REVIEW ARTICLE

NEAT1: a multifaceted long non-coding RNA in multiple myeloma

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Abstract

Multiple myeloma (MM) is a plasma cell dyscrasia sustained by the clonal proliferation of plasma cells within the bone marrow. MM is the second most common hematologic neoplasm and, despite the continuous effort to overcome this disease, it remains uncurable. Throughout the recent years, novel therapeutic targets have been investigated, leading to the development of novel treatments for MM patients. In the last 10 years, interest in the long non-coding RNA NEAT1 has grown significantly within the field of cancer, including MM. In this review we offer a panoramic view of the role of NEAT1 in MM, with a focus on its possible role as both a biomarker and therapeutic target.

Introduction

Multiple myeloma (MM) is a plasma cell disorder characterized by uncontrolled proliferation of monoclonal plasma cells within the bone marrow.[1] It is the second most common hematologic cancer, with 187,952 cases recorded in 2022.[2] Despite significant progresses in management, it remains incurable. Currently available therapies only allow temporary control of the disease, which becomes resistant to treatments over time, often resulting in disease refractoriness and relapse.[3]

The clinical onset of the disease is preceded by two asymptomatic phases named monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM). MGUS and SMM are distinguished by several characteristics, including: percentage of monoclonal plasma cells infiltrating the bone marrow (<10% in MGUS, between 10%-60% in SMM); serum levels of monoclonal immunoglobulins (<3 g/dL in MGUS, >3 g/dL in SMM); and the risk of progression to MM, which is 1% and 10%, respectively, within 5 years of diagnosis.[4]

The onset of MM is caused by the development of genetic mutations at the germinal center of B cells. These mutations result in a switch from a physiological polyclonal component to the selection of a monoclonal clone, which is characteristic of MGUS. The driving mutations are followed by a series of secondary genetic and epigenetic events that contribute to neoplastic progression. In parallel, progression to overt myeloma is facilitated by the occurrence of alterations within the bone marrow milieu, which nourishes the clonal plasma cells, and may also become immunosuppressive and supportive for the growth of the neoplastic cells.[1,3,5]

The completion of the Human Genome Project, together with the advent of next-generation sequencing technologies, has revealed that only 2-5% of the genome is protein-coding, while 75-90% is transcribed into non-coding RNA (ncRNA), which are involved in the regulation of gene expression and numerous cellular processes. ncRNA are distinguished into housekeeping ncRNA, ubiquitously expressed, and regulatory ncRNA, characterized by tightly controlled and tissue-specific expression. Of note, the dysregulation of regulatory ncRNA is implicated in numerous pathological processes, including cancer.[6,7]

According to their length, regulatory ncRNA are divided into short non-coding RNA (<200 nucleotides, such as microRNA, miRNA), and long non-coding RNA (lncRNA, >200 nucleotides). Unlike miRNA, the function of lncRNA does not depend on the nucleotide sequence, since it is poorly conserved between species, but rather on their three-di-

mensional structure. This characteristic gives them considerable functional versatility, enabling lncRNA to interact with nucleic acids (e.g., by acting as precursors or sequestering miRNA), proteins and enzymes (e.g., by recruiting or sequestering epigenetic enzymes).[6,7]

Interest in lncRNA has grown exponentially in recent years due to their properties, leading them to be considered and investigated as both potential therapeutic targets and biomarkers for the diagnosis and prognosis of a number of different diseases, including MM.[8-12]

Several lncRNA have been implicated in MM, acting as either oncogenic or tumor-suppressive regulators. Pro-tumor lncRNA promote growth, dissemination, and resistance to apoptosis of neoplastic plasma cells, while also contributing to remodeling of the tumor microenvironment (TME) to favor tumor growth. Conversely, tumor-suppressive lncRNA exert anti-proliferative, anti-metastatic, and pro-apoptotic effects. Notably, individual lncRNA can influence multiple pathways, highlighting their pivotal role in MM pathogenesis and progression. These pieces of evidence have led to a growing interest in the use of lncRNA in the clinical setting. Studies have highlighted the potential of lncRNA as diagnostic, prognostic, and therapeutic targets due to the correlation between lncRNA levels and stage of the disease, but also because of their association with the genetic status and clinical manifestations of patients with MM.[13,14]

Although there are no active clinical trials involving lncRNA in MM, several are investigating the use of lncRNA as biomarkers and therapeutic targets for other cancer types. Some of these are described in MM, highlighting their translational potential. For instance, MALAT1 is being evaluated as a biomarker of oral squamous cell carcinoma in the clinical trial NCT05708209. Similarly, H19 and HOTAIR are under investigation as diagnostic or therapeutic targets across multiple malignancies, including leukemia and solid tumors (NCT05943093, NCT00711997, NCT03469544).

In this context, NEAT1 (Nuclear Enriched Abundant Transcript 1) has gained interest in MM and is among the most investigated lncRNA, with multiple studies regarding its involvement in disease progression and therapy resistance.[15,16] NEAT1 is located on chromosome 11 (11q13.1) and encodes two isoforms: NEAT1_1 and NEAT1_2. These are derived from alternative transcript maturation events in the 3' untranslated region. Both transcripts participate in the formation of paraspeckles, sub-nuclear ribonucleoprotein structures involved in the regulation of gene expression, but only NEAT1_2 acts as the architectural scaffold required for paraspeckle assembly, whereas NEAT1_1 alone is not sufficient.[17,18] Moreover, NEAT1 can independently act by sequestering miRNA (competing endogenous RNA, ceRNA) or recruiting proteins and enzymes (scaffolding), thereby functioning as a central hub in the regulation of gene expression and epigenetic processes.[17] These processes are crucial for maintaining cellular homeostasis, which, if dysregulated, may lead to the development of pathological processes. Indeed, NEAT1, as well as several others lncRNA, are involved in different neoplastic diseases, including breast,[19] colorectal,[20] gastric,[21] lung[22] and ovarian cancer.[23] Taken together, these findings indicate that NEAT1 is a broadly relevant cancer-associated lncRNA.

This is particularly relevant in MM, in which plasma cells constantly produce large quantities of immunoglobulins and experience chronic endoplasmic reticulum overload. NEAT1 is the architectural scaffold of paraspeckles, which are directly implicated in stress buffering: therefore, among its various functions, the proteostasis/stress-adaptation axis currently appears to be the most mechanistically plausible and consequential in MM.[17,24]

The investigation of NEAT1 in MM is a relatively recent area of study. Although current data remain incomplete, emerging evidence suggests that NEAT1 exerts pleiotropic effects, favoring neoplastic growth and dissemination, stress resistance, immune escape, and resistance to therapy. As for other lncRNA, the multifunctional nature of NEAT1 makes it challenging to define a single, predominant biological role. Given the novelty of this topic and the limited evidence, a comprehensive overview of the current knowledge on NEAT1 in MM is essential to lay the groundwork for future research in this field.

This review aims to define the biological role of NEAT1 in MM, by delving into the molecular mechanisms in which it is involved and assessing its potential diagnostic and therapeutic applications in a clinical setting.

NEAT1 in the development of multiple myeloma

Given the pleiotropic nature of NEAT1 and the functional spectrum regarding the regulatory biology of lncRNA, we have listed every NEAT1–driven mechanism reported in the context of MM. For each interaction we have reported the inferred mode of action (ceRNA, scaffold, epigenetic regulator) and the most likely subcellular compartment in which the interaction occurs, when supported or reasonably inferred from the original data. These annotations are summarized in Table 1.

NEAT1 sustains multiple myeloma cell growth and dissemination

NEAT1 appears to play a pivotal role in MM growth by promoting tumor plasma cell proliferation and migration. Indeed, it has been implicated in the regulation of several pathways known to be involved in tumor progression.

Among them, the activation of the PI3K/AKT pathway is positively associated with NEAT1. This pathway promotes cell survival, growth, and cell cycle progression. Its dysregulation is implicated in the development of several neoplastic pro-

Table 1. Summary of reported NEAT1–dependent mechanisms relevant to multiple myeloma.

Process	Mechanism	Cancer context	NEAT1 function type	Compartment	Evidence	Reference
Growth and dissemination	NEAT1/miR-524-5p/HDAC1/PTEN → PI3K/AKT pathway	Laryngeal carcinoma	ceRNA	Cytoplasm	Inferred	29
	NEAT1/DDX5/β-catenin and TCF4 → Wnt/β-catenin pathway	Colorectal cancer	Scaffold	Nucleus	Inferred	19
	NEAT1/EZH2/H3K27/Wnt/β-catenin pathway inhibitors → Wnt/β-catenin pathway	Glioblastoma	Scaffold	Nucleus	Inferred	38
	NEAT1/miR-411-3p/FZD3 → Wnt/β-catenin pathway	Laryngeal squamous cell carcinoma	ceRNA	Cytoplasm	Inferred	39
	NEAT1/TPX2/AURKA → Cell cycle progression	Multiple myeloma	Scaffold	Nucleus	Inferred	44
Resistance to stress conditions	METTL3/NEAT1/CHD4/DSB → DNA DSB repair	Osteosarcoma	Scaffold	Nucleus	Inferred	47
	NEAT1/β-catenin/TCF7/IRE1α → UPR activation	Osteosarcoma	Scaffold	Nucleus	Inferred	37
	NEAT1/DYNLL1/p53 → DNA repair	Multiple myeloma	Epigenetic/p53 regulator	Nucleus	Inferred (unclear localization)	26
	NEAT1/Che-1/R-loop → IFN response	Multiple myeloma	Paraspeckle component	Nucleus	Described	53
	NEAT1/miR-485-5p/ABCB8 → Oxidative stress and resistance to chemotherapy	Multiple myeloma	ceRNA	Cytoplasm	Inferred	54
Immune escape	NEAT1/miR-214/B7-H3 → JAK2/STAT3 pathway	Multiple myeloma	ceRNA	Cytoplasm	Inferred	59
	NEAT1/EZH2/H3/PBX1 → NK cell maturation and activity	Multiple myeloma	Scaffold	Nucleus	Inferred	60
Therapy resistance	NEAT1/miR-193a/MCL1 → cell survival	Multiple myeloma	ceRNA	Cytoplasm	Inferred	67
	NEAT1/miR-29b-3p/Sp1 → cell survival, proliferation, and stress resistance	Multiple myeloma	ceRNA	Cytoplasm	Inferred	70

Each row indicates a published NEAT1–dependent interaction linked to biological processes relevant to multiple myeloma. For each mechanism, the cancer context, the inferred mode of action (ceRNA/scaffold/epigenetic regulator), and the most likely subcellular compartment are reported. "Inferred" indicates that subcellular localization was deduced based on the type of molecular interaction rather than directly demonstrated in the original study. ceRNA: competing endogenous RNA; DSB: double-strand breaks; UPR: unfolded protein response.

cesses and resistance to anticancer therapies.[25-27] Ligand-receptor interaction leads to the recruitment of kinase PI3K, which converts the phosphatidylinositol 4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 acts as a second messenger, promoting the phosphorylation and activation of the protein kinase AKT. Once activated, AKT phosphorylates downstream effectors involved in cell survival and growth.[28,29] Although it is unclear how NEAT1 regulates the pathway, studies have demonstrated how this occurs by regulating the tumor suppressor phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase (PTEN).[25] The phosphatase PTEN is one of the most important antagonists of the PI3K/AKT pathway, converting PIP3 to PIP2. Furthermore, loss of PTEN leads to constitutive AKT activation, promoting neoplastic development.[28,29] In particular, NEAT1 downregulation in MM cells resulted in PTEN upregulation and p-PI3K and p-AKT silencing.[25] However, the mechanism by which NEAT1 regulates PTEN in MM remains unclear. Research conducted on laryngeal cancer suggests that this occurs via the miR-524-5p/HDAC16 axis.[30] The miRNA miR-524-5p acts as tumor suppressor in various cancer types.[31-35] According to Zhang *et al.*, miR-524-5p targets and suppresses HDAC1, a histone deacetylase that suppresses PTEN expression.[30] In this process, NEAT1 acts as a sponge for miR-524-5p, preventing it from inhibiting HDAC1, thereby leading to HDAC1 upregulation and subse-

quent downregulation of PTEN (Figure 1A).[30] However, this is the only evidence concerning the biological mechanism of NEAT1 action against PTEN. This represents a first step towards identifying the role of NEAT1 in the regulation of the PI3K/AKT pathway, but it needs to be confirmed in MM. NEAT1 is also involved in the Wnt/β-catenin pathway, which plays a role in embryonic development and tissue regeneration. Impaired function of the pathway could lead to the development of neoplastic processes. Briefly, binding of WNT to a Frizzeld family G-protein-coupled receptor inhibits the β-catenin destruction complex. β-catenin accumulates within the cytoplasm and then translocates into the nucleus, where interacts with the T-cell factor/lymphoid enhancer factor-1 (TCF/Lef1) transcription complex. The TCF/Lef1 complex causes the transcription of several genes such as metalloproteases (MMP) and c-Myc, promoting tumor proliferation and invasion.[36-38] Regarding NEAT1 in MM, it was observed that NEAT1 overexpression induced

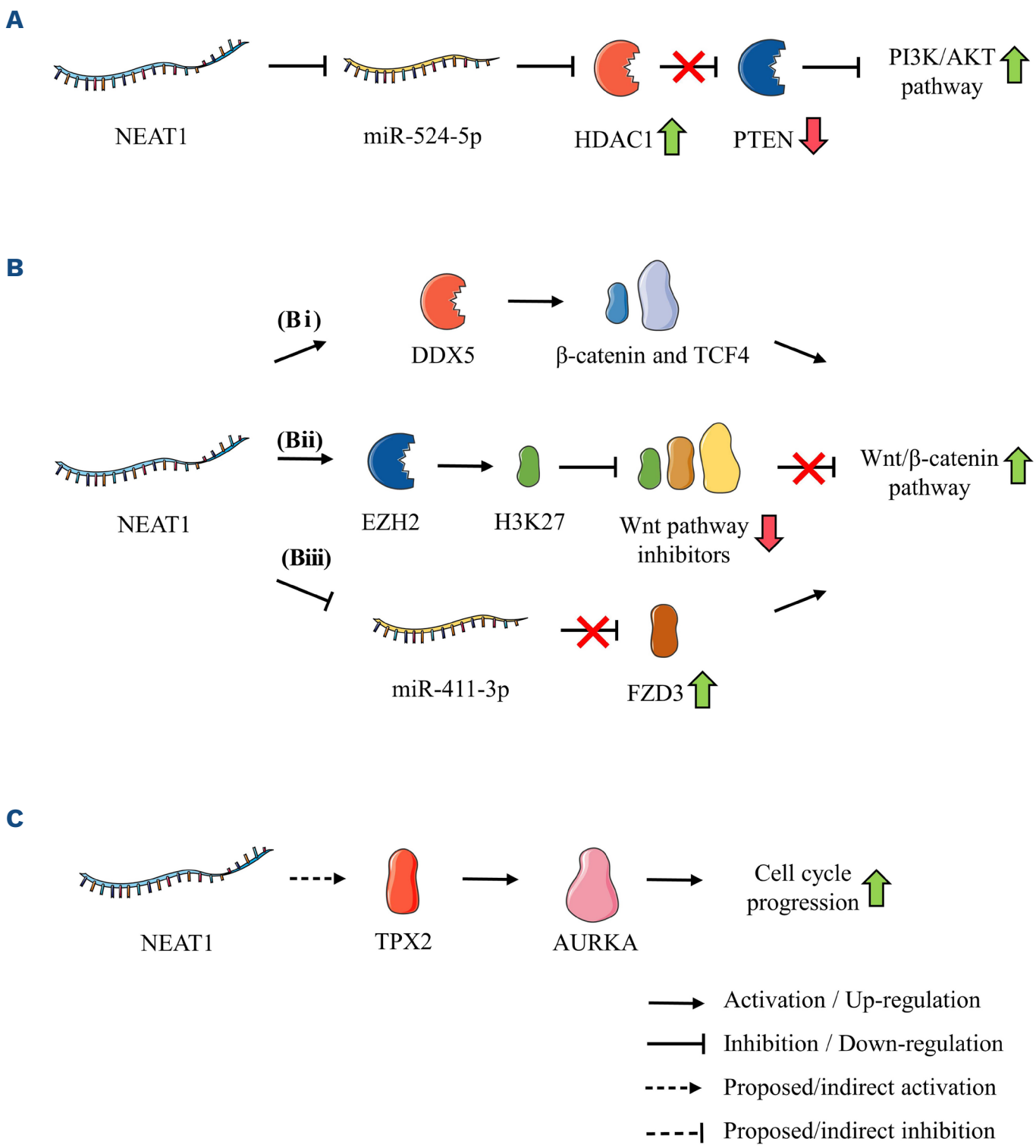

Figure 1. Potential mechanisms supporting NEAT1-dependent modulation of multiple myeloma cell growth and dissemination. (A) NEAT1 promotes PI3K/AKT pathway activation. In laryngeal cancer, NEAT1 acts as a sponge for miR-524-5p, relieving HDAC1 from its repression. Elevated HDAC1 suppresses PTEN, thereby favoring the pathway activation. (B) Proposed mechanisms of NEAT1 involvement in the Wnt/β-catenin pathway, described in different tumor contexts. (Bi) In colorectal cancer, NEAT1 binds the RNA helicase DDX5, which interacts with β-catenin and TCF4, enhancing their transcriptional activity. (Bii) In glioblastoma, NEAT1 recruits EZH2 to promote H3K27 methylation, thereby suppressing the expression of Wnt pathway inhibitors AXIN2, GSK3β, and ICAT. (Biii) In laryngeal squamous cell carcinoma, NEAT1 acts as a competing endogenous RNA for miR-411-3p, relieving repression of the Wnt receptor FZD3, which is consequently upregulated and contributes to pathway activation. (C) NEAT1 involvement in mitotic spindle formation. NEAT1 regulates AURKA activity through the allosteric regulator TPX2, thereby promoting AURKA activation and spindle assembly during mitosis, ultimately favoring cell cycle progression.

the upregulation of several elements of the Wnt/β-catenin pathway, such as nuclear β-catenin, c-Myc, MMP7 and survivin.[38] While it is the only observation of NEAT1 in the Wnt/β-catenin pathway in MM and, therefore, its mechanism of action has yet to be investigated, NEAT1 involvement in the Wnt/β-catenin pathway has been reported in various cancers, in which possible mechanisms of action have also been suggested. In colorectal cancer, NEAT1 binds DDX5 helicase, which interacts with β-catenin and TCF4, promoting their transcriptional activity (Figure 1Bi).[20] In glioblastoma, NEAT1 acts as a scaffold by recruiting the chromatin modifier EZH2, stimulating the methylation of the histone protein H3 at Lys27 (H3K27). This suppresses the expression of the pathway inhibitors AXIN2, GSK3β and ICAT (Figure 1Bii).[39] In laryngeal squamous cell carcinoma, NEAT1 acts as ceRNA for the miRNA miR-411-3p, which regulates the expression of the transmembrane receptor FZD3, a member of the WNT receptor family. FZD3 is then expressed at a higher level, favoring activation of the pathway (Figure 1Biii).[40] These findings suggest a direct role of NEAT1 in regulating the Wnt/β-catenin pathway: its role and the underlying mechanisms of actions remain to be further dissected and investigated within the context of MM.

NEAT1 also plays a role in the formation of the mitotic spindle by interacting with the serine/threonine kinase aurora kinase A (AURKA). In mitotic cells, Tyr288 phosphorylation leads to its activation, then it localizes to the centrosome thus regulating mitotic spindle formation.[41] Due to its role, this process is often dysregulated in cancerous cells.[42-44] It has been shown that AURKA is controlled by NEAT1 through TPX2, an allosteric regulator of AURKA, thereby promoting cell cycle progression and contributing to MM development (Figure 1C). However, the mechanism of action through which NEAT1 regulates TPX2 is not clear.[45] This is also the only evidence that NEAT1 has a role in regulating AURKA in neoplastic contexts. Further investigation and confirmation are required.

These findings support the potential role of NEAT1 in modulating MM cell proliferation and dissemination via PIK3/AKT, Wnt/β-catenin, and AURKA pathways. However, the precise mechanisms by which NEAT1 acts in these processes remain to be fully elucidated. A deeper understanding could contribute to the development of novel therapeutic strategies, given the pleiotropic functions of NEAT1.

NEAT1 confers cell resistance to stress conditions

This is a crucial aspect of tumor development, given that cancers often encounter extreme conditions, such as nutrient deficiency, hypoxia, and altered protein synthesis. Such conditions can lead to cellular stress and apoptosis. However, cancer cells react by implementing a wide range of responses to enable them to survive, grow and proliferate. Therefore, understanding these mechanisms is crucial for the research and development of new therapies. NEAT1 appears to play a role in this process by acting on several mechanisms that reduce cellular stress.

Focusing on MM, studies have reported how NEAT1 is expressed in response to stressful conditions. Specifically, the synthesis of NEAT1 is induced by exposure of MM cell cultures to hypoxic conditions and nutrient deficiency, thus resulting in enhanced synthesis of ataxia-telangiectasia-mutated (ATM) and DNA-dependent protein kinase catalytic subunit (DNA-PKcs), together with upregulation of the related targets (i.e., RPA32 and CHK2), which are involved in the repair of DNA double-strand breaks (DSB).[46] These mechanisms confer a survival advantage to cells under stress. Interestingly, this occurs via the NEAT1_2 isoform, which increases in relation to total NEAT1 expression. It has been hypothesized that NEAT1 expression is modulated in favor of the NEAT1_2 isoform to stimulate paraspeckle synthesis and counteract stress-related conditions.[47] A potential mechanism through which NEAT1 may promote the repair of DSB may be through the METTL3/NEAT1/CHD4 signaling axis, within the context of osteosarcoma cells. In response to DSB, the upregulated NEAT1 translocates into the nucleus, where it undergoes the addition of N6-methyladenosine (m^6A), a reaction catalyzed by the methyltransferase METTL3. The modified NEAT1 then accumulates at DNA breakpoints. Here, NEAT1 plays a key role in the formation of damage signaling foci, causing the release of CHD4 from the NuRD complex, known for its histone deacetylation activity. This inhibits deacetylation and promotes acetylation, opening the chromatin surrounding the DSB and facilitating the entry of repair factors (Figure 2A). An increase of NEAT1_2 levels is also evident here, confirming this isoform's central role in DSB repair.[48]

It has been hypothesized that NEAT1 plays a role in the metabolic pathway that activates the unfolded protein response (UPR). The UPR is a defense system that cells activate in response to the accumulation of misfolded or unfolded proteins in the endoplasmic reticulum. Its purpose is to re-establish proteostasis. Activation of the UPR may provide an overall advantage to tumor cells, as a result of enhanced resistance to apoptosis induced by the accumulation of misfolded proteins. This mechanism is activated by endoplasmic reticulum transmembrane protein sensors such as IRE1α, PERK and ATF6α3.[49] It has been hypothesized that UPR activation occurs via the NEAT1/β-catenin/TCF7/IRE1α axis. Specifically, NEAT1 promotes the accumulation and nuclear translocation of β-catenin, activating transcription factor 7 (TCF7). TCF7 induces the expression of the UPR system sensor IRE1α, thereby promoting activation of the UPR (Figure 2Bi).[38] However, in a letter published in 2019, the same researchers demonstrated that increased NEAT1 expression results in the downregulation of UPR pathways. Constitutive activation of the UPR results in apoptosis, so it was suggested that NEAT1 plays a role in promoting cell survival. In addition, reduced activation of pathways involved in DNA repair was

observed: this is due to the reduction of p53 activity caused by decreased DYNLL1 expression, essential for p53 trafficking (Figure 2Bii).[27] NEAT1 could modulate the activity of the UPR and p53. NEAT1 could maintain UPR activity at an intermediate level, leading to stress resistance and preventing apoptosis induced by its constitutive activation. The inhibition of p53-induced reparative pathways prevents cell cycle arrest and favors neoplastic growth. Although these are interesting

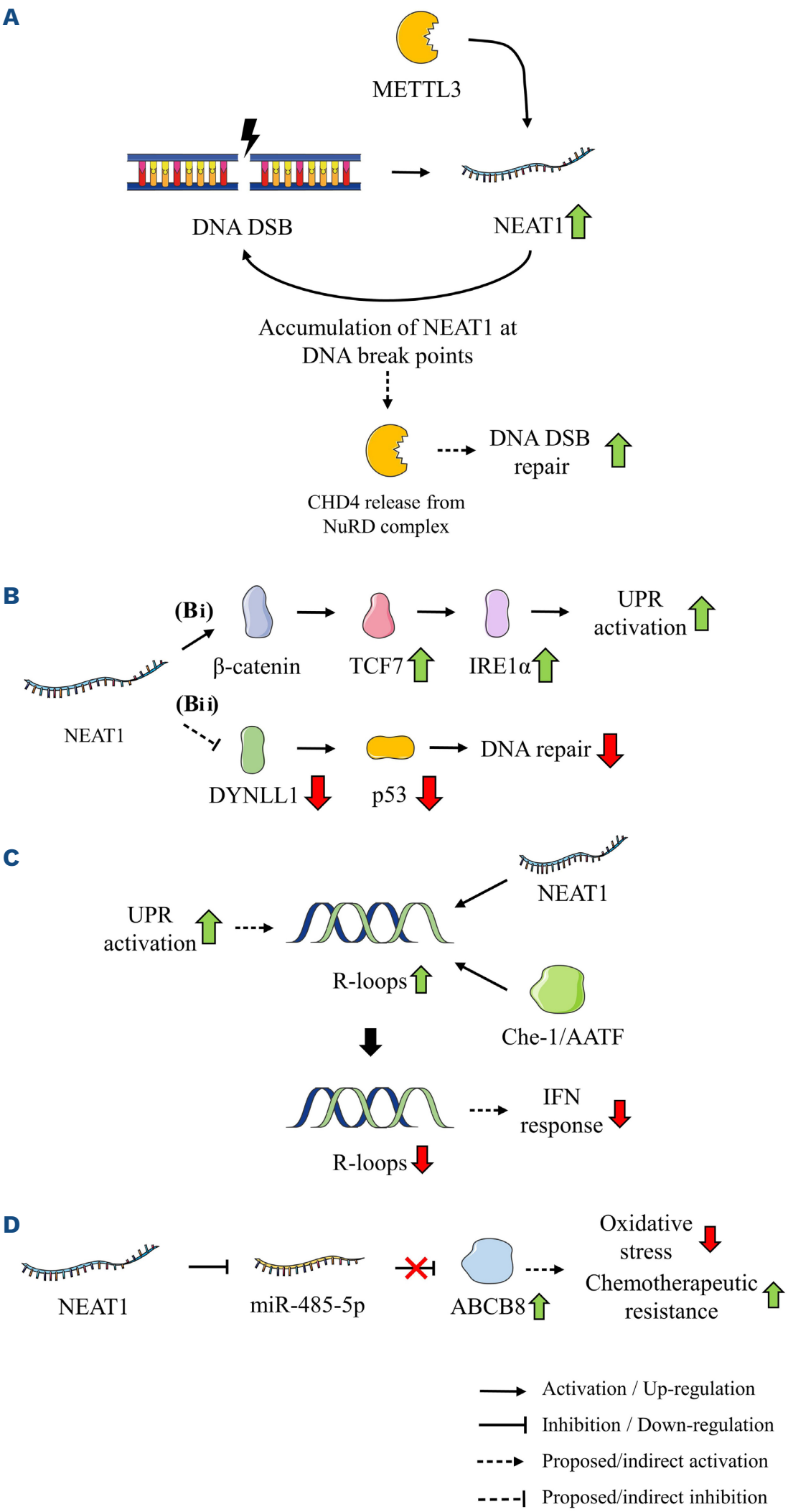

Figure 2. Potential mechanisms supporting NEAT1-dependent modulation of multiple myeloma cell resistance to stress-related conditions. (A) NEAT1 promotes repair of DNA double-strand breaks (DSB). In osteosarcoma cells, NEAT1 undergoes METTL3-mediated m^{6}A modification upon DNA damage and accumulates at breakpoints. There, NEAT1 promotes the release of CHD4 from the NuRD complex, reducing histone deacetylation and enhancing chromatin accessibility, thus facilitating the recruitment of DNA repair factors and DNA DSB repair. (B) NEAT1-mediated activation of the unfolded protein response (UPR) and DNA repair inhibition. (Bi) NEAT1 promotes β-catenin accumulation and nuclear translocation, activating the transcription factor TCF7. TCF7 induces expression of the UPR sensor IRE1α, thereby promoting UPR activation. (Bii) NEAT1 reduces DYNLL1 expression, causing reduced p53 trafficking and DNA repair inhibition. (C) NEAT1 regulation of inflammatory responses and R-loop formation. NEAT1, in conjunction with Che-1/AATF, promotes the resolution of R-loops, preventing their accumulation and subsequent activation of the IFN-mediated inflammatory response. Chronic UPR activation is hypothesized to contribute to R-loop formation. (D) NEAT1 modulation of chemoresistance via mitochondrial regulation. NEAT1 functions as a competing endogenous RNA for miR-485-5p, leading to upregulation of ABCB8. The mitochondrial membrane transporter ABCB8 protects cells against oxidative stress and promotes chemotherapeutic resistance.

hypotheses, they are not supported by much experimental evidence. Moreover, they contradict observations concerning other neoplastic processes in the literature. Indeed, NEAT1 has been shown to inhibit UPR activity, thereby promoting cellular stress and subsequent apoptosis.[50-52]

Another function exerted by NEAT1 is to regulate the formation of R-loops, structures formed during transcription. These complexes consist of three strands: the DNA:RNA hybrid formed between the nascent RNA and the template DNA strand, and the non-template DNA strand that is displaced during transcription. Incorrect formation or removal of these complexes can lead to increased genomic instability.[53] NEAT1, in conjunction with Che-1/AATF protein, promotes the resolution of these complexes, preventing their accumulation and subsequent activation of the interferon (IFN)-mediated inflammatory response. Furthermore, based on observations from several studies, it has been hypothesized that constitutive activation of the UPR may lead to the formation of R-loops (Figure 2C). The inflammation induced by accumulation of R-loops is defined "sterile inflammation", is harmless and, as observed for hematopoietic stem and progenitor cells, results in a proliferative advantage for MM cells. NEAT1 and Che-1 play a crucial role in this process by keeping R-loop levels under control and limiting extensive genomic damage and IFN-mediated apoptosis.[54] This biological mechanism is novel in the context of cancer. In summary, the proposed mechanism could promote cell survival under stressful conditions and determine a favorable microenvironment for neoplastic cells.

NEAT1 has also been reported as a ceRNA in the NEAT1/miR-485-5p/ABCB8 axis. NEAT1 acts as a ceRNA for the miRNA miR-485-p, causing upregulated expression of the target protein ABCB8 (Figure 2D).[16] ABCB8 is a mitochondrial membrane transporter that forms a multi-protein complex known as mitochondrial ATP-sensitive K^+ channel, which appears to protect the cell against oxidative stress and gives resistance to chemotherapy, such as doxorubicin. ABCB8 inhibits doxorubicin-induced iron accumulation in mitochondria, thus counteracting the activation of ferroptosis. It also favors the efflux of doxorubicin itself from mitochondria, thereby reducing associated damage.[55,56] However, the structure and the mechanism of the channel's function are still unclear, as is the function of ABCB8.[57]

NEAT1 plays a central role in cellular stress resistance by acting at multiple levels. It promotes the repair of DSB and regulates R-loops within the nucleus, modulates UPR signaling in the endoplasmic reticulum, and contributes to mitochondrial homeostasis. Although these are preliminary findings, NEAT1 represents a potential therapeutic target for restoring stress-induced apoptosis in MM. Importantly, these stress-adaptation circuits may represent the biological substrate underlying NEAT1-mediated resistance to therapy.

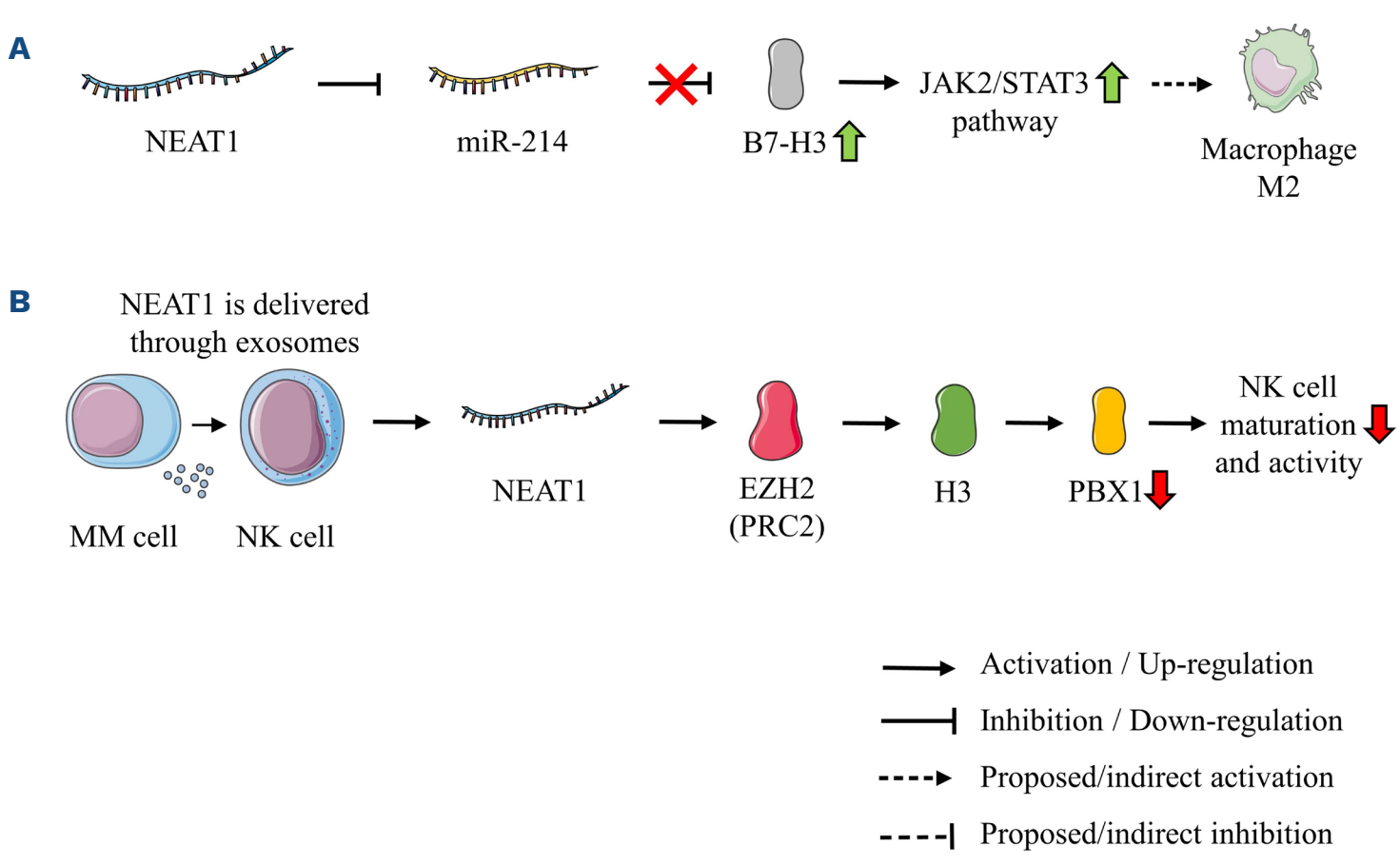

Figure 3. Potential mechanisms supporting NEAT1-dependent enhanced immune escape in multiple myeloma. (A) NEAT1-mediated promotion of immune escape via macrophage M2 polarization. NEAT1 functions as a competing endogenous RNA for miR-214, relieving its repression of the immunoregulatory molecule B7-H3. Upregulation of B7-H3 activates the JAK2/STAT3 pathway, promoting macrophage polarization towards the M2 phenotype. (B) NEAT1-mediated suppression of natural killer (NK) cell cytotoxicity. NEAT1 is delivered to NK cells via exosomes released by multiple myeloma cells. Within NK cells, NEAT1 recruits EZH2, a component of PRC2, leading to trimethylation of H3K27 and repression of the transcription factor PBX1. Downregulation of PBX1 impairs NK cell maturation and cytotoxic activity.

NEAT1 promotes immune escape

In addition to its involvement in several molecular mechanisms in MM cells, NEAT1 may also regulate the TME. In recent years, interest in the TME and its bidirectional interactions with tumor cells has increased significantly. Malignant cells can actively remodel the microenvironment to support their own growth and survival. The TME comprises a heterogeneous population of cells with diverse roles and phenotypes. In MM, the TME contributes to tumor development and progression. NEAT1 is involved in this context, particularly by acting on macrophages and natural killer (NK) cells.[58-60]

In MM, infiltrating macrophages, known as tumor-associated macrophages, display an M2-like phenotype, supporting tumor growth, survival, and immune evasion.[61] NEAT1 has been shown to promote the polarization of macrophages towards an M2 phenotype via the NEAT1/miR-214/B7-H3 axis. NEAT1 acts as a ceRNA for miR-214 and prevents the repressive effect of miR-214 on B7-H3 mRNA, an immunoregulatory molecule. In this context, B7-H3 promotes the activation of the JAK2/STAT3 pathway contributing to M2 polarization of macrophages and the maintenance of an immunosuppressive microenvironment (Figure 3A).[59,62]

In the context of MM, NEAT1 does not act directly on tumor cells but exerts its effects on NK cells. The primary function on NK cells is to recognize and eliminate infected or neoplastic cells without prior antigen sensitization. Specifically, NEAT1 is delivered via exosomes released by MM cells, which are then internalized by NK cells. Within the NK cells, NEAT1 downregulates PBX1 expression by recruiting EZH2, a component of polycomb repressive complex 2 (PRC2). PRC2 is responsible for the trimethylation of lysine 27 of histone H3.[63] This modification results in the repression of PBX1, a transcription factor known to support NK cell maturation and activity.[64] As a result, PBX1 downregulation impairs the cytotoxic activity of NK cells and facilitates immune evasion by MM cells (Figure 3B).[60] EZH2 has already been described as a negative regulator of NK cell maturation and function. Consistent with the observations involving NEAT1, it has been hypothesized that EZH2 may suppress NK cell activity via PBX1 repression.[65]

Although the evidence regarding NEAT1's involvement in TME modulation remains limited, there are diverse mechanisms of action that are particularly noteworthy. These findings suggest that NEAT1 may exert similar complex effects on other cellular components within the microenvironment. Therefore, expanding the investigation to additional cell populations will be essential to elucidate NEAT1's role and its potential as a therapeutic target.

Therapy resistance

Drug resistance represents one of the main challenges in the management of MM. Despite the availability of various therapeutic strategies, the disease tends to become resistant over time, necessitating a change in therapy. This can pose challenges not only in terms of a patient's tolerance to new drugs but also regarding the psychological impact of therapeutic uncertainty. Therefore, alongside the development of new therapies, it is crucial to deepen our understanding of the molecular mechanisms that drive treatment resistance.

Dexamethasone is one of the most widely used glucocorticoids in the treatment of MM. It binds the cytosolic glucocorticoid receptor, forms a complex that translocates into the nucleus and modulates gene expression. Dexamethasone induces apoptosis through several mechanisms, including the activation of pro-apoptotic genes (such as BIM) and the repression of anti-apoptotic genes (such as BCL-2 and MCL1).[66] It also alters mitochondrial membrane potential and aggravates endoplasmic reticulum stress. NEAT1 is implicated in dexamethasone resistance in MM. NEAT1 acts along the NEAT1/miR-193a/MCL1 axis as a ceRNA for the miRNA miR-193a, which can suppress the expression of the anti-apoptotic protein MCL1. Elevated levels of NEAT1 inhibit miR-193a activity, favoring MCL1 expression and contributing to the survival of MM cells (Figure 4A).[67] Furthermore, high NEAT1 levels are associated with greater dexamethasone resistance, thus suggesting a potential predictive and prognostic role of NEAT1.[68]

The high rate of immunoglobulin synthesis in MM cells makes proteasome inhibitors, such as bortezomib, particularly effective in the treatment of MM. However, as with other treatments, resistance to bortezomib appears over time. Although the underlying mechanisms are not yet fully understood, NEAT1 contributes to this process. It functions as a ceRNA for the miRNA miR-29b-3p in the NEAT1/miR-29b-3p/Sp1 axis, thereby promoting the expression of the transcription factor Sp1. Sp1 is known to support cell proliferation, survival, and stress resistance in MM.[69] Furthermore, Sp1 promotes the transcription of anti-apoptotic genes and of NEAT1. This creates a positive feedback loop that reinforces the resistance (Figure 4B). High levels of NEAT1 have been associated with an increased risk of developing bortezomib resistance, suggesting its potential role as a prognostic biomarker.[70]

The currently available evidence suggests that NEAT1 is involved in drug resistance and could be a valuable therapeutic target. Its expression could also provide prognostic and predictive indications, paving the way for more targeted and personalized therapeutic strategies in MM treatment.

The potential role of NEAT1 in clinical practice

As mentioned before, NEAT1 supports the proliferation and progression of MM exerting an important role in the processes of carcinogenesis. Based on current evidence, it

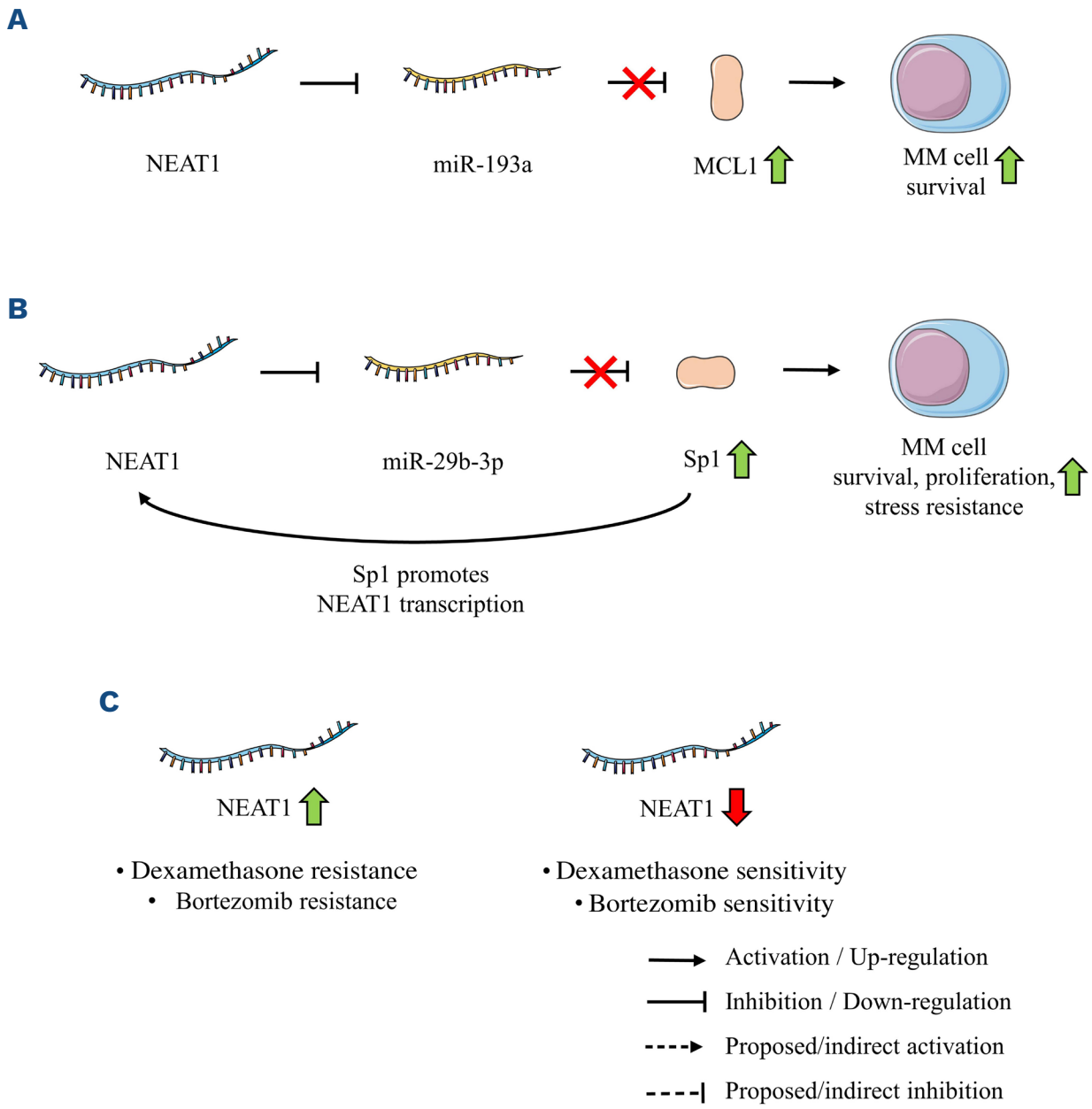

Figure 4. Potential mechanisms supporting NEAT1-dependent modulation of drug resistance in multiple myeloma. (A) NEAT1-mediated dexamethasone resistance. NEAT1 functions as a competing endogenous RNA (ceRNA) for miR-193a, preventing miR-193a from repressing the anti-apoptotic protein MCL1. Elevated NEAT1 levels sustain MCL1 expression, promoting survival of multiple myeloma (MM) cells and contributing to dexamethasone resistance. (B) NEAT1-mediated bortezomib resistance. NEAT1 acts as a ceRNA for miR-29b-3p, relieving its repression of the transcription factor Sp1. Upregulated Sp1 supports cell proliferation, survival, and stress resistance, and promotes transcription of anti-apoptotic genes as well as NEAT1 itself. This positive feedback loop reinforces resistance to bortezomib in MM cells. (C) Schematic therapeutic implication of NEAT1 targeting in MM. Inhibition of NEAT1 (e.g., by antisense oligonucleotides) would disrupt the NEAT1-dependent axes that mediate resistance to dexamethasone (NEAT1/miR-193a/MCL1) and bortezomib (NEAT1/miR-29b-3p/Sp1), potentially restoring sensitivity to both agents.

represents both a potential target for the development of novel therapies and a useful biomarker for MM diagnosis and to predict specific therapies for MM patients.

The upregulation of NEAT1 is associated with poor overall survival in MM.[16,59,71] Moreover, high expression of NEAT1 is associated with a poor prognosis of MM patients.[16] The first study on NEAT1 levels in MM highlighted its downregulation in bone marrow-derived plasma cells as compared to its levels in the normal cellular counterpart in healthy donors. However, further investigations have shown that NEAT1 is expressed at higher levels in MM than in healthy donors and patients with other hematologic malignancies.[27,68,72,73] This, together with other clinical features, could help to differentiate MM among the various blood neoplasms. Interestingly, levels of NEAT1 increase in both the bone marrow and peripheral blood of MM patients, and higher NEAT1 expression is associated with dexamethasone resistance and a critical prognosis.[67,68]

These observations pave the way to a potential role of NEAT1 as a biomarker for the diagnosis of MM and as a predictor of the prognosis of the disease.

A recent study on MM cells demonstrated that the knockdown of NEAT1 has similar biological effects as those of treatment with AURKA inhibitors, and that these two approaches impact molecular pathways similarly.[74] The combination of NEAT1 silencing and inhibitors of AURKA has a strong impact on the organization of microtubules and the assembly of mitotic spindle, resulting in cell death. Moreover, MM patients who have high levels of both NEAT1 and AURKA have a poor clinical outcome.[45] A low level of NEAT1

affects the miR-485-5p/ABCB8 axis, altering biological processes in MM cells. Further investigation should focus on this axis because ABCB8 is involved in MM drug-sensitivity and resistance mechanisms. This axis could represent a potential therapeutic target for MM treatment.[16]

Another strategy to hamper the pro-tumoral role of NEAT1 is its silencing with locked nucleic acid (LNA)-gapmer antisense oligonucleotide technology. The LNA is a structurally specific nucleotide transformer that improves the stability, selectivity and affinity of the gapmer oligonucleotide by introducing an LNA modification.[75] This novel drug candidate inhibits proliferation and induces apoptosis in both *in vivo* and *in vitro* MM models.[15,75] NEAT1 targets downregulated genes involved in DNA repair functions causing massive DNA damage. The loss of function of NEAT1 has a synergistic role and chemosensitizing effect in combination with the drugs conventionally administered for the treatment of MM (e.g., bortezomib and carfilzomib).[15]

Among currently available RNA-targeting modalities, antisense oligonucleotides, at present, represent the most realistic strategy for NEAT1 inhibition in MM. However, while proof-of-concept efficacy is encouraging, formal preclinical toxicology, on-target/off-target safety evaluation, and dose–response feasibility studies in MM models are still lacking. Moreover, potential compensatory effects exerted by other nuclear lncRNA (e.g., MALAT1) remain unexplored and may influence the effectiveness of NEAT1 inhibition. These aspects currently represent an open translational challenge for the field.

Conclusions

A growing body of evidence firmly establishes NEAT1 as a crucial player in pathogenesis, progression, and drug resistance in the context of MM.

It has been clearly shown that NEAT1 exerts a significant influence over a variety of essential cellular processes, including proliferation, apoptosis, immune evasion, and the cellular response to chemotherapy. This multifaceted role not only highlights NEAT1 as a key regulator of MM biology but also underscores its dual function as both a valuable prognostic biomarker and a promising therapeutic target. Elevated levels of NEAT1 have been consistently associated with poor outcomes of the patients, drug resistance, and aggressive disease phenotypes, indicating its potential utility in patient stratification and personalized treatment planning.

Innovative therapeutic approaches aimed at silencing NEAT1, particularly using LNA-gapmer antisense oligonucleotide technology, have demonstrated encouraging results in preclinical models. These approaches effectively inhibit tumor growth, induce apoptosis, and significantly enhance chemosensitivity, especially when combined with established proteasome inhibitor-based therapies. This combinatorial strategy not only improves therapeutic efficacy but also provides a potential avenue to overcome the persistent challenge of drug resistance that limits current MM treatment success.

Despite these promising developments, the molecular mechanisms through which NEAT1 regulates MM pathophysiology remain incompletely understood. NEAT1's interactions with key signaling pathways, gene regulatory networks, and its influence on the TME warrant further in-depth investigation. Indeed, data related to the mechanisms of action of NEAT1 are limited. Observations made in other neoplastic contexts were included in this review, with the aims of proposing a mechanism that could address current gaps in MM research and establishing a foundation for further research to confirm or refute the proposed hypotheses. Another open question concerns the positioning of NEAT1 within the MM lncRNA landscape. Specifically, NEAT1 has not yet been systematically compared to other lncRNA in patient cohorts or functional screening. This currently represents a gap in the field, thus indicating the need for further investigation.

Defining how NEAT1 fits into the context of MM is another unresolved issue. Data from the largest CRISPR/Cas13 dataset suggest that NEAT1 is not a pan-essential lncRNA but rather a context-dependent one.[76] To further elucidate its function, future loss-of-function CRISPR-based screening studies could help better characterize the contribution of NEAT1 and other lncRNA in MM biology. Moreover, systematic investigations exploring potential correlations between NEAT1 expression and MM-specific cytogenetic abnormalities, mutational profiles, or epigenetic modifications are still lacking.

Elucidating these complex mechanisms will be critical to optimizing NEAT1-targeted therapies and ensuring their safety and effectiveness in clinical settings. Ultimately, advancing our understanding of NEAT1 will facilitate the translation of experimental insights into novel, targeted therapeutic strategies that improve patients' outcomes and offer new hope in the management of MM.

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Contributions

GB, AS and AMR designed the structure of the review article. GB and ST drafted the manuscript and prepared the figures.

MS, FR, RM, AA, SM and SS collected the related studies and participated in discussions. AMR and AS revised the manuscript. All authors reviewed the manuscript.

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