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Review Article

RNA Binding Proteins and Osteosarcoma

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Abstract

Osteosarcoma, the most prevalent form of bone cancer, is primarily attributed to the abnormal behavior of bone-forming mesenchymal stem cells and its occurrence as the third most common cancer among children is of concern. Recent investigations have uncovered the novel roles of RNA- binding proteins (RBPs) in addition to controlling mRNA processing and translation, with notable mutations observed in various malignancies, including osteosarcoma. Although the exact mechanisms linking RBPs and osteosarcoma remain elusive, multiple studies have indicated the critical involvement of specific RBPs in this disease. This review aims to provide a comprehensive overview of RBPs and their impact on osteosarcoma, with a specific focus on the underlying molecular mechanisms and potential therapeutic strategies. Furthermore, the review also discusses research advancements concerning RBPs in osteosarcoma attempting to shed light on the dysregulation of these proteins as a significant contributor to the development and progression of the disease.

Keywords: rna binding proteins; osteosarcoma; gene expression regulation; cancer; molecular targets

Introduction

Osteosarcoma is a rare bone tumor that predominantly affects adolescents (15-19 years) and individuals over 75 years (Czarnecka et al., 2020). It arises from osteoblast cells and is characterized by the loss of growth control and metastatic abilities (Eaton et al., 2021). Among the malignant bone and joint tumours in children, osteosarcoma exhibits high incidence rate and the lowest 5-year survival rate compared to other paediatric malignancies (Xing et al., 2022). Although current therapeutic strategies for osteosarcoma involve a combination of surgery, chemotherapy, and radiotherapy, amputation was historically the primary treatment approach. However, despite these treatments, the prognosis for osteosarcoma patients remains unsatisfactory, with low 5-year survival rates (Zhang et al., 2021). Therefore, there is a critical need to explore innovative approaches for diagnosing and prognosing osteosarcoma to improve patient outcomes. Gene expression in eukaryotic cells is tightly regulated through various mechanisms, including transcription, translation, protein degradation, mRNA splicing, and protein folding (Brar and Weissman, 2015). RNA-binding proteins (RBPs) are a family of cellular proteins that play crucial roles in post-transcriptional gene expression regulation (Hentze, Castello, Schwarzl & Preiss, 2018). Dysregulation of RBPs has been implicated in a wide range of chronic conditions, including muscular, neurological, and cancerous diseases (Gebauer, Schwarzl, Valcarcel, & Hentze, 2021). Emerging evidence suggests that alterations in RNA metabolism mediated by RBPs contribute to the development and progression of tumors, making RBPs potential therapeutic targets (Chen et al., 2022). At the molecular level, osteosarcoma is associated with genetic lesions affecting tumor suppressors, tumor promoters, transcription factors, and circular RNAs, which contribute to tumor progression (Rickel, Fang & Tao, 2017). Recent genomic studies have identified numerous RNA-binding proteins (RBPs) as key players in the pathophysiology and drug resistance of various cancers (Masuda & Kuwano, 2019). Several recent studies have highlighted the significant involvement of RBPs in the disease and identified them as potential targets for drug discovery (Hu et al., 2020; Li et al., 2018). This review aims to critically examine the latest advancements in RBPs associated with osteosarcoma, exploring their roles in the disease's pathophysiology, and discussing the potential therapeutic implications for future research. By deepening our understanding of the specific roles of RBPs in osteosarcoma, this review aims to critically examine the latest advancements in RBPs associated with osteosarcoma, exploring their roles in the disease's pathophysiology, and discussing the potential therapeutic implications for future research. By deepening our understanding of the specific roles of RBPs in osteosarcoma, this review aims to contribute to the development of improved diagnostic and treatment strategies for this disease. Figure 1a provides a visual representation of the interactions between RBPs and various RNA species, including rRNAs, ncRNAs, snRNAs, miRNAs, mRNAs, tRNAs, and snoRNAs. These interactions occur through the attachment of RBPs to RNA-binding domains, facilitating their involvement in a wide range of biological processes.

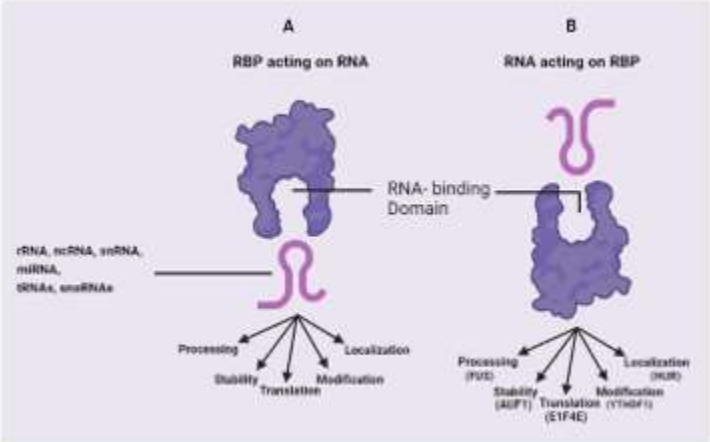

Figure 1a: Interactions of RBPs with diverse RNA Species. (**a**) RNA binding protein (RBP) can interact with RNA via a defined RNA binding domain to control RNA metabolism and function. (**b)** In reverse, RNA binds to RBP and influences its fate and function.

Recent research has shown that several RNA binding proteins, including SC35, hnRNPLL, PTBP1, and ELAVL1, play important roles in RNA processing by selectively recognizing exon inclusion splicing sites (Díaz-Muñoz and Turner, 2018). However, it should be emphasized that RNA Binding Proteins (RBPs) have long been widely recognized as crucial regulatory elements in the control of gene expression. The regulatory influence of RBPs extends beyond RNA processing and encompasses other crucial aspects of gene expression, such as RNA stability, transcription, and splicing. The multifaceted nature of RBPs in general and their diverse regulatory functions are illustrated in Figure 1b, emphasizing their key roles in gene expression regulation.

Structure and function of RNA binding proteins

Posttranscriptional mechanisms have emerged as important regulators of gene expression, orchestrating vital processes such as cell proliferation, differentiation, and cancer. While microRNAs have received significant attention for their role in mRNA stability, recent findings highlight the importance of RNA binding proteins (RBPs) in the regulation of mRNA decay and stabilization (Baou, Norton, and Murphy, 2011). The human genome encodes at least 1,500 RBPs with known RBDs, with the most prevalent being the RNA recognition motif (RRM) (240 RBPs), the heterologous ribonucleoprotein (hnRNP) K-homology domain (KH) (60 RBPs), and the C3H1 zinc-finger (ZF) domain (50 RBPs). RBPs constitute a diverse family of cellular proteins that govern post-transcriptional control over protein expression (Hentze, Castello, Schwarzl, and Preiss, 2018). By interacting with coding and non-coding RNAs, as well as other proteins, RBPs form functional ribonucleoprotein complexes (RNPs) that control RNA expression through degradation, stability modulation, polyadenylation, and inactivation (Pereira, Billaud, and Almeida, 2017). Numerous RBPs possess well-defined RNA binding domains (RBDs) that exhibit unique interactions with RNA sequences and structures (Dominguez et al., 2018). A prominent group of RBPs, known as AU-RBPs, specifically bind to adenine-uracil-rich elements located in the 3' untranslated region of mRNA. Examples of such proteins include HUR, HUD, TTP, BRF1, and KSRP, which can either stabilize or destabilize mRNA transcripts (Dolicka et al., 2020). The balance between stabilizing and destabilizing AU-RBPs within the cellular environment, along with their competition for RNA targets, governs the fate of RNA molecules (Gracin, 2019). To effectively recognize a variety of targets and control catalytic activity, the RNA recognition and binding domains are located between catalytic domains. The arrangement of several RBD modules generates various macromolecular binding surfaces and binding to RNA relies on the size of the linker between two RBDs, longer linkers can detect different targets while shorter linkers only recognise continuous nucleic acid sequences (Yan et al., 2022). Helicases, deaminases, and RNAse III domains are a few other catalytic domains found in these proteins (Chatterji and Rustgi 2018).

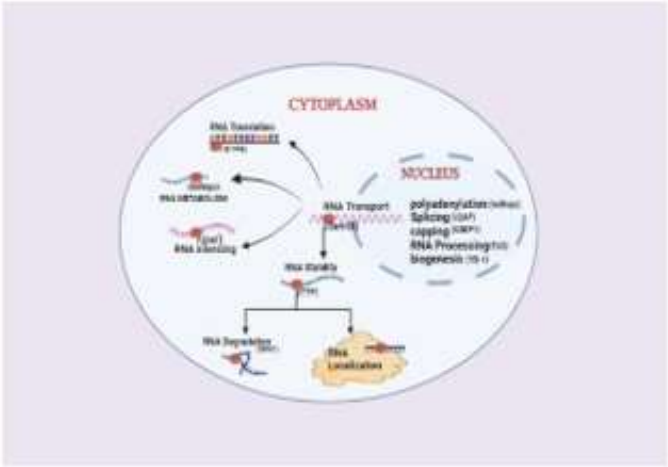

Figure 1b. A representation of locations and roles of RBPs. RBPs are multifaceted and are well-known for controlling RNA stability, translation, splicing, transport, degradation, silencing, biogenesis and capping. These functions occur in different cellular compartments.

Intracellular Localization of RBPs

The localization of RNA binding proteins (RBPs) can vary depending on their roles in RNA processing, which takes place in various cellular compartments (Quenault et al., 2011). Specific targeting signals present in the primary sequence of RBPs direct their localization to the cytoplasm or nucleus through nuclear localization signals (NLS) or nuclear export signals (NES), respectively (Trothen et al., 2022). While earlier studies focused on examining the nucleotide bases in mRNA sequences to understand stability and function (Shimanovsky, Feng, & Potkonjak, 2003), recent data reveal that heterogeneous RBPs bind to these transcripts and regulate their localization and stability in specific cellular compartments (Quenault, Lithgow & Traven, 2011). For example, Nostrand et al. (2020) demonstrated that RBPs such as BOP1, UTP18, and WDR3 are localized in the nucleolus and participate in RNA processing, while FASTKD2 and DHX30 reside in the mitochondria. It is important to note that certain RBPs shuttle between the cytoplasm and nucleus. For instance, HuR is primarily found in the nucleus under normal cellular conditions but translocates to the cytoplasm in response to intrinsic and/or external stress (Schultz et al., 2020). In the cytoplasm, HuR stabilizes and enhances the translation of target mRNAs, thereby promoting gene expression. Similarly, ZFP36L1 and ZFP36L2 undergo nucleo-cytoplasmic shuttling, allowing them to regulate mRNA stability and translation in different cellular compartments (Gingerich et al., 2016). Interestingly, ZFP36L3 is exclusively localized in the cytoplasm, suggesting a unique role for this RBP in the regulation of mRNA stability and translation (Gingerich et al., 2016). Understanding the subcellular localization and function of RBPs is crucial for deciphering their biological activities, as these factors determine their molecular interactions and regulatory mechanisms.

Post-translational modifications of RBPs

Post-translational modifications (PTMs) of proteins have a significant impact on their physiological and pathological roles. Remarkably, RNA-binding motifs within RNA-binding proteins (RBPs) contain motifs for PTMs, including acetylation, hydroxylation, sumoylation, phosphorylation, glycosylation, methylation, and splicing (Brown, Mhanty, & Howe, 2015). PTMs of RBPs can exert profound effects on cellular physiology by altering their affinity for RNA, subcellular localization, and turnover of mRNA molecules (Velázquez-Cruz, Baños-Jaime, Díaz-Quintana, De la Rosa, & Díaz-Moreno, 2021). One example of an RBP that undergoes PTMs and plays a role in cancer is heterogeneous ribonucleoprotein K (hnRNPK). This protein is involved in regulating various cellular stress responses and DNA repair mechanisms. PTMs of hnRNPK have been implicated in the pathogenesis of several cancers (Xu et al., 2019). These PTMs can modulate hnRNPK's function and its association with RNA targets, contributing to the development and progression of cancer. Consequently, PTMs of hnRNPK and other RBPs have emerged as potential therapeutic targets in cancer treatment. The therapeutic potential of targeting PTMs in RBPs is demonstrated by the study of Maniaci et al. (2022), which focuses on ovarian cancer. Their study demonstrates that arginine methylation of a broad range of RBPs by protein arginine methyltransferases (PRMTs) can influence RNA-RBP binding. Furthermore, the analysis of certain proteins, such as ZFP36L1, often reveals multiple bands on a Western blot. In contrast, its closely related protein, ZFP36L2, is observed as a single intact band (Solaiman et al unpublished data). This observation supports the view of existence of isoforms and post-translational modifications (PTMs) r in specific proteins within this class. Overall, the PTMs of RBPs represent an important layer of regulation that impacts their functional properties and their involvement in various cellular processes, including cancer.

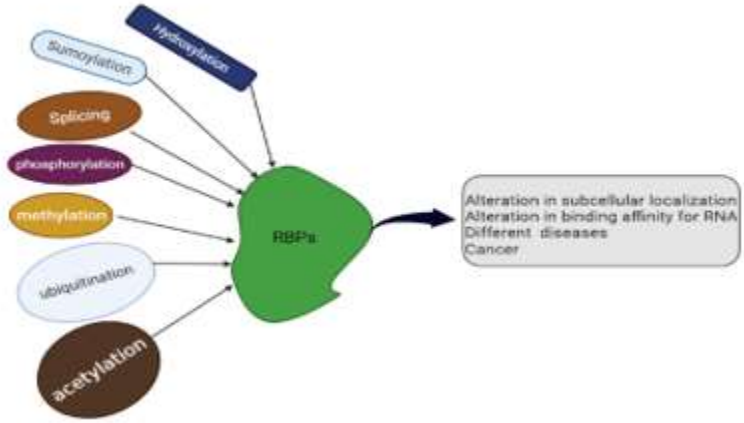

Figure 2: RBPs and posttranslational modifications. PTMs such as acetylation, sumoylation, splicing, phosphorylation, methylation, hydroxylation and ubiquitination could promote alterations in RBPs subcellular localization, different diseases, RNA affinity to bind and carcinogenesis.

RBPs and Genome Instability

RBPs play three critical roles in maintaining genomic integrity. Firstly, they refine the proteome complexity required for the DNA damage response (DDR) through transcriptional and post- transcriptional regulation of gene expression. Secondly, they protect against harmful DNA/RNA hybrids. Thirdly, they directly contribute to DNA repair processes. RBPs are consistently targeted by DNA damage signalling at the post-translational, subcellular, and expression levels (Dutertre et al., 2014, Sidali et al 2022). RBPs influence mRNA expression, stability, and function through alternative splicing, binding, compartmentalization, and polyadenylation (Marchesini, Fiorini & Colla, 2017). Alternative splicing, which involves rearrangement of exons, is an adaptation of the human genome for protein expression. RBPs can exploit spliceosomes to induce genome instability, leading to carcinogenesis. Spliceosomes interact with RBPs and mRNA at specific exon junctions to regulate cell-specific and compartment-specific mRNA splicing (Pereira et al., 2017). Abnormal expression of heterogeneous nuclear ribonucleoproteins (hnRNPs) and serine/arginine-rich (SR) proteins in many cancers suggests their significant role in tumour progression (Qin et al., 2020). These proteins act as selective splicing regulators that bind to spliceosome points, thereby regulating splicing. While pre- mRNA sequences determine splice site recognition and regulation (Fu & Ares, 2014), altered RBP function can also impact these events (Pereira et al., 2017). For example, PSF, an RNA-binding protein, dysregulates spliceosome gene expression in advanced prostate cancer, highlighting the influence of RBPs on splicing patterns and their potential role in cancer onset and progression (Takayama et al., 2017). Interestingly, AU-rich element RBPs have been implicated in direct DNA repair (DDR). Vogel et al. (2016) demonstrated that simultaneous deletion of zfp36pl1 and zfp36l2

led to increased levels of H2AX, a DNA double-strand break marker, in early developing T cells in the thymus. Furthermore, variations in HuR activity in response to DNA damage have been shown to influence the expression of DDR-related genes (Sidali et al., 2022).

RBP	Expression in osteosarcoma	Target mRNA	Function	References
AUFI	Upregulated	VEGF-A	Promotes angiogenesis	Al-Khalaf and Aboussekhra, 2019
HUR	Upregulated	YAP	Increases cell migration and stemness	Increases cell migration and stemness
IGF2BP1	Upregulated	Wnt/β-catenin pathway	Promotes cellular proliferation	Alyam et al., 2019
PUM2	Downregulated	miR-19, miR-590-3p	Suppresses the RhoA/ROCK pathway leading to the inhibition of RhoA/ROCK signalling	Hu et al., 2018
YTHDF1	Upregulated	CCR4-NOT transcription complex	Promotes cell proliferation and migration	Wei et al., 2022
RBFOX2	Upregulated	CD44	Regulates alternative splicing cancer progression and metastasis	Zhang et al., 2017
LIN28B	Upregulated	Let-7	Inhibits the maturation of Let- 7 miRNA	Li et al., 2019
PTB	Upregulated	CD44, Bcl-x, Cyclin D1	Promotes cell proliferation and survival	He et al., 2014
FUS	Upregulated	Various target RNAs	Acts as an oncogene by promoting cell proliferation and inhibiting apoptosis	Zhang et al., 2020
hnRNP K	Upregulated	EGFR	Enhances EGFR expression and signalling	Lv et al., 2019

Table 1: summarizes RBPs and roles in Osteosarcoma.

Overview of RNA binding proteins in cancer

Various researchers have extensively investigated alterations in the expression of RBPs in cancer. Lee, Kang, and Lee (2020) conducted a comprehensive study elucidating the changes in RBP expression associated with cancer phenotypes. While a bioinformatics study by Wang, Liu, and Shyr (2015) found only minor changes in RBP mRNA levels in cancer, it is crucial to note that the mutations in RBPs can have significant downstream effects that contribute to pathogenesis of malignancies. Increased activity of RBPs has also been implicated in the development of certain cancers such as melanoma and pancreatic ductal adenocarcinoma (Kang et al., 2020). For example, a recent study reported high expression of eukaryotic translation initiation factor 2 subunit beta (EIF2S2) in numerous tumours, where it interacts with a long non-coding RNA (LINC1600) and prevents the degradation of MYC protein (Zhang et al., 2020). Additionally, dysregulated expression of RBPs can impact the metastatic phenotype of cancer. For example, CPEB1 exhibits downregulation in metastatic breast cancer tissues, contributing towards the promotion of epithelial-mesenchymal transition (EMT) and facilitating the metastatic progression of breast cancer (Wang, Sun, Lei & Zhang, 2022). An example of this is a study that utilized transcriptome and interactome data to demonstrate that hsa-miR-224-5p, a member of the RBP-ncRNA circuit, may promote tumour metastasis by upregulating the epithelial-mesenchymal transition (EMT) process (Jiang, Chen, Bei, Shao & Xu, 2021). These findings highlight the complex involvement of RBPs in cancer development and progression. Altered activity of RNA binding proteins (RBPs) in cancer encompasses various mechanisms, including genetic alterations, transcriptional and post-transcriptional control, and post-translational modifications of the encoded proteins, such as acetylation, phosphorylation, or ubiquitination (Pereira, Billaud, & Almeida, 2017).

Genetic Alterations

While alterations in genome sequences have long been associated with cancer, mutations specifically affecting RBPs and their nucleic acid sequences have been less frequently reported (Wang et al., 2015). However, mutations in RBPs involved in regulating the expression of proto-oncogenes have been found to be positively correlated with cancer occurrence and progression. For instance, a study demonstrated a putative link between refractory chronic lymphocytic leukemia (CLL) and genomic deletions in the RBPJ-associated molecule (RAM), which is part of the NOTCH1 gene family regulating cell differentiation, growth, and apoptosis (Edelman et al., 2020). Additionally, mutations affecting spliceosomes have been associated with an increased risk of developing myelodysplastic syndromes (Niño, Scotto di Perrotolo, & Polo, 2022). A systems biology study by Nik-Zainal in 2016 identified the *ZFP36L1* gene as one of the driver genes implicated in breast cancer. Interestingly, these newly discovered genes were found to be recessive rather than dominant in breast cancer, indicating that both copies of the gene must be mutated

for cancer to develop.

Post-transcriptional regulation of gene expression by RBPs

RBPs can regulate the activity of coding and non-coding RNA through processes such as splicing, direct binding and inhibition, gene silencing, regulation of ribosomal RNA processing machinery, and regulation of protein shuttling to Cajal bodies (Ji & Tulin, 2013). Dysregulation of these events has been observed in various neurodegenerative diseases and cancers. A notable example is the work by Lino et al. (2020), which demonstrated that the RNA binding protein non-POU domain-containing octamer binding (NONO) is an important mediator of breast cancer through post-transcriptional alteration of E2F transcription factor 8 and S-phase associated kinase 2, genes involved in breast cell division and differentiation. Additionally, a study by Loh et al. in 2020 showed that silencing ZFP36L1 increased tumour cell development, while forced expression of ZFP36L1 in cancer cells significantly decreased both in vitro and in vivo cell proliferation. These findings highlight the crucial role of ZFP36L1 as a post- transcriptional inhibitor of aberrant hypoxia signalling and improper cell-cycle progression.

RBPs in skeletal development

Skeletal development and remodelling are crucial for maintaining the biomechanical properties of bones (Niu et al., 2017). The skeletal system, as a specialized form of connective tissue, consists of osteoblasts, osteoprogenitor cells, and osteoclasts (Salhotra, Shah, Levi & Longaker, 2020). Osteoblasts, responsible for bone mineralization, derive from osteoprogenitor cells, which, in turn, arise from pluripotent mesenchymal stem cells (Kenkre & Bassett, 2018). Bone growth occurs through endochondral formation, where the growth plate, composed of chondrocytes, undergoes cellular hypertrophy (Shim, 2015). These hypertrophic cells are subsequently mineralized by osteoblasts. The formation of bone is regulated by a diverse array of transcription factors (Niu et al., 2017). This includes ligases, kinases, and splice proteins. Zinc-finger factor Sp7, along with other transcription factors like Runx2, DLX-5, and MSX-2, plays a crucial role in regulating chondrocyte differentiation and the maturation of mesenchymal precursor cells into osteoblasts and osteocytes (Niu et al., 2017). The expression of these transcription factors is also regulated at the post-transcriptional level by the Smad family of proteins, which bind to miRNAs, thereby inhibiting the protein expression of the transcription factors (Loboda, Sobczak, Jozkowicz & Dulak, 2016). Recent studies have shed light on the role of RNA- binding proteins (RBPs) in skeletal development. For example, circular RNA (cirStag1) was found to bind and localize human RNA-binding protein (HuR), which, in turn, activates the cytoplasmic Wnt signalling pathway, promoting the osteogenic maturation of bone marrow mesenchymal stem cells (BMSCs) (Chen, 2022). Additionally, RBPs such as AUF1 have been shown to regulate rapid angiogenesis in growing bones by binding and stabilizing the mRNAs of VEGF-A and its positive regulator HIF-1alpha (Al-Khalaf & Aboussekhra, 2019).

RBPs in Osteosarcoma

RBPs are implicated in various cancer-promoting events, including increased proliferation, cancer stemness, epithelial-mesenchymal transition (EMT), metastasis, invasion, angiogenesis, and resistance to apoptosis (Nag, Goswami, Mandal & Ray, 2022). Additionally, altered expression of RBPs can serve as a biomarker for evaluating drug response, prognoses, and therapeutic monitoring (Zhang, Miao, Wu, Jia & Cheng, 2021). One important RBP in osteosarcoma is AUF1 (also known as hnRNPD), which consists of four isoforms (p37AUF1, p40AUF1, p42AUF1, and p45AUF1) generated by alternative splicing of a pre-mRNA (White, Matsangos & Wilson, 2017). These isoforms exist as dimers in both the nuclear and cytoplasmic compartments (Jonas, Calin & Pichler, 2020). AUF1 recognizes and binds to AU-rich elements (AREs) within the 3' untranslated regions (UTRs) of many mRNAs, including those encoding proto-oncogenes, cytokines, hormones, cell receptors, growth factors, and G-protein coupled receptors (White et al., 2017). AUF1 can also bind to long non-coding RNAs (lncRNAs) and influence pre-mRNA decay, stability, or ribosomal translation (Khabar, 2017).

The role of AUF1 in osteosarcoma pathogenesis is multifaceted. Initial studies suggested a potential decrease in carcinogenesis with AUF1 involvement (Zucconi & Wilson, 2011). However, more recent evidence supports an increased expression of AUF1 in cancer progression. For example, AUF1 promotes tumor invasiveness in osteosarcoma by binding to and stabilizing the mRNA of the pro- angiogenic factor VEGF-A (Al-Khalaf & Aboussekhra, 2019). Additionally, AUF1 may promote the EMT phenotype by directly stabilizing SNAIL1 and TWIST1 mRNA (AlAhmari, Al-Khalaf, Al-Mohanna, Ghebeh & Aboussekhra, 2020). Furthermore, AUF1 acts as a potent stabilizer of the mRNA encoding zinc-finger E-box binding 1 (ZEB1), a transcription factor implicated in cancer initiation, invasion, metastasis, and drug resistance in various solid cancers, including retinoblastoma, neuroblastoma, and osteosarcoma (Fratini et al., 202). While the role of HuR, a member of ELAV family of RBPs in cancer pathogenesis has shown conflicting results, its involvement in osteosarcoma is well established. Increased HuR expression has been found to stabilize and enhance the expression of YAP, a transcription factor associated with the EMT phenotype, angiogenesis, and drug resistance in osteosarcoma ((Rajasingh, 2015, Xu et al., 2018, Mukherjee et al., 2011).

Additionally, studies indicate that knockout of HuR in osteosarcoma reduces cancer metastasis by decreasing the stability of its target mRNA, AGO2 (Liu et al., 2021). HuR has also been implicated in promoting the invasion of osteosarcoma cells through its interaction with lncRNAs (Li et al., 2018) and repressing apoptosis by modulating miR-142-3p expression (Pan et al., 2018). A prognostic marker of osteosarcoma IGF2BP1 expression contributes to the development of osteosarcoma both in humans and canine species (Pfaff et al., 2014). Müller et al in 2020 demonstrated the promotion of G1/S cell cycle translation by stabilising mRNAs encoding positive regulators like E2F1 IGF2BP-RNA complexes in a target-dependent manner, in vitro studies, revealed that the KH domain in this RBP was primarily responsible for RNA binding (Huang et al., 2018). Furthermore, unregulated IGF2BP1 was seen to promote the proliferation of pancreatic cancer cells via the AKT signalling pathway (Wan et al., 2019). IGF2BP1 stable knockdown cell lines were up to 10-fold more sensitive to doxorubicin, a drug used to treat osteosarcoma, than the control cell line (Pfaff et al., 2014, Hamilton et al., 2015). Notably, both Pumilio proteins PUM1 and PUM2 have been found to be upregulated in the majority of acute myeloid leukemia (AML) samples and leukemic cell lines (Smialek et al., 2021, Gong et al., 2022). In the context of osteosarcoma (OS), PUM2 overexpression has been shown to inhibit OS cell proliferation, migration, and stemness through competitive binding to the 3'UTR of STARD13 with miR-590-3p and miR-9 (Hu et al., 2018).

RBPs and therapeutic perspectives

RBPs play a crucial role not only in the initiation of cancers but also in determining therapeutic response and predicting survival in cancer patients (Masuda & Kuwano, 2019; Wu et al., 2021). The dysregulation of specific RBPs has been linked to poor prognosis and treatment resistance in various cancer types. For instance, reduced expression of RBMS3 has been associated with unfavorable outcomes in breast cancer, while its downregulation in ovarian cancer is correlated with poor response to antineoplastic drugs (Zhu et al., 2019; Wu et al., 2019). In glioblastoma, the upregulation of IGF2BP2 has been identified as a marker of disease progression and decreased survival (Cao, Mu & Huang, 2018). A proteomic screen of RBPs in osteosarcoma revealed six drugs that have the potential to modify treatment outcomes for patients (Mohammad et al., 2022). Additionally, Li et al. (2021) identified more than 30 RBPs that could serve as prognostic targets for personalized management of

osteosarcoma. These findings highlight the potential of RBPs as valuable therapeutic targets and prognostic indicators in osteosarcoma and other cancers.

Conclusion and future perspectives

It is important to note that our understanding of the intricate relationship between RBPs and osteosarcoma is still evolving underlining the importance of more research in this area. Many RBPs have been found to simultaneously regulate multiple genes involved in osteosarcoma development, leading to diverse changes in cancer progression. Further research is needed to unravel the precise mechanisms by which RBPs contribute to osteosarcoma pathogenesis and identify novel therapeutic strategies.

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