating factors‐mediated ceRNA networks were identified in four hormone‐dependent (HD) cancer types: prostate, breast, colorectal, and endometrial. The shared ceRNAs across HD cancer types were further investigated using survival analysis, functional enrichment analysis, and protein–protein interaction network analysis. Three genes, XTP8/DEPDC1B, BUB1 and RRM2, were identified as shared ceRNAs among PRAD, COLCA and UCEC. XTP8/DEPDC1B has been identified as a prostate cancer metastasis oncogene. It was positively correlated with metastasis status, high Gleason score, advanced

tumor stage and poor prognosis. Moreover, mechanistic investigations found that XTP8/DEPDC1B induced EMT and enhanced proliferation by binding to Rac1 and enhancing the Rac1 - PAK1 pathway. EMT plays an important role in empowering cancer cells to adapt and survive at the start of the metastatic stage. The role of XTP8/DEPDC1B in COLCA and UCEC has not been described in previous bioinformatics or functional studies. The survival analyses of shared ceRNAs among two HD cancer combinations have shown that 12 (KIF4A, KPNA2, TPX2, TUBA1C, RAD54L, MTFR2, ANLN, RACGAP1, FAM83D, KNSTRN, CCNE1 and DSCC1) out 88 and 6 (KPNA2, CCNF, CKAP2L, TTK, XTP8/DEPDC1B and MCM2) out of 77 ceRNAs shared among BRCA - UCEC and COLCA - UCEC pairs, respectively, have exhibited the survival significance in both cancers included in the combinations (Li et al., 2019; Jayarathna et al., 2022).

XTP8 Protein in Signal Transduction

XTP8/DEPDC1B affects AKT1 and ERK signaling and show that expression of XTP8/DEPDC1B is a strong candidate biomarker for breast, lung, pancreas, and renal cell cancers. These initial studies implicate XTP8/DEPDC1B as a protein partner of the p856 subunit of PIK3, as a regulator of ERK and AKT cross talk, and as a cell de-adhesion mitotic checkpoint. Moreover, XTP8/DEPDC1B is regulated by Raf1 and is a direct target of SOX10 and so may be a central promoter of angiogenesis and metastasis.

Liu et al reported XTP8/DEPDC1B is a downstream effector of Raf-1 and long noncoding RNA lncNB1, and an upstream positive effector of pERK (Liu et al., 2019). Consistently, XTP8/DEPDC1B knockdown is associated with downregulation of ligand-stimulated pERK expression. Liu et al demonstrate here that XTP8/DEPDC1B N-terminus binds to the p85 subunit of PI3K, and XTP8/DEPDC1B overexpression results in decreased ligand-stimulated tyrosine phosphorylation of p85 and downregulation of pAKT1. Collectively, Liu et al propose that XTP8/DEPDC1B is a novel cross-regulator of AKT1 and ERK, two of the prominent pathways of tumor progression. The data showing high levels of XTP8/DEPDC1B mRNA and protein during the G2/M phase have significant implications in cell entry into mitosis. Indeed, XTP8/DEPDC1B accumulation during the G2/M phase has been associated with disassembly of focal adhesions and cell de-adhesion, referred to as a XTP8/DEPDC1B -mediated de-adhesion mitotic checkpoint. XTP8/DEPDC1B is a direct target of transcription factor SOX10, and SOX10- XTP8/DEPDC1B-SCUBE3 axis has been associated with angiogenesis and metastasis (Liu et al., 2019). The Scansite analysis of the XTP8/DEPDC1B amino acid sequence shows binding motifs for three well-established cancer therapeutic targets CDK1, DNA-PK, and aurora kinase A/B. Finally, a survey of the publicly available datasets indicates that high XTP8/DEPDC1B expression is a viable biomarker in breast, lung, pancreatic and renal cell carcinomas, and melanoma. Currently, the systems and integrative biology of XTP8/DEPDC1B is far from comprehensive. Future investigations are necessary in order to understand how XTP8/DEPDC1B might impact AKT, ERK, and other networks, albeit in a context-dependent manner, and influence the actionable molecular, spatial, and temporal vulnerabilities within these networks in cancer cells (Liu et al., 2019).

Treatment of MDA-MB-231 breast cancer cells with c-raf-1 antisense oligodeoxynucleotide (AS-raf-ODN) resulted in knockdown of Raf-1 and concomitant decrease in XTP8/DEPDC1B mRNA and protein expression (Rudin et al., 2004; Boudreau et al., 2007). Genomic XTP8/DEPDC1B is localized at the human chromosome 5q12.1. Sequence homology search of the chromosome 5 genomic DNA revealed several CCAAT-boxes and E-boxes (CANNTG) within the putative XTP8/DEPDC1B promoter region. The CCAAT boxes are potential binding sites of transcription factor NF-Y, whereas E-boxes have been shown to bind upstream stimulatory factors (USFs) (Roy et al., 1991). Similar to cyclin B, XTP8/DEPDC1B mRNA is likely to be regulated by transcriptional enhancer CCAAT/E-box motifs in a cell cycle-dependent manner. XTP8/DEPDC1B transcript (3.0 kb) was detected in just a few adult human normal tissues (testes, bone marrow, placenta) and in most of the human cancer cell lines tested. In other studies, RNA sequencing of MYCN amplified and non-amplified human neuroblastoma cell lines led to identification of a long noncoding RNA lncNB1 as an overexpressed transcript in MYCN amplified neuroblastoma cells. Here, lncNB1 was shown to bind to the ribosomal protein RPL35, leading to enhanced synthesis of E2F1 protein which, in turn, promotes XTP8/DEPDC1B gene transcription and tumorigenesis (Liu et al., 2019). More recently, an in silico approach led to identification of five consensus binding motifs of a neural crest lineage transcription factor SOX10 within the XTP8/DEPDC1B promoter region. Consistently, XTP8/DEPDC1B is a direct downstream target of SOX10 in melanoma cells (Driehuis et al., 2020). Together these data suggest context-dependent regulation of XTP8/DEPDC1B mRNA expression in cancer cells by Raf-1, lncNB1, and SOX10.

Target of ERK-2 (TOE-2) protein is DEP domain-containing protein. The mammalian homolog with the most closely related DEP domain to TOE-2 is XTP8/DEPDC1B. Until recently, little was known about the function of XTP8/DEPDC1B, but it was recently implicated in canonical Wnt signaling. When in a complex with the corepressor Groucho, the transcription factor

T-Cell Factor (TCF) represses the expression of Wnt target genes; however, when β-catenin accumulates as a result of Wnt signaling, it enters the nucleus, binds TCF and activates the expression of Wnt target genes. Reduction in XTP8/DEPDC1B function led to decreased expression of TCF induced transcripts, and increased XTP8/DEPDC1B levels increased expression of those transcripts. These results indicated that Wnt signaling may play a central role in the mechanism of XTP8/DEPDC1B protein function (Gurling et al., 2015).

Human genome is expressed in a mirror pattern, in which the majority of transcripts are accompanied by their shadow RNAs like mirrors when they are aligned along the genomic reference backbone, this phenomenon was named the "mirror RNAs". This mirror pattern may be related to their functionalities and molecular mechanisms. Transcripts produced from the XTP8/DEPDC1B and PDE4D genes were primarily expressed in a unidirectional manner like mirror RNAs (Bythwood et al., 2015). Thangavelu et al also found XTP8/DEPDC1B significantly co-expressed with CENP-I (Thangavelu et al., 2017).

XTP8 Protein Mediated Epithelial-to-mesenchymal Transition

Epithelial–mesenchymal transition (EMT) is a cellular process that plays an integral role in embryogenesis, wound repair, and tumor progression (Hao et al., 2019). Through EMT, interactions between cells and the extracellular matrix undergo significant alterations, which results in the detachment of epithelial cells from one another and from the basal membrane. In neoplastic diseases, EMT bestows upon cancer cells an enhanced capacity for initiating tumors and metastasis, as well as increased treatment resistance (Gusinac et al., 2021). During EMT, there is upregulation of vimentin, N-cadherin, and Snail, coinciding with downregulation of the epithelial marker E-cadherin (Veloso et al., 2020). EMT plays a pivotal role in the progression of nonepithelial tumors, including glioblastoma and osteosarcoma. EMT is an independent prognostic indicator for glioblastoma and a potential therapeutic target (Chen et al., 2023).

Metastasis is the major cause of prostate cancer (PCa)-related mortality. Epithelial-mesenchymal transition (EMT) is a vital characteristic feature that empowers cancer cells to adapt and survive at the beginning of metastasis. Therefore, it is essential to identify the regulatory mechanism of EMT in metastatic prostate cancer (mPCa) and to develop a novel therapy to block PCa metastasis. Li et al discovered a novel PCa metastasis oncogene, XTP8/DEPDC1B, which was positively correlated with the metastasis status, high Gleason score, advanced tumor stage, and poor prognosis. Functional assays revealed that XTP8/DEPDC1B enhanced the migration, invasion, and proliferation of PCa cells in vitro and promoted tumor metastasis and growth in vivo. Mechanistic investigations clarified that XTP8/DEPDC1B induced EMT and enhanced proliferation by binding to Rac1 and enhancing the Rac1-PAK1 pathway. This XTP8/DEPDC1B-mediated oncogenic effect was reversed by a Rac1-GTP inhibitor or Rac1 knockdown. XTP8/DEPDC1B-Rac1-PAK1 signaling pathway may serve as a multipotent target for clinical intervention in mPCa (Li et al. 2020).

XTP8 Expression and Autoimmune Diseases

Systemic lupus erythematosus (SLE) displays the characteristics of abnormal activity of the immune system, contributing to diverse clinical symptoms. In order to find new therapeutic targets, Chen et al determined three co-expression modules strongly linked to immune cells. Five characteristic genes (CXCL1, CXCL2, CXCL8, CXCR1 and TK1) were screened and ROC curves proved the excellent diagnostic performance of this LASSO model. Inflammatory chemokines presented widespread up-regulations in serum of systemic lupus erythematosus patients, demonstrating the activation of inflammatory response. TK1 expression was remarkably elevated in SLE BMSCs than controls. TK1 overexpression enhanced IL-1β expression, apoptosis, cell cycle arrest, and senescent phenotypes of SLE BMSCs and the opposite results were proved in TK1-silenced SLE BMSCs. Additionally, it was determined 49 hub genes including XTP8/DEPDC1B. Collectively, these findings demonstrate that silencing TK1 alleviates inflammation, growth arrest and senescence in BMSCs of SLE, which highlights TK1 as a promising therapeutic target against SLE (Chen et al., 2022).

XTP8 Expression and Diabetic Nephropathy

The underlying molecular mechanisms of diabetic nephropathy have yet not been investigated clearly. To identify key genes involved in the pathogenesis and prognosis of diabetic nephropathy, Joshi et al downloaded next-generation sequencing data set GSE142025 from Gene Expression Omnibus database having 28 diabetic nephropathy samples and nine normal control samples (Joshi et al., 2022). The differentially expressed genes between diabetic nephropathy and normal control samples were analyzed. Biological function analysis of the differentially expressed genes was enriched by Gene Ontology and REACTOME pathways. Then, the protein–protein interaction network, modules, miRNA-differentially expressed gene regulatory network and transcription factor-differentially expressed gene regulatory network were

established. A total of 549 differentially expressed genes were detected including 275 upregulated and 274 downregulated genes. The biological process analysis of functional enrichment showed that these differentially expressed genes were mainly enriched in cell activation, integral component of plasma membrane, lipid binding, and biological oxidations. Analyzing the protein–protein interaction network, miRNA-differentially expressed gene regulatory network and transcription factor-differentially expressed gene regulatory network. The receiver operating characteristic (ROC) curve analysis confirmed that hub genes were of diagnostic value. Taken above, using integrated bioinformatics analysis, it has identified key genes and pathways in diabetic nephropathy, which could improve the understanding of the cause and underlying molecular events, and these key genes and pathways might be therapeutic targets for diabetic nephropathy. Among them, XTP8/DEPDC1B expression was found significantly decreased in the diabetic nephropathy group (−1.43627513-fold).

XTP8 Expression and Lymphoma

Canine lymphoma is the most common haematological malignancy in dogs and is typically treated with multidrug chemotherapy. Most cases are at risk of relapse after several courses of chemotherapy and the oncogenic mechanism remains unknown. In the study to identify genes expressed in canine lymphoma by cDNA microarray, Morinaga et al found elevated expression of XTP8/DEPDC1B in canine lymphoma cells compared with cells and tissues from healthy dogs. Canine XTP8/DEPDC1B protein was detected in 13 of 41 lymphoma specimens by immunohistochemistry, but was not detected in lymph nodes from normal dogs. Immunoreactive XTP8/DEPDC1B protein was also detected in several other types of canine tumor. The association of XTP8/DEPDC1B with canine cancer and the results suggest that XTP8/DEPDC1B might serve as a potential marker or therapeutic target for canine malignancies.

Prognosis of hepatosplenic T-cell lymphoma (HSTCL) is very poor, while the molecular mechanism of this disease has rarely been investigated and remains mysterious. By screening of differentially expressed genes (DEGs) of patients with HSTCL and normal controls, Do et al explored the pathogenesis, and provide guidance for the gene diagnosis and precise treatment of HSTCL. The genetic chip data GSE57520 of HSTCL was searched from the GEO database, and the quality control and DEGs screening were performed through BART online tools. In addition, FunRich software was used to perform gene enrichment and pathway analysis on the screened DEGs. Subsequently protein-protein interaction (PPI) network was constructed via the STRING database and analyzed using the visual module of Cytoscape software. A total of 4,759 DEGs were obtained, including 2,501 up-regulated genes and 2,258 down-regulated genes. The analysis of gene ontology (GO) showed that DEGs in cytology component (CC) mainly involved cytoplasm, nucleus, plasma membrane, Golgi apparatus, lysosome, and endoplasmic reticulum. Besides, DEGs in molecular function (MF) mainly included transcription factor activity, catalytic activity, transporter activity, transcription regulator activity, receptor signaling pathway complex, receptor activity. Moreover, DEGs in biological processes (BP) are mainly involved in base regulation, transport, energy pathways, metabolism, protein metabolism, and apoptosis. The results of the Kyoto Gene and Genome Encyclopedia (KEGG) analysis showed that the DEGs mainly include TRAIL, Beta1 integrin, integrin family, proteoglycan, S1P, and ErbB. Combined with Cytoscape software cytoHubba plug-in, PPI analysis showed that KIF20A, DLGAP5, PBK, TOP2A, ASPM, NEK2, KIF14, and XTP8/DEPDC1B were the most abundant core genes. Module analysis showed that the three gene modules with the highest scores were mainly related to mitosis, epithelial cell adhesion and signal transduction, and the process of DNA damage. The DEGs of HSTCL patients versus healthy control groups were obtained through a variety of bioinformatics methods. KIF20A and DLGAP5 may become potential therapeutic targets for HSTCL. Also, the most abundant signaling pathway in DEGs was the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) - related pathway. Besides, related genes and expression characteristics of HSTCL pathogenesis were reanalyzed from distinctive perspectives, which might provide specific diagnostic markers and targeted therapy for HSTCL. Rac1/PAK1 primarily functions in tumor metastasis. Both the GEFT and XTP8/DEPDC1B can interact with Rac1 to activate Rac1 and downstream PAK1, thus promoting EMT and enhancing the invasion and migration of tumor cells. LIMK1/cofilin, downstream of Rac1/PAK1, is one of the major ways for Rho GTPase to regulate actin cytoskeleton. XTP8/DEPDC1B can promote tumor cell invasion and migration by activating the Rac1/PAK1/LIMK1/cofilin pathway (Ma et al., 2023).

Kulkarni et al explored the association of differential gene expression with imatinib mesylate and omacetaxine mepesuccinate toxicity in lymphoblastoid cell lines. In this study, 34 genes were found differentially expressed upon treatment as well as associated with sensitivity of drug response (SDR). After treatment of lymphoblastoid cell lines with imatinib mesylate and omacetaxine mepesuccinate, XTP8/DEPDC1B expression levels decreased by −0.1807 and −0.7007, respectively. These results indicated that XTP8/DEPDC1B expression levels determined the SDR of

lymphoblastoid cell lines to chemotherapies (Kulkarni et al., 2012).

Diffuse large B cell lymphoma (DLBCL), the most common form of blood cancer. The genetic and clinical heterogeneity of DLBCL poses a major barrier to diagnosis and treatment. Differentially expressed genes were screened between DLBCL and the corresponding normal tissues. Kinesin family member 23 (KIF23) showed higher expression in DLBCL and was identified as a risk factor in DLBCL. Besides, XTP8/DEPDC1B was found up-regulated in DLBCL comparing with normal tissues. The findings of this study suggested that both KIF23 and XTP8/DEPDC1B are potential biomarkers for the diagnosis and prognosis of DLBCL (Gong et al., 2022).

XTP8 Expression and Gastric Cancer

XTP8/DEPDC1B expression closely related to the development of gastric cancer (GC). Jia et al explored a panel of 37 pairs of GC tissues and adjacent normal tissues for their expression of XTP8/DEPDC1B protein. As qRT-PCR data revealed, XTP8/DEPDC1B was highly expressed in GC tissues relative to normal ones. Similarly, XTP8/DEPDC1B was upregulated in GC cells than that of human gastric mucosal cells. XTP8/DEPDC1B level was found correlated with lymphatic metastasis, distant metastasis, and survival of GC. XTP8/DEPDC1B level was positively correlated with lymphatic metastasis and distant metastasis of GC patients, rather than age, gender, and tumor staging. In addition, the Kaplan-Meier curves revealed poorer survival in GC patients with a high expression level of XTP8/DEPDC1B. To confirm the relationship between XTP8/DEPDC1B expression and GC development, Jia et al conducted knockdown experiment on XTP8/DEPDC1B, and found that the reduction of XTP8/DEPDC1B expression significantly suppressed the proliferation and metastasis of GC cell lines MKN-45 and SGC-7901. In addition, the silence of XTP8/DEPDC1B attenuated the migration and invasion capacities of these GC cells. To elucidate the working mechanism of XTP8/DEPDC1B protein in the development of GC, TGIF1 protein was attracted for TGIF1 can control the malignant progression by affecting the metastasis of tumor cells. Jia et al used dual-luciferase reporter gene assay to identify the interaction between XTP8/DEPDC1B and TGIF1. The decline of the luciferase activity after co-transfection of pcDNA-TGIF1 and pmirGLO-XTP8/DEPDC1B-WT supported the findings that TGIF1 was the target of XTP8/DEPDC1B. Transfection with sh-XTP8 upregulated TGIF1 level in GC cells, while the transfection with si-TGIF1 upregulated the XTP8/DEPDC1B level. A negative correlation was discovered between the expression levels of XTP8/DEPDC1B and TGIF1 in GC tissues. TGIF1 was found to be lowly expressed in GC tissues and cells. In the follow-up data, GC patients with a low expression level of TGIF1 suffered poorer survival. Transfection with si-TGIF1 effectively downregulated TGIF1 level in MKN-45 and SGC-7901 cells, showing a satisfactory transfection efficacy. It is believed that XTP8/TGIF1 axis regulated the progression of GC (Jia et al., 2020).

Control of a cancer cell's entry into mitosis can affect the rate of proliferation and responsiveness to mitotic poisons such as the taxanes and Vinca alkaloids. Boudreau et al explore the role of DEPDC1B (BRCC3, XTP8, XTP1) in controlling entry into mitosis (Boudreau et al., 2007). Schmidt et al propose that XTP8/DEPDC1B affects AKT1 and ERK signaling and show that expression of XTP8/DEPDC1B is a strong candidate biomarker for breast, lung, pancreas, and renal cell cancers (Schmidt et al., 2020). These initial studies implicate XTP8/DEPDC1B as a protein partner of the p856 subunit of PIK3, as a regulator of ERK and AKT cross talk, and as a cell de-adhesion mitotic checkpoint. Moreover, XTP8/DEPDC1B is regulated by Raf1 and is a direct target of SOX10 and so may be a central promoter of angiogenesis and metastasis (Schmidt et al., 2020).

Li et al found that XTP8/DEPDC1B is overexpressed in GC tissues and is positively related to its pathological grade. XTP8/DEPDC1B knockdown restrained the growth and migration of GC cells, while XTP8/DEPDC1B overexpression promoted cell proliferation and suppressed apoptosis. A mechanistic study indicated that XTP8/DEPDC1B knockdown inhibited cyclin-dependent kinase 6 (CDK6) expression and that CDK6 might be a potential downstream molecule of XTP8/DEPDC1B. Further study confirmed that CDK6 depletion also suppressed GC cell proliferation and migration and increased GC cell apoptosis. Moreover, rescue experiments verified that CDK6 knockdown abated the promotion of XTP8/DEPDC1B overexpression on GC progression (Li et al., 2023).

XTP8 Expression and Esophageal Cancer

Esophageal cancer (EC) is a common human malignancy worldwide. Esophageal squamous cell carcinoma (ESCC) is the predominant subtype in China. The tumorigenesis mechanism in ESCC is unclear. Zhang et al conducted a study to identify key transcription factors (TFs) in ESCC and elucidate the mechanism of it. A total of 1,248 dysregulated genes were selected as DEGs in ESCC. A total of 26 TFs and corresponding target-genes were identified. The ESCC-specific transcriptional regulatory network was constructed. The network was consisted of 882 edges and 631 nodes. BRCA1, SOX10, ARID3A, ZNF354C and NFIC had the highest connectivity with DEGs. All these 1,248 DEGs were

significantly enriched in cell cycle, DNA replication and oocyte meiosis pathways. The qRT-PCR results were consistent with microarray analysis. High expression of SREBF1 and TFAP2A were significantly correlated with the longer overall survival time of patients with ESCC. BRCA1, SOX10, ARID3A, ZNF354C and NFIC might be the key TFs in carcinogenesis and development of ESCC by regulating their corresponding target-genes involved in cell cycle, DNA replication and oocyte meiosis pathways. SREBF1 and TFAP2A may be two potential prognostic biomarkers of ESCC. In the regulated genes by transcription factor ARID3A, XTP8/DEPDC1B is one of the key targets for this process, indicating XTP8/DEPDC1B is play a role in the carcinogenesis of ESCC (Zhang et al., 2018).

XTP8 Expression and Colorectal Cancer

Colorectal cancer (CRC) is one of the most common primary intestinal malignancies in the world, with the fourth highest fatality. Due to the gradual increase in morbidity and mortality, CRC has been summarized as a major threat to human health. In the past few years, the clinical management of CRC includes a combination of surgery, radiotherapy and chemotherapy, molecular targeted drugs, biological therapy, and immunotherapy. Given the reported involvement of XTP8/DEPDC1B in the progression of some cancers, its role in CRC was explored (Han et al., 2023). XTP8/DEPDC1B expression in CRC was assessed based on database and tissue microarray (TMA). In addition, the knockdown and overexpression of XTP8/DEPDC1B in CRC cell lines were constructed using small hairpin RNA (shRNA) interference. The biological function of XTP8/DEPDC1B in CRC was evaluated in vitro and in vivo through loss/gain-of function assays. The results demonstrated that XTP8/DEPDC1B was highly expressed in CRC. Furthermore, XTP8/DEPDC1B had the ability to promote CRC proliferation and migration coupled by cell apoptosis. In vivo results showed that XTP8/DEPDC1B knockdown significantly inhibited the growth of xenograft tumors. Additionally, the results of antibody array indicated increased apoptosis promoting proteins and decreased apoptosis-inhibiting proteins in XTP8/DEPDC1B-knockdown CRC cells. XTP8/DEPDC1B played a key driver role in CRC progression, and inhibition of its expression may be a potential target for precision medicine in CRC.

XTP8 Expression and Hepatocellular Carcinoma

HCC is one of the most common cancer in the world and the main cause of cancer death. Chronic hepatitis B virus (HBV) infection is the major cause of HCC. Carcinogenesis of HCC has close relationship with the XTP8/DEPDC1B expression status (Han et al., 2019), although there is a negative result (Sun et al., 2020).

HBx, as a transactivator, plays an important role in the occurrence and development process of HCC leading by HBV infection. XTP8/DEPDC1B, related to HBx, however, there are no studies on the function of XTP8/DEPDC1B in HCC. Han et al demonstrated that XTP8/DEPDC1B was significantly up-regulated in HCC tissues compared with non-cancerous tissues in Oncomine, TCGA and GEO database. Moreover, Kaplan-Meier Plotter analysis indicated that patients with higher XTP8/DEPDC1B expression had significantly lower overall survival. The immunohistochemical results suggested that XTP8/DEPDC1B protein expression in HCC tissues was dramatically higher compared with control normal tissues. In vivo xenograft experiments on nude mice, the overexpression of XTP8/DEPDC1B promoted the tumorigenic ability of HepG2 cells. In HepG2 and Huh7 cells, XTP8/DEPDC1B upregulated FOXM1 expression to promote cell proliferation and inhibited cell apoptosis. FOXM1 knockdown reduced promoter activity of XTP8/DEPDC1B to downregulate XTP8/DEPDC1B expression. Thiostrepton, an inhibitor of FOXM1, decreased XTP8/DEPDC1B expression. Therefore, this study demonstrates that XTP8/DEPDC1B is a valuable prognostic predictor for HCC and there is a novel positive regulatory feedback loop between XTP8/DEPDC1B and FOXM1 promoting the development of HCC (Han et al., 2019).

Hepatocellular carcinoma (HCC) in young subjects is rare but more devastating. It is hypothesized that genes and etiological pathways are unique to young HCC (≤40 years old at diagnosis) patients. Wang et al compared the gene expression profiles between young HCCs and HCCs from elderly patients. XTP8/DEPDC1B gene expression was found significant increased (2.08-fold) comparing with HCC patients in elderly (Wang et al., 2013). This result indicated that XTP8/DEPDC1B preferentially expressed in the young HCC patients.

The function and mechanism of XTP8/DEPDC1B protein in the development of HCC remain largely unknown. Dang et al used immunohistochemical staining to detect the expression level of XTP8/DEPDC1B in tumor tissues and adjacent normal tissues. After XTP8/DEPDC1B and CDK1 knockdown in cell lines HEP3B2.1-7 and SK-HEP-1, MTT assay and colony formation assay was used to detect cell growth, flow cytometry assay was used to investigate cell apoptosis and cell cycle, wound-healing assay and Transwell assay were used to examine the tumor cell migration. Moreover, a xenograft model was constructed to research functions of XTP8/DEPDC1B in tumor growth in vivo. The results show that XTP8/DEPDC1B knockdown inhibit the progression of HCC, through inhibiting

cell proliferation, migration, colony formation, leading to G2 phase arrest, and promoting cell apoptosis in vitro, and CDK1 was selected for further mechanic research according to the results of Human GeneChip prime view. The results of recovery experiment displayed that the functions of XTP8/DEPDC1B on HCC progression were mediated by CDK1. XTP8/DEPDC1B knockdown can also inhibit tumor growth in vivo. The study confirmed that XTP8/DEPDC1B knockdown restrains the tumor growth in vitro and vivo, and it can interact with CDK1 and rescued by CDK1. The study suggested that XTP8/DEPDC1B was as a potential therapeutic target involved in HCC growth and progression (Dang et al., 2021).

Immune microenvironment implicated in liver cancer development. Nevertheless, previous studies have not fully investigated the immune microenvironment in liver cancer. First, the TCGA-LIHC, ICGC-FR, and ICGC-JP cohorts were selected for the analysis, which were merged into a combined cohort. Then, 53 immune terms were quantified in this combined cohort with large populations using the ssGSEA algorithm. Next, a prognostic approach was established based on five immune principles (CORE.SERUM.RESPONSE.UP, angiogenesis, CD8.T.cells, Th2.cells, and B.cells) was established, which showed great prognostic prediction efficiency. Clinical correlation analysis demonstrated that high-risk patients could reveal higher progressive clinical features. Next, to examine the inherent biological variations in high- and low-risk patients, pathway enrichment tests were conducted. DNA repair, E2F targets, G2M checkpoints, hedgehog signaling, mTORC1 signaling, and MYC target were positively correlated with the risk score. Examination of genomic instability revealed that high-risk patients may exhibit a higher tumor mutation burden score. Meanwhile, the risk score showed a strong positive correlation with the tumor stemness index. In addition, the Tumor Immune Dysfunction and Exclusion outcome indicated that high-risk patients could be higher responsive to immunotherapy, whereas low-risk patients may be higher responsive to Erlotinib. Six characteristic genes DEPDC1, XTP8/DEPDC1B, NGFR, CALCRL, PRR11, and TRIP13 were identified for risk group prediction. This study identified a signature as a useful tool to indicate prognosis and therapy options for liver cancer patients.

Gu et al performed weighted gene co-expression network analysis (WGCNA) to explore hub genes that have high correlation with clinical information. In this study, it was found 13 hub genes (GTSE1, PLK1, NCAPH, SKA3, LMNB2, SPC25, HJURP, XTP8/DEPDC1B, CDCA4, UBE2C, LMNB1, PRR11, and SNRPD2) that have high correlation with histologic grade in HCC by analyzing TCGA LIHC dataset. All of these 13 hub genes could be used to effectively distinguish high histologic grade from low histologic grade of HCC through analysis of the ROC curve. The overall survival and disease-free survival information showed that high expression of these 13 hub genes led to poor prognosis. Meanwhile, these 13 hub genes had significantly different expression in HCC tumor and non-tumor tissues. The authors downloaded GSE6764, which contains corresponding clinical information, to validate the expression of these 13 hub genes. At the same time, quantitative real-time PCR was performed to validate the differences in the expression tendencies of these 13 hub genes between HCC tumor tissues and non-tumor tissues and high histologic grade and low histologic grade. Gu et al also explored mutation and methylation information of these 13 hub genes for further study. In summary, 13 hub genes correlated with the progression and prognosis of HCC were discovered by WGCNA in the study, and these hub genes may contribute to the tumorigenesis and tumor progression of HCC (Gu et al., 2020).

Liver hepatocellular carcinoma (LIHC) is one of the most lethal tumors worldwide, and while its detailed mechanism of occurrence remains unclear, an early diagnosis of LIHC could significantly improve the 5-years survival of LIHC patients. Currently, XTP8/DEPDC1B has been reported to participate in the regulation of cell mitosis, transcription, and tumorigenesis. To explore the valuable diagnostic and prognostic markers for LIHC and further elucidate the mechanisms underlying XTP8/DEPDC1B related LIHC, numerous databases, such as Oncomine, Gene Expression Profiling Interactive Analysis (GEPIA), UALCAN, Kaplan-Meier plotter, and The Cancer Genome Atlas (TCGA) were employed to determine the association between the expression of XTP8/DEPDC1B and prognosis in LIHC patients. Generally, the XTP8/DEPDC1B mRNA level was highly expressed in LIHC tissues, compared with that in normal tissues. High XTP8/DEPDC1B expression was associated with poor overall survival (OS) in LIHC patients, especially in stage II, IV, and grade I, II, III patients. The univariate and multivariate Cox regression analysis showed that XTP8/DEPDC1B was an independent risk factor for OS among LIHC patients. In addition, the protein expression of XTP8/DEPDC1B was validated using Human Protein Atlas database. Furthermore, the expression of XTP8/DEPDC1B was confirmed by quantitative real-time polymerase chain reaction (qRT-PCR) assay using five pairs of matched LIHC tissues and their adjacent noncancerous tissues. The KEGG pathway analysis indicated that high expression of XTP8/DEPDC1B may be associated with several signaling pathways, such as MAPK signaling, the regulation of actin cytoskeleton, p53 signaling, and the Wnt signaling pathways. Furthermore, high XTP8/DEPDC1B expression may be significantly associated with various cancers. Conclusively, XTP8/DEPDC1B may be an independent risk factor for OS among LIHC cancer patients

and may be used as an early diagnostic marker in patients with LIHC (Fan et al., 2022).

Shen et al explored the association between XTP8/DEPDC1B and the downstream signal, kinesin family member 23 (KIF23), using LinkedOmics and STRING database, and subsequently confirmed by co-immunoprecipitation assay. The expression levels of XTP8/DEPDC1B and KIF23 in normal hepatic epithelial cells and HCC cell lines were assessed by RT-qPCR and Western blotting, respectively. Following transfection with small interference RNA-DEPDC1B, the influences of XTP8/DEPDC1B knockdown on cell proliferation, colony formation, cell cycle, cell invasion, migration, and KIF23 expression were evaluated. In addition, the effects of KIF23 overexpression on the above aspects of HCC cells were also determined, as well as the expression level of p53 signaling-related proteins. The results indicated that XTP8/DEPDC1B was highly expressed in HCC cells. XTP8/DEPDC1B knockdown inhibited the proliferation, migration, invasion, cycle, and KIF23 expression in HCC cells. Moreover, KIF23 overexpression reversed the inhibitory effect of XTP8/DEPDC1B knockdown in HCC cells and the activation of the p53 signaling. XTP8/DEPDC1B knockdown exerts anti-cancer role in HCC by activating the p53 signaling through KIF23 (Shen et al.,2022).

Integrated bioinformatics analysis reveals the function and prognostic value of OSBPL3 in hepatocellular carcinoma (Su et al., 2023). More recently, six hub genes, namely CEP55, KIF23, XTP8/DEPDC1B, ANLN, IQGAP1, and ECT2, were identified related to OSBPL3 from the interaction network. These results indicated XTP8/DEPDC1Bmight play a key role in the development of HCC.

In analysis of the role of m6A and lncRNAs in prognosis and immunotherapy of hepatocellular carcinoma, Xu et al found XTP8/DEPDC1B expression is a predictor of prognosis and immunotherapy of hepatocellular carcinoma (Xu et al., 2022).

XTP8 Expression and Cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common primary tumor of the hepatobiliary system. At present, the therapeutic efficiency of cholangiocarcinoma is fairly low and the prognosis is poor. The root cause is that the molecular mechanism of the occurrence and development of CCA is largely unclear. Zhang et al clarified the role of XTP8/DEPDC1B in the progress of CCA through cellular biology research strategies and further clarify the molecular mechanism of CCA. Clinical tissue-related detection showed that the expression level of XTP8/DEPDC1B in tumor tissues was significantly higher than that in normal tissues and was positively correlated with tumor grade. Knockdown of the endogenous XTP8/DEPDC1B of CCA cells can significantly inhibit cell proliferation and migration, while promoting cell apoptosis and blocking the cell cycle. XTP8/DEPDC1B overexpression induced the opposite effects. Studies in animal models also showed that the downregulation of XTP8/DEPDC1B can reduce the tumorigenicity of CCA cells. In addition, through gene profiling analysis and molecular biology studies, it was found that CDK1 may be an important downstream mediator of XTP8/DEPDC1B, the protein stability of which was significantly decreased through the ubiquitin–proteasome system in XTP8/DEPDC1B knockdown cells. Moreover, knockdown of CDK1 can weaken the promotion of CCA caused by XTP8/DEPDC1B overexpression. The results showed that XTP8/DEPDC1B plays an important role in the development of CCA and its targeted inhibition may become one of the important methods to inhibit the progress of CCA (Zhang et al., 2022).

XTP8 Expression and Prognosis of Soft-Tissue Sarcomas

Pollino et al examined the value of XTP8/DEPDC1B expression in the prognostic role of XTP1/DEPDC1B and SDP35/DEPDC1A in high grade soft-tissue sarcomas (Pollino et al., 2018). SDP35/DEPDC1A and XTP1/DEPDC1B gene were down-regulated in adjacent normal tissues while sarcoma specimens presented high mRNA levels, significantly related to metastasis-free survival. Gene expression further increased in paired metastatic lesions. Immunohistochemical staining showed a variable expression in intensity and distribution, with a significantly higher probability of metastatic disease in patients up-regulating SDP35/DEPDC1A. Western blotting assessed high levels of proteins in STS specimens and indicated a stronger expression of SDP35/DEPDC1A in metastases when compared to primary tumors. Multivariate analyses highlighted that SDP35/DEPDC1A abundance, grade III and no history of radiation therapy were significant independent risk factors. Niu et al studied the specific factors to determine radiotherapy sensitivity of different cancers, and found that XTP8/DEPDC1B expression level is a key factor. Functional validation using siRNA knockdown in multiple tumor cell lines showed that C13orf34, MAD2L1, PLK4, TPD52, and XTP8/DEPDC1B each significantly altered radiation sensitivity in at least two cancer cell lines. Knockdown of C13orf34, XTP8/DEPDC1B, and TPD52 desensitized all four cell lines (HupT3, HeLa, A549 and MIA-PaCa2) to radiation treatment (Niu et al., 2010).

XTP8 Expression and Malignant Melanoma

Melanoma is one of the most devastating human cancers and is responsible for more than 80% of all skin cancer deaths.

Malignant melanoma (MM) remains the leading cause of skin cancer related death, which has very poor prognosis because of locoregional recurrence and distant metastasis. XTP8/DEPDC1B, has been proved to be associated with some types of malignant tumors. However, the role of XTP8/DEPDC1B in MM is still unknown. The results indicated significantly up-regulated expression of XTP8/DEPDC1B in tumor tissues. Moreover, knockdown of XTP8/DEPDC1B could inhibit cell proliferation while inducing cell apoptosis. The in vivo study demonstrated the significant suppression of tumor growth by knockdown of XTP8/DEPDC1B. Finally, the results of antibody array proved the up-regulation of pro-apoptotic proteins and the down-regulation of anti-apoptotic proteins by XTP8/DEPDC1B knockdown. Therefore, it could be concluded that XTP8/DEPDC1B was involved in the development and progression of MM, which may act as promotor for MM and could be a potential therapeutic target (Xu et al., 2019).

The effect and mechanism of XTP8/DEPDC1B protein in the angiogenesis and metastasis are very complicated. The ability of melanoma to acquire metastasis through the induction of angiogenesis is one of the major causes of skin cancer death. Hu et al found that high transcript levels of XTP8/DEPDC1B in cutaneous melanomas are significantly associated with a poor prognosis. Tissue microarray analysis indicates that XTP8/DEPDC1B expression is positively correlated with SOX10 in the different stages of melanoma. Consistently, XTP8/DEPDC1B is both required and sufficient for melanoma growth, metastasis, angiogenesis, and functions as a direct downstream target of SOX10 to partly mediate its oncogenic activity. In contrast to other tumor types, the XTP8/DEPDC1B-mediated enhancement of melanoma metastatic potential is not dependent on the activities of RHO GTPase signaling and canonical Wnt signaling, but is acquired through secretion of signal peptide, CUB domain and EGF like domain containing 3 (SCUBE3), which is crucial for promoting angiogenesis in vitro and in vivo. Mechanistically, XTP8/DEPDC1B regulates SCUBE3 protein stability through the competitive association with ubiquitin ligase cell division cycle 16 (CDC16) to prevent SCUBE3 from undergoing degradation via the ubiquitin-proteasome pathway. Importantly, expression of SOX10, XTP8/DEPDC1B, and SCUBE3 are positively correlated with microvessel density in the advanced stage of melanomas. In conclusion, it is revealed that a SOX10-DEPDC1B-SCUBE3 regulatory axis promotes melanoma angiogenesis and metastasis, which suggests that targeting secreted SCUBE3 can be a therapeutic strategy against metastatic melanoma (Hu et al., 2022).

XTP8 Expression and Breast Cancer

Gene expression is governed by complex networks, and differences in expression patterns between distinct biological conditions may therefore be complex and multivariate in nature. Current statistical methods for detecting differential expression merely consider the univariate difference in expression level of each gene in isolation, thus potentially neglecting many genes of biological importance. The novel proteins DEPDC1 and XTP8/DEPDC1B, both containing RhoGAP domains. This may implicate them in the regulation of various Rho GTPases, which are currently being investigated as cancer-therapy targets. Genes with multivariate expression patterns discovered by the RIT algorithm for the breast cancer data, both DEPDC1 and XTP8/DEPDC1B are claimed as the novel genes closely related to the development of breast cancer (Nilsson et al., 2007).

XTP8/DEPDC1B expression is also related to the recurrence of breast cancer. A considerable proportion of estrogen receptor (ER)-positive breast cancer recurs despite tamoxifen treatment, which is a serious problem commonly encountered in clinical practice. Han et al tried to find novel prognostic markers in this subtype of breast cancer. Comparative genomic hybridization (CGH) was performed with 1,440 human bacterial artificial chromosome (BAC) clones to assess copy number changes in 28 fresh-frozen ER positive breast cancer tissues. The array CGH analysis with BAC clones could detect various genomic alterations in ER-positive breast cancers, and Recurrence group samples showed a significantly different pattern of DNA copy number changes than did non-recurrence group samples (none). The result indicated that the amplification of copy number of XTP8/DEPDC1B gene is related to the recurrence of the breast cancer (Han et al., 2006).

The histone demethylase PHF8 has been implicated in multiple pathological disorders, including X-linked mental retardation and tumorigenesis. However, it is not clear how the abundance and function of PHF8 are regulated. Six representative genes implicated in cell cycle regulation, such as CCNA2, TGFB2, XTP8/DEPDC1B, CCNE2, BRCA1, and CP110, and was validated their expressions in MCF-7 cells by qRT-PCR. The results indicated that the mRNA levels of CCNA2, TGFB2, XTP8/DEPDC1B, and CCNE2 but not those of BRCA1 and CP110 decreased upon knockdown of either USP7 or PHF8, albeit to variable extents. The results showed that, similarly to H3K4me3, recruitment of FLAG-PHF8 was detected in the promoter regions of CCNA2, TGFB2, XTP8/DEPDC1B, CCNE2, and USP7. Furthermore, ChIP assays in MCF-7 cells also detected the occupancy of endogenous PHF8 on the promoters of these genes, which was significantly weakened when USP7 was knocked down. Consistently, it was found that, compared with control cells, PHF8-deficient cells displayed a substantial retention of H3K9me1 in the promoters of CCNA2, TGFB2, XTP8/DEPDC1B, CCNE2, and USP7, and

H3K9me2 in the promoter of CCNE2. Together, these results indicate that CCNA2, TGFB2, XTP8/DEPDC1B, CCNE2, and USP7 are indeed targeted by PHF8. These experiments also indicate that USP7 itself is transcriptionally regulated, via positive feedback, by PHF8.

XTP8 Expression and Cervical Cancer

High-risk human papillomavirus (HPV) is a causal factor for cervical cancer, of which HPV16 is the predominant genotype, but the detailed mechanism remains to be elucidated. Chen et al performed transcriptome sequencing in cervical cancer tissues with HPV16-positive and normal tissues with HPV16-negative, and SiHa cells with or without HPV16 E6/E7 knockdown, and identified 140 differential expressed genes (DEGs) in two data sets. Chen et al carried out a series of bioinformatic analyses to learn more about the 140 DEGs, and found that 140 DEGs were mostly enriched in cell cycle and DNA repair through Kyoto Encyclopedia of Genes and Genomes pathway enrichment, Gene Ontology annotation, and gene set enrichment analysis. A total of 20 genes were screened by co-expression analysis; of those, the expressions of 6 genes were verified by qRT-PCR. Further, Chen et al also found that E2F family, NF-Y, AhR:Arnt, and KROX family may be involved in modulating DEGs by TransFind prediction. TF2DNA database and co-expression analysis suggested that 12 TFs (ZNF367, TLX2, XTP8/DEPDC1B, E2F8, ZNF541, EGR2, ZMAT3, HES6, CEBPA, MYBL2, FOXM1, and RAD51) were upstream modulators of DEGs. These findings may provide a new understanding for effects of HPV oncogenes in the maintenance of cancerous state at the transcriptional level (Chen et al., 2020).

XTP8 Expression and Ovarian Cancer

Epithelial ovarian cancer (EOC) is the first leading cause of gynecologic cancer deaths and ranks fifth in cancer deaths for women worldwide. Serous ovarian cancer is the most common histological subtype of EOC. About 70% of patients present with stage III and IV disease due to lack of effective screening programme. Despite recent advances in therapies, their prognosis remains dismal, and over 60% of patients diagnosed with late-stage EOC will recur or die within 5 years of their diagnosis (Mullen et al., 2019). Therefore, it is vitally important to elucidate the molecular mechanisms leading to EOC. Aberrant expression of XTP8/DEPDC1B (DEP domain-containing protein 1B) has been shown to be associated with various types of malignant tumors. However, little is known about the role of XTP8/DEPDC1B in epithelial ovarian cancer (EOC). Wu et al investigate the expression and role of XTP8/DEPDC1B in EOC. Immunohistochemical staining of 60 high-grade serous ovarian cancer (HGSOC) showed that XTP8/DEPDC1B expression was associated with response to first line chemotherapy, and XTP8/DEPDC1B expression was higher in platinum-resistant patients than in platinum-sensitive patients. However, there was no association between XTP8/DEPDC1B expression and age, preoperative CA125 level, ascites status, location, FIGO stage, and residual disease. Furthermore, this study demonstrated that increased XTP8/DEPDC1B expression was correlated with reduced overall survival (OS) and progression-free survival (PFS) time in patients with HGSOC. Multivariate analysis showed that XTP8/DEPDC1B independently predicted OS in patients with HGSOC. However, XTP8/DEPDC1B expression was not an independent prognostic factor for PFS in patients with HGSOC. Moreover, the study demonstrated that XTP8/DEPDC1B could promote the proliferation of OVCAR3 and SKOV3 cells by enhancing AKT phosphorylation at Ser473. Treatment with MK2206 and LY294002 significantly suppressed cell proliferation that is induced by XTP8/DEPDC1B up-regulation in both OVCAR3 and SKOV3 cells. Together, these results revealed that XTP8/DEPDC1B was an independent prognostic factor for OS in patients with HGSOC, and XTP8/DEPDC1B may promote the proliferation of EOC cells via enhancing AKT phosphorylation at Ser473.

XTP8 Expression and Lung Cancer

Non-small cell lung cancer (NSCLC) remains a highly challenging and deadly malignancy with limited improvements in prognosis over years. Further understanding the molecular events involved in NSCLC oncogenesis and progression will help develop new and effective therapeutic strategies. It is found that up-regulation of XTP8/DEPDC1B in NSCLC cell lines and clinical specimens, as well as its inverse correlation with patient survival. Ectopic expression of XTP8/DEPDC1B endowed NSCLC cells with enhanced migration and invasion, while silencing its expression suppressed these traits. Mechanistic study showed that XTP8/DEPDC1B was able to activate Wnt/β-catenin signaling, and that depletion of TCF4 or LEF1 abrogated the biological effects of XTP8/DEPDC1B on cellular migration and invasion. XTP8/DEPDC1B might confer metastasis-related malignant phenotype to NSCLC in a Wnt/β-catenin dependent manner, providing new insights in developing novel anti-NSCLC strategies (Yang et al., 2014). In the 102 candidate molecules, Chen et al found XTP8/DEPDC1B is an up-regulated gene in SCLC tissues (Chen et al., 2020).

XTP8/DEPDC1B expression is a prognostic biomarker on cancer growth and its association with the immune

microenvironment in lung adenocarcinoma (LAC). Inhibition of Serum Amyloid A-like 1 (SAAL1) expression could inhibit cancer progression and improve the prognosis of cancer patients. The intersection of the prognostic genes and SAAL1 co-expressed genes in LAC was obtained. The expression levels of the intersection genes CCNB1, SGO1, GTSE1, E2F7, MCM4, DLGAP5, CDCA2, CENPK, FAM111B, SPC24, XTP8/DEPDC1B, CENPH, CDC25C, PARPBP, FANCI, SPC25, KIF18A, BUB1B, KIF20A, SGO2, and TTK in LAC tissues were obtained, and their relationship with living states in LAC patients was estimated using K-M survival and differential expression analysis. The intersection between prognostic factors of LAC patients and SAAL1-related genes included 21 genes. The expression levels of CCNB1, SGO1, GTSE1, E2F7, MCM4, DLGAP5, CDCA2, CENPK, FAM111B, SPC24, XTP8/DEPDC1B, CENPH, CDC25C, PARPBP, FANCI, SPC25, KIF18A, BUB1B, KIF20A, SGO2, and TTK were significantly increased in unpaired and paired LAC tissues. In addition, elevated CCNB1, SGO1, GTSE1, E2F7, MCM4, DLGAP5, CDCA2, CENPK, FAM111B, SPC24, XTP8/DEPDC1B, CENPH, CDC25C, PARPBP, FANCI, SPC25, KIF18A, BUB1B, KIF20A, SGO2, and TTK expression levels had something to do with short OS, DSS, and PFI in LAC patients (Tong et al., 2023). Inhibition of SAAL1 expression could regulate cancer growth via cyclin D1 and Bcl-2. SAAL1 is a promising prognostic biomarker in LAC patients.

Lung adenocarcinoma (LUAD) is the most common type of lung cancer. XTP8/DEPDC1B expression was higher in tumor tissues than that in normal tissues from patients with LUAD and LUSC. These results were confirmed in clinical samples from patients using immunohistochemistry. Analysis of a dataset from The Cancer Genome Atlas (TCGA) showed that high XTP8/DEPDC1B expression was associated with poor prognosis only in patients with LUAD. Similarly, high XTP8/DEPDC1B expression was related to shorter overall survival (OS) and progression-free interval (PFI) in patients with LUAD. These associations were not observed in LUSC. Functional enrichment analysis suggested that XTP8/DEPDC1B promoted tumor development in LUAD by regulating the cell cycle. High XTP8/DEPDC1B expression predicts poor prognosis in patients with LUAD. Thus, XTP8/DEPDC1B has potential as a therapeutic target for LUAD (Li et al., 2022).

Studies have shown that smokers have a higher frequency of genomic alterations in lung cancer than nonsmokers have. In addition, a genome analysis found that some somatic cell mutations in LUAD were associated with smoking phenotype. Ren found that XTP8/DEPDC1B expression is a significantly worse survival predictor and specifically related to the LUAD development in the ever-smokers (Ren et al., 2020).

XTP8 Expression and Pancreatic Cancer

Pancreatic cancer is a dismal disease with a mortality rate almost similar to its incidence rate. To date, there are neither validated predictive nor prognostic biomarkers for this lethal disease. Bianconi et al investigated the association of 18 biochemical parameters obtained from routine diagnosis and the clinical outcome of the 30 patients enrolled in the clinical trial. Formalin-fixed paraffin-embedded (FFPE) tumor tissues were analysed to identify molecular biomarkers via RNA seq and the Illumina TruSeq Amplicon Cancer panel which covers 48 hotspot genes. Univariate analyses revealed that the expression level of XTP8/DEPDC1B in the long survival group was significantly lower than that in short survival group. The expression level of XTP8/DEPDC1B and CCDN2 were found to be independent predictors of overall survive (OS) when individual P-values were analysed in the multivariate analysis according to the likelihood ratio test (Bianconi et al., 2017). This result is a evidence for XTP8/DEPDC1B expression level serving as a survival predictor for pancreatic cancer patients.

Pancreatic ductal adenocarcinoma (PDAC) is the most common and among the deadliest of pancreatic cancers. Its 5-year survival is only less than 8%. Pancreatic cancers are a heterogeneous group of diseases, of which PDAC is particularly aggressive. Like many other cancers, PDAC also starts as a pre-invasive precursor lesion (known as pancreatic intraepithelial neoplasia, PanIN), which offers an opportunity for both early detection and early treatment. Even advanced PDAC can benefit from prognostic biomarkers. However, reliable biomarkers for early diagnosis or those for prognosis of therapy remain an unfulfilled goal for PDAC.

XTP8/DEPDC1B is overexpressed in multiple tumors, such as breast cancer, oral cancer and non-small cell lung cancer, plays a significant role in cell movement, cell cycle and cytoskeleton reorganization. In order to explore the function of XTP8/DEPDC1B in PC, the function of XTP8/DEPDC1B in the migration and invasion of PC was evaluated by wound healing and Transwell assays in vitro and PC-derived liver metastasis models in vivo. It was found XTP8/DEPDC1B was overexpressed in PC cell lines. XTP8/DEPDC1B regulated cell migration and invasion. XTP8/DEPDC1B regulated the Rac1/PAK1-LIMK1-cofilin1 signaling pathway by interacting with Rac1. Rac1 inhibition suppressed XTP8/DEPDC1B-induced migration and invasion in PC in vitro and XTP8/DEPDC1B-induced liver metastasis in vivo. XTP8/DEPDC1B promoted cell migration and invasion by activating the Rac1/PAK1-LIMK1-cofilin 1 signaling pathway, thus providing a potential therapeutic target against PC (Zhang et al., 2020).

Yang et al set up a 13-mRNA (including XTP8/DEPDC1B)-based prognostic model to predict chemotherapeutic response of NSCLC patients, and results showed that the high-risk score of this model was related to poor prognosis and an immunosuppressive tumor immune microenvironment (TIME) (Yang et al., 2021).

Mishra et al selected 153 PDAC patients from the TCGA database and used their clinical, DNA methylation, gene expression, and micro-RNA (miRNA) and long non-coding RNA (lncRNA) expression data for multi-omics analysis. Differential methylations at about 12,000 CpG sites were observed in PDAC tumor genomes, with about 61% of them hypermethylated, predominantly in the promoter regions and in CpG-islands. To correlate promoter methylation and gene expression for mRNAs, it was identified 17 genes that were previously recognized as PDAC biomarkers. Similarly, several genes (B3GNT3, DMBT1, XTP8/DEPDC1B) and lncRNAs (PVT1, and GATA6-AS) are strongly correlated with survival, which have not been reported in PDAC before. Other genes such as EFR3B, whose biological roles are not well known in mammals are also found to strongly associated with survival. It has further identified 406 promoter methylation target loci associated with patient's survival, including known esophageal squamous cell carcinoma biomarkers, cg03234186 (ZNF154), and cg02587316, cg18630667, and cg05020604 (ZNF382) (Mishra et al., 2019). Overall, this is one of the first studies that identified survival associated genes using multi-omics data from PDAC patients.

The expression levels of XTP8/DEPDC1B were detected in 79 pairs of PDAC and adjacent noncancerous tissues. Patients with PDAC that exhibited higher XTP8/DEPDC1B expression levels, were shown to have a poorer prognosis. Functional studies showed that knocking down XTP8/DEPDC1B inhibited PDAC cell migration and invasion, while overexpressing XTP8/DEPDC1B promoted these processes. Western blotting analysis and immunofluorescence demonstrated that XTP8/DEPDC1B overexpression induced the epithelialtomesenchymal transition (EMT). Further mechanistic studies revealed that XTP8/DEPDC1B was able to activate the Akt/glycogen synthase kinase3β (GSK3β)/Snail signaling pathway. The results of the present study showed that XTP8/DEPDC1B may serve as an oncogene that contributes to PDAC cell migration and invasion by inducing EMT via Akt/GSK3β/Snail pathway activation (Liu et al., 2020).

XTP8 Expression and Bladder Cancer

Bladder cancer is one of the most commonly diagnosed malignant tumors in the urinary system and causes a massive cancer-related death. The promising new therapeutic options currently under research include the use of immune-checkpoint inhibitors, antigen-drug conjugates, and targeted approaches that attack long noncoding RNAs, microRNAs, PARP1, and receptor signaling pathways. In exploring the role and mechanism of XTP8/DEPDC1B in the development of bladder cancer, the analysis of clinical specimens revealed the upregulated expression of XTP8/DEPDC1B in bladder cancer, which was positively related to tumor grade. In vitro and in vivo studies showed that XTP8/DEPDC1B knockdown could inhibit the growth of bladder cancer cells or xenografts in mice. The suppression of bladder cancer by XTP8/DEPDC1B was executed through inhibiting cell proliferation, cell migration, and promoting cell apoptosis. Moreover, a mechanistic study found that (Src homology 2 domain containing transforming protein 1 (SHC1) may be an important route through which XTP8/DEPDC1B regulates the development of bladder cancer. Knockdown of SHC1 in XTP8/DEPDC1B-overexpressed cancer cells could abolish the promotion effects induced by XTP8/DEPDC1B. XTP8/DEPDC1B was identified as a key regulator in the development of bladder cancer, which may be used as a potential therapeutic target in the treatment of bladder cancer (Lai et al., 2020). SHC1 may be an important route of XTP8/DEPDC1B regulating the development of bladder cancer. In XTP8/DEPDC1B-overexpressed cancer cells, the knockdown of SHC1 could abolish the promotion effects caused by XTP8/DEPDC1B (Zhang et al., 2022).

XTP8 Expression and Prostate Cancer

Prostate cancer (PCa) is a highly aggressive malignant tumor and the biological mechanisms underlying its progression remain unclear. Bai et al investigated the expression and clinical significance of XTP8/DEPDC1B in tumor tissues from patients diagnosed with PCa. A total of 80 prostate tissue samples were collected following prostatectomy to generate a tissue microarray for immunohistochemical analysis of XTP8/DEPDC1B protein expression. High throughput sequencing of mRNAs from 179 prostate tissue samples, either from patients with PCa or from healthy controls, was included in the Taylor dataset. The expression levels of XTP8/DEPDC1B in tumor tissues from patients with PCa were revealed to be significantly increased compared with those in normal prostate tissues. Increased expression of XTP8/DEPDC1B was significantly associated with advanced clinical stage, advanced T stage and lymph node metastasis. Kaplan-Meier analysis demonstrated that patients with high levels of XTP8/DEPDC1B mRNA had significantly shorter biochemical recurrence (BCR)-free survival times. Multivariate analysis using Cox proportional hazards model revealed that levels of XTP8/DEPDC1B

mRNA were significant independent predictors of BCR-free survival time of patients with PCa. Therefore, the expression of XTP8/DEPDC1B may be used as an independent predictor of biochemical recurrence-free survival time of patients with PCa (Bai et al., 2017).

Prostate cancer (CaP) is the second leading cause of cancer related death in USA. In human CaP, gene fusion between androgen responsive regulatory elements at the 5'-untranslated region of TMPRSS2 and ETS-related genes (ERG) is present in at least 50% of prostate tumors. Out of the 526 statistically significant differentially expressed genes, 232 genes are up-regulated and 294 genes are down-regulated in response to ERG. XTP8/DEPDC1B is a representative differentially expressed gene in ERG+ LnTE3 cells treated with ERG (Kumar et al., 2019).

Ma et al performed weighted gene co-expression network analysis in PCa dataset from the Cancer Genome Atlas database to identify the key module and key genes related to the progression of PCa. Furthermore, another independent datasets were used to validate these findings. A total of 744 differentially expressed genes were screened out and 5 modules were identified for PCa samples from the Cancer Genome Atlas database. It is found the brown module was the key module and related to tumor grade and tumor invasion depth. Besides, 24 candidate hub genes were screened out and 2 genes (BIRC5 and XTP8/DEPDC1B) were identified and validated as real hub genes that associated with the progression and prognosis of PCa. Moreover, the biological roles of BIRC5 were related to G-protein coupled receptor signal pathway, and the functions of XTP8/DEPDC1B were related to the G-protein coupled receptor signal pathway and retinol metabolism in PCa. Taken together, it has been identified 1 module, 24 candidate hub genes and 2 real hub genes, which were prominently associated with PCa progression (Ma et al., 2020).

Previous studies indicated XTP8/DEPDC1B played an important role in regulating cell cycle and migration. In non-small cell lung cancer, ectopic expression of XTP8/DEPDC1B enhanced migration and invasion of cancer cells via activating Wnt/β-catenin signaling. Cui et al found that the expression levels of XTP8/DEPDC1B in PCa tissues were significantly higher than that in non-tumor tissues. Furthermore, the results showed XTP8/DEPDC1B was upregulated in high pathology stage PCa. Kaplan-Meier analysis showed that Lower XTP8/DEPDC1B expression level was associated with better survival of PCa patients. GO and KEGG pathway analysis of XTP8/DEPDC1B co-expressed genes showed XTP8/DEPDC1B played an important role in regulating PCa proliferation and cell cycle progression. It is believed that this study will provide a potential new therapeutic and prognostic target for prostate cancer (Cui et al., 2017).

XTP8 Expression and Multiple Myeloma

Multiple myeloma (MM) is an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells within the bone marrow. The identification and investigation of key molecules involved in the pathogenesis of MM hold paramount clinical significance. This study primarily focuses on elucidating the role of XTP8/DEPDC1B within the context of MM. Abundant expression of XTP8/DEPDC1B were affirmed in MM tissues and cell lines. Notably, XTP8/DEPDC1B depletion exerted inhibitory effects on MM cell proliferation and migration while concurrently facilitating apoptosis and G2 cell cycle arrest. These outcomes stand in stark contrast to the consequences of XTP8/DEPDC1B overexpression. CCNB1 was identified as a putative downstream target, characterized by a co-expression pattern with XTP8/DEPDC1B, mediating XTP8/DEPDC1B's regulatory influence on MM. Additionally, these results suggest that XTP8/DEPDC1B knockdown may activate the p53 pathway, thereby impeding MM progression. To corroborate these in vitro findings, it conducted in vivo experiments that further validate the regulatory role of XTP8/DEPDC1B in MM and its interaction with CCNB1 and the p53 pathway. XTP8/DEPDC1B is a potent promoter in the development of MM, representing a promising therapeutic target for MM treatment. This discovery bears significant implications for future investigations in this field (Fei et al., 2023).

Previously pituitary tumor transforming gene 1 (PTTG1) was identified as a gene that is significantly upregulated in the haematopoietic compartment of the myeloma-susceptible C57BL/KaLwRij mouse strain, when compared with the myeloma-resistant C57BL/6 mouse. Over-expression of PTTG1 has previously been associated with malignant progression and an enhanced proliferative capacity in solid tumors. PTTG1 was found to be over-expressed in 36–70% of MM patients, relative to normal controls, with high PTTG1 expression being associated with poor patient outcomes. In addition, patients with high PTTG1 expression exhibited increased expression of cell proliferation-associated genes including CCNB1, CCNB2, CDK1, AURKA, BIRC5 and XTP8/DEPDC1. Knockdown of Pttg1 in 5 TGM1 cells decreased cellular proliferation, without affecting cell cycle distribution or viability, and decreased expression of CCNB1, BIRC5 and DEPDC1 in vitro. Notably, PTTG1 knockdown significantly reduced MM tumor development in vivo, with an 83.2% reduction in tumor burden at 4 weeks (Noll et al., 2015).

XTP8 Expression and Esophageal Squamous Cell Carcinoma

Given that XTP8/DEPDC1B plays a key role in multiple

cancers, the role of this molecule in ESCC was explored to identify potential targets for ESCC patients. XTP8/DEPDC1B was found overexpressed in ESCC. High expression of XTP8/DEPDC1B was significantly negatively correlated with overall survival in patients with ESCC. Moreover, knockdown of XTP8/DEPDC1B inhibited ESCC cell proliferation, clone formation, migration, tumor formation and promoted apoptosis. Furthermore, knockdown of XTP8/DEPDC1B leaded to significant downregulation of GABRD in ESCC cells. Meanwhile, GABRD expression was upregulated in ESCC, and its silencing can inhibit the proliferation and migration of the tumor cells. Interestingly, there was a protein interaction between XTP8/DEPDC1B and GABRD. Functionally, GABRD knockdown partially reversed the contribution of XTP8/DEPDC1B to ESCC progression. In addition, GABRD regulated ESCC progression may depend on PI3K/AKT/mTOR signaling pathway. XTP8/DEPDC1B collaborated with GABRD to regulate ESCC progression, and inhibition of this signaling axis may be a potential therapeutic target for ESCC (Yuan et al., 2022).

XTP8 Expression and Glioblastoma

Glioblastoma (GBM) is the most common primary malignant brain tumor in adults with a poor prognosis. XTP8/DEPDC1B has been shown to be associated with some types of malignancies. However, the role and underlying regulatory mechanisms of XTP8/DEPDC1B in GBM remain elusive. Chen et al examined the expression levels in GBM tissues, and the effect of XTP8/DEPDC1B expression on the glioblastoma cell viability and apoptosis. The results proved that XTP8/DEPDC1B was significantly upregulated in tumor tissues, and silencing XTP8/DEPDC1B could inhibit proliferation, migration and promote apoptosis of GBM cell. In addition, human apoptosis antibody array detection showed that after XTP8/DEPDC1B knockdown, the expression of apoptosis-related proteins was downregulated, such as IGFBP-2, Survivin, N-cadherin, Vimentin and Snail. knockdown of XTP8/DEPDC1B significantly inhibited tumor growth in vivo. XTP8/DEPDC1B was involved in the development and progression of GBM, which may be a potential therapeutic target and bring a breakthrough in the treatment (Chen et al., 2020).

XTP8 Expression and Oral Cancer

Su et al found that it was a guanine nucleotide exchange factor and induced both cell migration in a cultured embryonic fibroblast cell line and cell invasion in cancer cell lines; moreover, it was observed to promote anchorage-independent growth in oral cancer cells. XTP8/DEPDC1B plays a role in regulating Rac1 translocated onto cell membranes, suggesting that XTP8/DEPDC1B exerts a biological function by regulating Rac1. In oral cancer tissue samples, 6 out of 7 oral cancer tissue test samples overexpressed XTP8/DEPDC1B proteins, compared with normal adjacent tissue. XTP8/DEPDC1B was a guanine nucleotide exchange factor and induced both cell migration in a cultured embryonic fibroblast cell line and cell invasion in cancer cell lines; moreover, it was observed to promote anchorage-independent growth in oral cancer cells. XTP8/DEPDC1B exerts a biological function by regulating Rac1. Proliferation was linked to a novel XTP8/DEPDC1B-Rac1-ERK1/2 signaling axis in oral cancer cell lines (Su et al., 2014).

With the incidence rate of oral carcinogenesis increasing in the Southeast-Asian countries, due to increase in the consumption of tobacco and betel quid as well as infection from human papillomavirus (HPV), specifically type 16, it becomes crucial to predict the transition of premalignant lesion to cancerous tissue at an initial stage in order to control the process of oncogenesis. E2 is known to interact with and downregulate several proteins (CPB2, HSPBAP1, RBM26, etc.), one of them being XTP8/DEPDC1B, which recently was found to be overexpressed in oral cancer. This can be possibly explained by the disruption of the E2 ORF upon the integration of viral genome into the host genome. XTP8/DEPDC1B, downregulated in the presence of E2 protein, was recently found to be overexpressed in oral cancer, which can possibly be explained by the disruption of the E2 open reading frame upon the integration of viral genome into the host genome. XTP8/DEPDC1B mediates its effect by directly interacting with Rac1 protein, which is known to regulate important cell signaling pathways. Therefore, XTP8/DEPDC1B can be a potential biomarker as well as a therapeutic target for diagnosing and curing the disease. However, the lack of 3D model of the structure makes the utilization of XTP8/DEPDC1B as a therapeutic target difficult. The present study focuses on the prediction of a suitable 3D model of the protein as well as the analysis of protein-protein interaction between XTP8/DEPDC1B and Rac1 protein using PatchDock web server along with the identification of allosteric or regulatory sites of XTP8/DEPDC1B (Ahuja et al., 2016).

Su et al studied how the XTP8/DEPDC1B (defined like guanine nucleotide exchange factor) induced both cell migration in a cultured embryonic fibroblast cell line (Su et al., 2019). Moreover, it was recorded to favor anchorage-independent growth in oral cancer cells. It was demonstrated that XTP8/DEPDC1B exerts a biological function by regulating Rac1. To determine whether XTP8/DEPDC1B played a role

in the induction of cell proliferation, contributing to faster wound healing, the authors evaluated the growth rate of cells expressing XTP8/DEPDC1B and control cells founding no substantial difference between the growth rates of XTP8/DEPDC1B-expressing cells and control cells. However, the authors concluded that oral cancer samples overexpressed XTP8/DEPDC1B proteins, compared with normal adjacent tissue, and so XTP8/DEPDC1B plays a role in the development of oral cancer (Cervino et al., 2019).

XTP8 Expression and Colon Adenocarcinoma

Global cancer statistics in 2020 showed that colon cancer (CC) ranked fifth in incidence and mortality among all cancers worldwide, with nearly 1.148 million new cases and 578,000 deaths, accounting for approximately 6.0% of all new cases and deaths of malignancies. A risk assessment model for prognostic prediction of colon adenocarcinoma (COAD) was established based on weighted gene co-expression network analysis (WGCNA). From the Cancer Genome Atlas (TCGA) database, RNA-seq data and clinical data of COAD patients were retrieved. After screening of differentially expressed genes (DEGs), WGCNA was performed to identify gene modules and screen those associated with COAD progression. Then, via protein-protein interaction (PPI) network construction of module genes, hub genes were obtained, which were then subjected to the least absolute shrinkage and selection operator (LASSO) and Cox regression to build a hub gene-based prognostic scoring model. The receiver operating characteristic curve (ROC curve) was plotted for the optimal cutoff (OCO) of the risk score, based on which, patients were assigned to high or low-risk groups. Areas under the ROC curve (AUCs) was calculated, and model performance was visualized using Kaplan–Meier (KM) survival curves and verified in the external dataset GSE29621. Finally, the model's independent prognostic value was evaluated by univariate and multivariate Cox regression analyses, and a nomogram was built. Results. Totally 2840 DEGs were screened from COAD dataset of TCGA, including 1401 upregulated ones and 1439 downregulated ones, which were divided into 10 modules by WGCNA. The eigenvalue of the black module was found to have a high correlation with COAD progression. PPI interaction networks were constructed for genes in the black module, and 34 hub genes were obtained by using the MCODE plug-in. A LASSO-Cox regression approach was utilized to analyze the hub genes, and a prognostic risk score model based on the signatures of 9 genes (CHEK1, XTP8/DEPDC1B, FANCI, MCM10, NCAPG, PARPBP, PLK4, RAD51AP1, and RFC4) was constructed. KM analysis identified shorter overall lower survival in the high-risk group. The model was verified to have favorable predictive ability through training set and validation set. The nomogram, composed of tumor node metastasis (TNM) staging and risk score, was of good predictability. Conclusions. The COAD prognostic risk model constructed upon the signatures of 9 genes (CHEK1, XTP8/DEPDC1B, FANCI, MCM10, NCAPG, PARPBP, PLK4, RAD51AP1, and RFC4) can effectively predict the survival status of COAD patients (Yang et al., 2022).

It has been reported that XTP8/DEPDC1B serves several roles in the occurrence and development of various types of cancer. The mRNA and protein expression levels of XTP8/DEPDC1B and nucleoporin 37 (NUP37) in CRC cell lines were assessed. XTP8/DEPDC1B and NUP37 were upregulated in CRC cell lines. XTP8/DEPDC1B and NUP37 silencing both inhibited the proliferation, migration and invasion capabilities of CRC cells and promoted cell apoptosis and cell cycle arrest. Furthermore, NUP37 overexpression reversed the inhibitory effects of XTP8/DEPDC1B silencing on the behavior of CRC cells. Animal experiments demonstrated that XTP8/DEPDC1B knockdown inhibited the growth of CRC in vivo by targeting NUP37. In addition, XTP8/DEPDC1B knockdown inhibited the expression levels of the PI3K/AKT signalingrelated proteins in CRC cells and tissues by also binding to NUP37. Overall, the current study suggested that XTP8/DEPDC1B silencing could alleviate the progression of CRC via targeting NUP37 (Xiong et al., 2023).

Future Perspectives

Molecular targets functioning at the interface of multiple signaling pathways are likely to engage a broad spectrum of downstream effectors and thereby contribute to plasticity of both the canonical pathways and genome-wide networks, two of the major challenges in tackling tumor evolution and therapy response. While these understanding of the XTP8/DEPDC1B systems and integrative biology as yet is rudimentary, several reports to date and new data presented here provide evidence of XTP8/DEPDC1B as a model target with multipronged influence on the tumor systems biology. Current highlights of this area of research are listed as follows (1). XTP8/DEPDC1B is a new binding partner of the p85 subunit of PI3K (2). XTP8/DEPDC1B cross-regulates AKT and ERK pathways through downregulating the ligand-stimulated tyrosine phosphorylation of p85 and expression of pAKT1 and promoting pERK, a hallmark of tumor progression. (3) High XTP8/DEPDC1B expression during the G 2/M phase is a cell de-adhesion mitotic checkpoint, a prerequisite for cell entry into mitosis (4). XTP8/DEPDC1B mRNA expression is upregulated via expression of Raf-1 and long noncoding RNA lncNB1, and XTP8/DEPDC1B is a direct target of transcription factor

SOX10. XTP8/DEPDC1B prevents SCUBE3 degradation, and SOX10- DEPDC1B-SCUBE3 axis promotes angiogenesis and metastasis. DEPDC1B-SCUBE3 axis promotes angiogenesis and metastasis. Future investigations are necessary to (a) address whether XTP8/DEPDC1B functions to integrate, albeit in a context-dependent manner, the AKT and ERK networks and known feedback mechanisms and (b) identify the actionable molecular, spatial, and temporal vulnerabilities within the XTP8/DEPDC1B-guided versions of the integrated AKT and ERK networks in cancer cells. In addition, XTP8/DEPDC1B amino acid sequence shows binding motifs for three clinically relevant therapeutic targets CDK1, DNA-PK, and aurora kinase A/B. These partnerships and functionalities, if validated, are likely to further implicate XTP8/DEPDC1B in regulation of DNA damage–repair and cell cycle progression processes critical to disease prognosis and therapy response.

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