haematologica
Journal of the Ferrata Storti Foundation

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Received: September 23, 2025.
Accepted: December 12, 2025.

Citation: Gabriele Benini, Sara Taranto, Margherita Sciume', Fabio Rigali, Raffaella Marcheselli, Andrea Abate, Stefania Mitola, Sandra Sigala, Antonio Sacco and Aldo Roccaro. NEAT1: a multifaceted long non-coding RNA in multiple myeloma.
Haematologica. 2025 Dec 18. doi: 10.3324/haematol.2025.289258 [Epub ahead of print]

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

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Not applicable

COMPETING INTEREST

A.M.R.: research funding from AstraZeneca; European Hematology Association; Transcan2-ERANET; Italian Association for Cancer Research; International Waldenström's Macroglobulinemia Foundation and The Leukemia&Lymphoma Society; Associazione Italiana contro Leucemie, Linfomi e Mieloma (AIL) Brescia; and honoraria from Abbvie, AstraZeneca, Beigene, Janssen, Roche.

A.S.: research funding from Associazione Italiana contro Leucemie, Linfomi e Mieloma (AIL) Brescia

The remaining authors declare no competing financial interests

FUNDING

A.M.R.: Associazione Italiana per la Ricerca sul Cancro AIRC IG-24689 and Associazione Italiana contro le Leucemie-linfomi e Mieloma Brescia (AIL Brescia)

AUTHORS' CONTRIBUTIONS

G.B., A.S. and A.M.R.: designed the review article structure.

G.B., S.T.: drafted the manuscript and prepared the figures.

M.S., F.R., R.M., A.A., S.M., S.S.: collected the related studies and participated in discussions.

A.M.R, A.S.: revised the manuscript.

All authors reviewed the manuscript.

ACKNOWLEDGMENTS

This work was supported in part by Associazione Italiana per la Ricerca sul Cancro AIRC IG-24689 and Associazione Italiana contro le Leucemie-linfomi e Mieloma Brescia (AIL Brescia).

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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 represents the second most common hematologic neoplasm and, despite the continuous effort to overcome this disease, it remains an uncurable disease. Throughout the recent years, novel therapeutic targets have been investigated, leading to the development of novel treatments for MM patients. In the last ten years, the interest for the long non-coding RNA NEAT1 has significantly grown 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 biomarker and therapeutic target.

Keywords: long non-coding RNA; multiple myeloma; NEAT1**;** biomarkers; therapeutic targets.

Introduction

Multiple myeloma (MM) is a plasma cell disorder characterized by uncontrolled proliferation of monoclonal plasma cells within the bone marrow (BM).[1] It is the second most common hematological cancer, with 187.952 cases recorded in 2022.[2] Despite significant progresses, 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 (<3g/dL in MGUS, >3g/dL in SMM); and the risk of progression to MM, which is 1% and 10% respectively, within five years of diagnosis.[4]

MM onset is caused by the development of genetic mutations at the germinal centre 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 BM milieu, which nourishes the clonal plasma cells, and, also may 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 RNAs (ncRNAs), which are involved in the regulation of gene expression and numerous cellular processes. NcRNAs are distinguished in housekeeping, ubiquitously expressed, and regulatory, characterized by a tightly controlled and tissue-specific expression. Of note, the dysregulation of regulatory ncRNAs is implicated in numerous pathological processes, including cancer.[6,7]

According to their length, regulatory ncRNAs are divided into short non-coding RNAs (<200 nucleotides, such as microRNAs, miRNAs), and long non-coding RNAs (lncRNAs, >200 nucleotides). Unlike miRNAs, the function of lncRNAs does not depend on the nucleotide sequence, since is poorly conserved between species, but rather than on the three-dimensional structure. This characteristic gives them considerable functional versatility, enabling lncRNAs to interact with both nucleic acids (e.g. by acting as precursors or sequestering miRNAs), proteins and enzymes (e.g. by recruiting or sequestering epigenetic enzymes).[6,7]

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

Although there are no active clinical trials involving lncRNAs in MM, several are investigating the use of lncRNAs as biomarkers and therapeutic targets for other cancer types. Some of these are described in MM, highlighting their translational potential. For instance, MALAT1 is evaluated as a biomarker of oral squamous cell carcinoma in 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 lncRNAs, with multiple studies regarding its involvement in disease progression and therapy resistance.[15,16] NEAT1 is located on chromosome 11 (11q13.1) and encodes for two isoforms: NEAT1_1 and NEAT1_2. These are derived from alternative transcript maturation events in the 3' UTR 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 lncRNAs, are involved in different neoplastic diseases, including breast[19], colorectal[20], gastric[21], lung[22] and ovarian cancer.[23] Taken together, these evidences indicate that NEAT1 is a broadly relevant cancer-associated lncRNA.

This is particularly relevant in MM, where plasma cells constantly produce large quantities of immunoglobulins and experience chronic endoplasmic reticulum (ER) 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 suggest that NEAT1 exerts pleiotropic effects, favoring neoplastic growth and dissemination, stress resistance, immune escape, and resistance to therapy. Like other lncRNAs, multifunctional nature of NEAT1 makes it challenging to define a single, predominant biological role. Given the novelty of this topic and the limited evidences, 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 multiple myeloma development

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

NEAT1 sustains MM 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 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 processes and resistance to anti-cancer 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). PIP_3 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 lead 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] MiRNA miR-524-5p acts as tumor suppressor in various cancer types.[31–35] According to the Authors, miR-524-5p targets and suppresses HDAC1, a histone deacetylase that suppresses PTEN expression. In this process, NEAT1 acts as a sponge for miR-524-5p, preventing it from inhibiting HDAC1, thereby leading to HDAC1 upregulation and subsequent 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. TCF/Lef1 complex causes the transcription of several genes such as metalloproteases (MMPs) and c-Myc, promoting tumor proliferation and invasion.[36–38] Regarding NEAT1 in MM, it has been observed that NEAT1 overexpression induced 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, reporting also on possible mechanisms of action. In colorectal cancer, NEAT1 binds DDX5 helicase, which interacts with β-catenin and TCF4, promoting their transcriptional activity (**Figure 1B1**).[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 1B2**).[39] In laryngeal squamous cells carcinoma, NEAT1 acts as ceRNA for miRNA miR-411-3p, which regulates the expression of the transmembrane receptor FZD3, member of the WNT receptors family. FZD3 is then expressed at a higher level, favoring the pathway activation (**Figure 1B3**).[40] These findings suggest a direct role of NEAT1 in regulating Wnt/β-catenin pathway: its role and the underlying mechanisms of actions remains to be further dissected and investigated within the context of the MM.

NEAT1 also plays a role in the formation of the mitotic fuse 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 the 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 the cell cycle progression and contributing to MM development (**Figure 1C**). However, the mechanism of action through NEAT1 regulates TPX2 is not clear.[45] This is also the only evidence of NEAT1's 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 NEAT1’s pleiotropic functions.

NEAT1 confers cell resistance to stress conditions

This is a crucial aspect of tumor development, given that cancer 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 ATM and DNA-PKcs, together with upregulation of the related targets (i.e. RPA32 and CHK2), which are involved in the repair of the DNA double-strand breaks (DSBs).[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. Authors have 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 DSBs has been described through the METTL3/NEAT1/CHD4 signaling axis, within the context of osteosarcoma cells. In response to DSBs, the upregulated NEAT1 translocates into the nucleus, where it undergoes the addition of N6-methyladenosine (m□A), 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 ER. Its purpose is to re-establish proteostasis. Activation of the UPR may provide an overall advantage to tumor cells, as result of enhanced resistance to apoptosis induced by the accumulation of misfolded proteins. This mechanism is activated by ER 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 the transcription factor 7 (TCF7). TCF7 induces the expression of the UPR system sensor IRE1α, thereby promoting the activation of the UPR (**Figure 2B1**).[38] However, in a letter published in 2019, the same Authors demonstrated that increased NEAT1 expression results in the downregulation of UPR pathways. Constitutive activation of the UPR results in apoptosis, thus making Authors hypothesizing a role of NEAT1 in promoting cells 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 2B2**).[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 favor neoplastic growth. These are interesting hypotheses, although they are not supported by much experimental evidences. 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 the subsequent activation of the interferon (IFN)-mediated inflammatory response. Furthermore, based on observations from several studies, Authors 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-loops 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 ceRNA in the NEAT1/miR-485-5p/ABCB8 axis. NEAT1 acts as ceRNA for the miRNA miR-485-p, causing the 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, appears to protect the cell against oxidative stress and gives chemotherapeutic resistance, such as to 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 ABCB8’s function.[57]

NEAT1 plays a central role in cellular stress resistance by acting at multiple levels. It promotes the repair of DSBs and regulates the R-loops within the nucleus, modulates UPR signaling in the ER, 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.

NEAT1 promotes immune escape

In addition to its involvement in several molecular mechanisms in MM cells, NEAT1 may also regulates the TME. In recent years, the interest in the TME and its bidirectional interactions with tumor cells have significantly grown. 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 contribute to the tumor development and progression. Also, NEAT1 is involved in this context, particularly by acting on macrophages and on Natural Killer (NK) cells.[58–60]

In MM, infiltrating macrophages, known as tumor-associated macrophages (TAMs), 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 contribute 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 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 maturation and function. Consistent with the observations involving NEAT1, it has been hypothesized that EZH2 may suppress NK cells activity via PBX1 repression.[65]

Although the evidences regarding NEAT1's involvement in TME modulation remain limited, there are diverse mechanisms of action 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 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 understand the molecular mechanisms that drive treatment resistance.

Dexamethasone (DEX) is one of the most widely used glucocorticoids in the treatment of MM. It binds the cytosolic glucocorticoid receptor (GR), forms a complex that translocates into the nucleus and modulates gene expression. DEX 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 ER stress. NEAT1 is implicated in DEX resistance in MM. NEAT1 acts along the NEAT1/miR-193a/MCL1 axis as ceRNA for the miRNA miR-193a, which can suppress the expression of the anti-apoptotic protein MCL1. Elevated levels of NEAT1 inhibit the miR-193a activity, favoring MCL1 expression and contributing to MM cells survival (**Figure 4A**).[67] Furthermore, high NEAT1 levels are associated with greater DEX resistance, thus suggesting a potential predictive and prognostic role of NEAT1.[68]

The high rate of immunoglobulins 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 remain not fully elicited and 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 reinforce 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.

NEAT1 potential role 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 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 (OS) in MM.[16,59,71] Moreover, high expression of NEAT1 levels is associated with poor prognosis of MM patients.[16] The first study on NEAT1 in MM highlighted its down-regulation in BM-derived plasma cells as compared to the normal cellular counterpart in healthy donors (HDs). However, further investigations have shown that NEAT1 is expressed at a higher levels in MM than in HDs and patients with other hematological 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 BM and peripheral blood of MM patients, and higher NEAT1 expression is associated with DEX resistance and a critical prognosis.[67,68]

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

A recent study on MM cells demonstrates that the knock-down of NEAT1 have similar biological effects compared to treatment with AURKA inhibitors, and these two approaches similarly impact molecular pathways.[74] The combination of NEAT1 silencing and the inhibitors of AURKA strongly impact on the organization of microtubule and on the assembly of mitotic spindle resulting in cell death. Moreover, MM patients that simultaneously present high levels of NEAT1 and AURKA exhibit a poor clinical outcome.[45] A low level of NEAT1 impact on the miR-485-5p/ABCB8 axis altering biological processes in MM cells. Further investigation should be addressed 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 the Locked Nucleic Acid (LNA)-Gapmer antisense oligonucleotide (ASO) 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 chemo-sensitizing effect in combination with the conventional administered drugs for the treatment of MM (e.g. bortezomib and carfilzomib).[15]

Among currently available RNA-targeting modalities, ASOs represent at present 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 effect exerted by other nuclear lncRNAs (e.g. MALAT1) remains 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 the pathogenesis, progression, and drug resistance within the context of MM.

The Literature has clearly shown how NEAT1 exerts 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 patient outcomes, 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 ASO 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 tumor microenvironment warrant further in-depth investigation. Indeed, data related to mechanism of action of NEAT1 are limited. Observations made in other neoplastic contexts were included in this review, with the aim to: (i) to propose a mechanism that could address current gaps in MM research; (ii) to establish 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 lncRNAs 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 within the context of MM remains an open question. 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 lncRNAs 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 within clinical settings. Ultimately, advancing our understanding of NEAT1 will facilitate the translation of these experimental insights into novel, targeted therapeutic strategies that improve patient outcomes and offer new hope in the management of multiple myeloma.

ABBREVIATIONS

ASO: antisense oligonucleotide
AURKA: Aurora kinase A
BM: Bone marrow
ceRNA: competing endogenous RNA
DEX: Dexamethasone
DSBs: DNA double-strand breaks
ER: endoplasmic reticulum
GR: glucocorticoid receptor
HDs: healthy donors
IFN: interferon
LNA: Locked Nucleic Acid
lncRNAs: Long non-coding RNAs
NK: Natural Killer
MMPs metalloproteases
mRNAs: microRNAs
MGUS: Monoclonal gammopathy of undetermined significance
MM: Multiple myeloma

m^{6}A: N6-methyladenosine

NEAT1: Nuclear Enriched Abundant Transcript 1

ncRNAs: Non-coding RNAs

OS: overall survival

PIP2: phosphatidylinositol 4,5-bisphosphate

PIP3: phosphatidylinositol-3,4,5-trisphosphate

PTEN: phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase

PRC2: Polycomb Repressive Complex 2

SMM: Smouldering multiple myeloma

TCF/Lef1: T cell factor/lymphoid enhancer factor-1

TCF7: transcription factor 7

TME: tumor microenvironment

UPR: unfolded protein response

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TABLES AND FIGURE LEGENDS

Table 1

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/DSBs → DNA DSBs 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 chemotherapeutic resistance	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

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

Each row indicates a published NEAT1–dependent interaction linked to biological processes relevant to MM. 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.

Figure 1. Potential mechanisms supporting NEAT1-dependent modulation of MM 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 suppress PTEN, thereby favoring the pathway activation.

(B) Proposed mechanisms of NEAT1 involvement in the Wnt/β-catenin pathway, described in different tumor contexts. (**B1**) In colorectal cancer, NEAT1 binds the RNA helicase DDX5, which interacts with β-catenin and TCF4, enhancing their transcriptional activity. (**B2**) In glioblastoma, NEAT1 recruits EZH2 to promote H3K27 methylation, thereby suppressing the expression of Wnt pathway inhibitors AXIN2, GSK3β, and ICAT. (**B3**) In laryngeal squamous cell carcinoma, NEAT1 acts as a ceRNA 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.

Figure 2. Potential mechanisms supporting NEAT1-dependent modulation of MM cell resistance to stress-related conditions.

(A) NEAT1 promotes DNA DSBs repair. 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 DSBs repair.

(B) NEAT1-mediated activation of the UPR and DNA repair inhibition. (**B1**) 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. (**B2**) 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 ceRNA for miR-485-5p, leading to upregulation of ABCB8. The mitochondrial membrane transporter ABCB8 protects cells against oxidative stress and promotes chemotherapeutic resistance.

Figure 3. Potential mechanisms supporting NEAT1-dependent enhanced immune escape in MM.

(A) NEAT1-mediated promotion of immune escape via macrophage M2 polarization. NEAT1 functions as a ceRNA 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 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.

Figure 4. Potential mechanisms supporting NEAT1-dependent modulation of drug resistance in MM.

(A) NEAT1-mediated DEX resistance. NEAT1 functions as a ceRNA for miR-193a, preventing miR-193a from repressing the anti-apoptotic protein MCL1. Elevated NEAT1 levels sustain MCL1 expression, promoting survival of MM cells and contributing to DEX 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 ASO) 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.

Figure 1

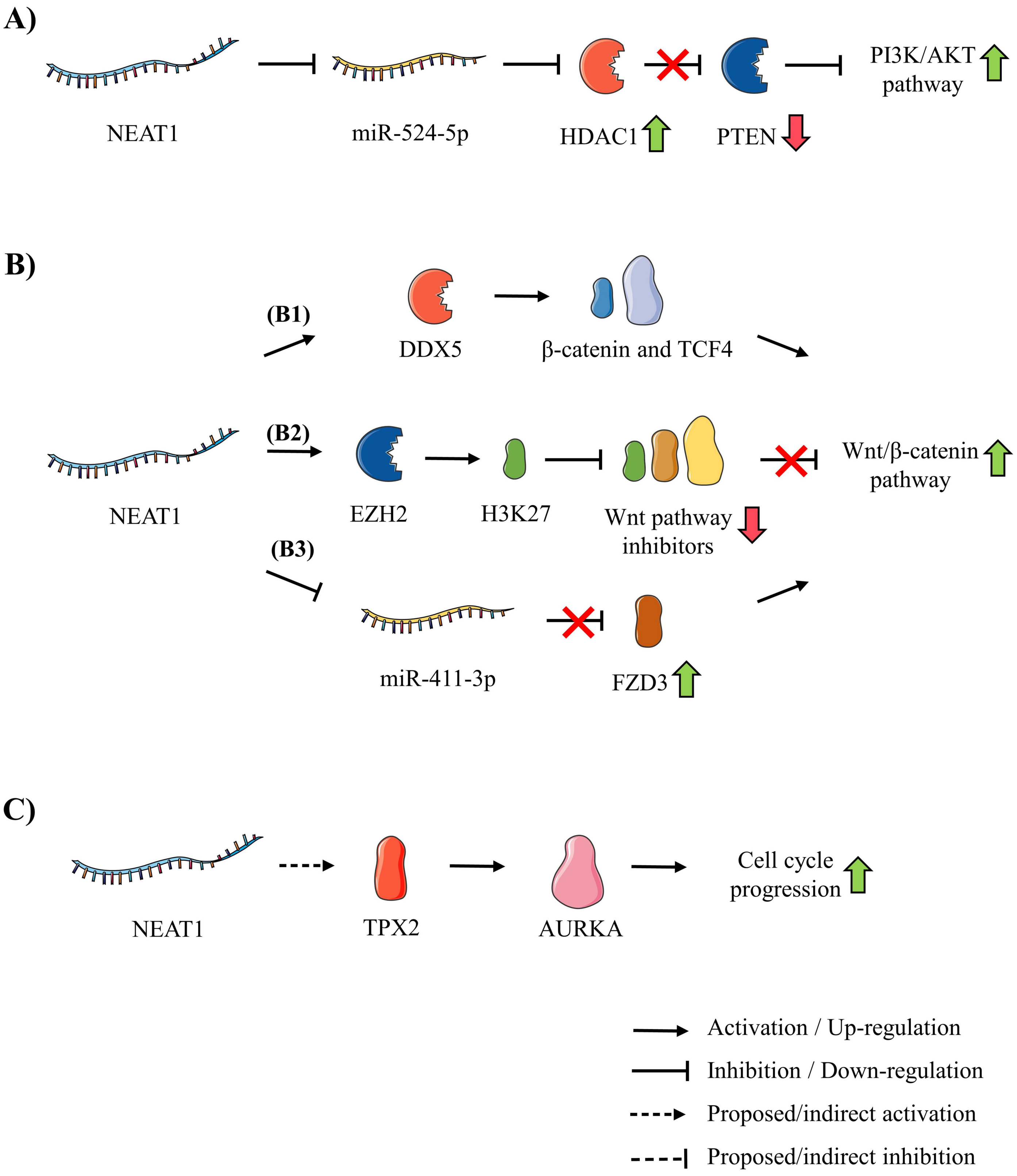

A)
NEAT1
miR-524-5p
HDAC1
PTEN
PI3K/AKT pathway
B)
(B1)
DDX5
β-catenin and TCF4
(B2)
NEAT1
EZH2
H3K27
Wnt pathway inhibitors
Wnt/β-catenin pathway
(B3)
miR-411-3p
FZD3
C)
NEAT1
TPX2
AURKA
Cell cycle progression
Activation / Up-regulation
Inhibition / Down-regulation
Proposed/indirect activation
Proposed/indirect inhibition

Figure 2

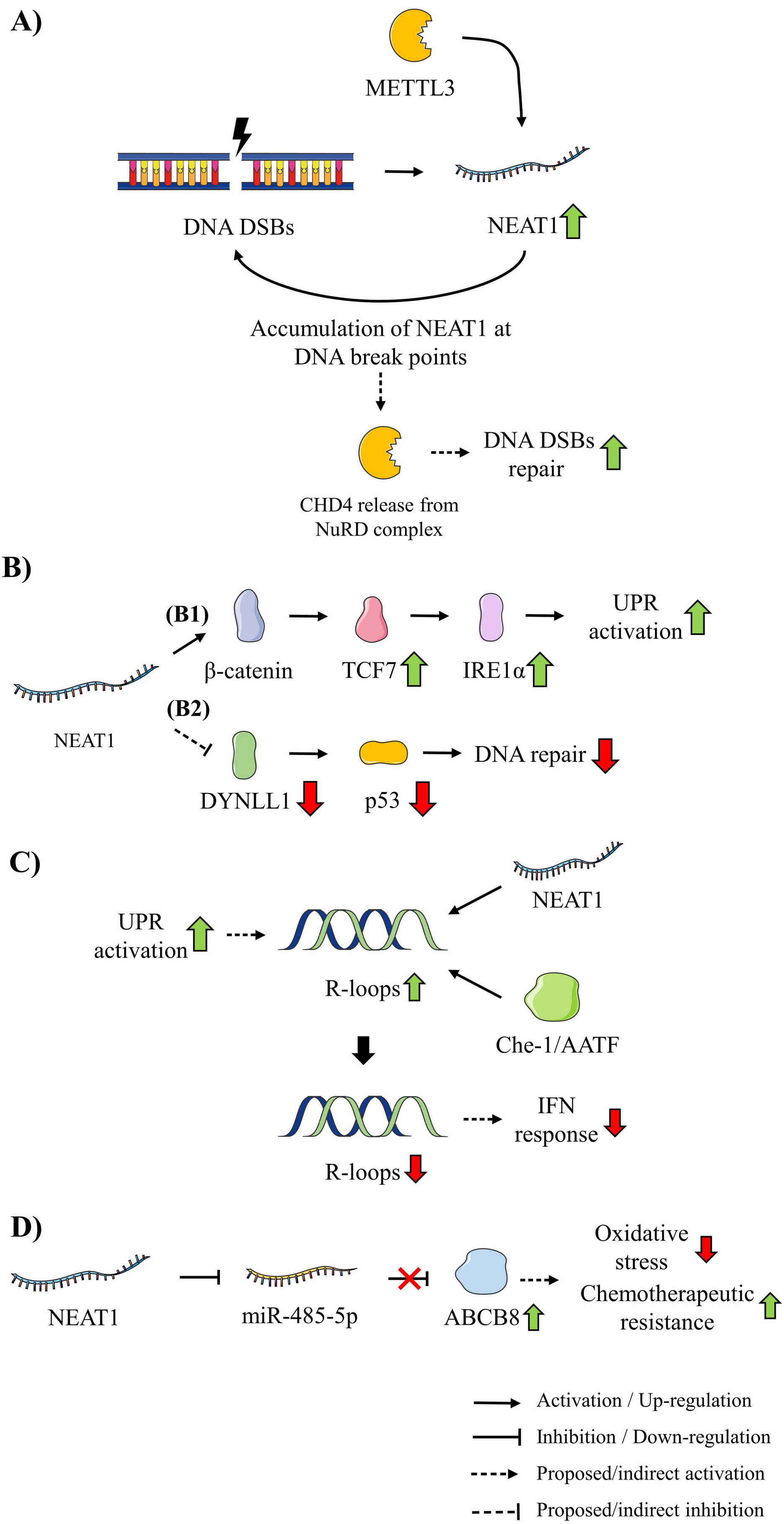

A)
METTL3
DNA DSBs
NEAT1
Accumulation of NEAT1 at DNA break points
CHD4 release from NuRD complex
DNA DSBs repair
B)
(B1)
β-catenin
TCF7
IRE1α
UPR activation
NEAT1
(B2)
DYNLL1
p53
DNA repair
C)
NEAT1
UPR activation
R-loops
Che-1/AATF
IFN response
R-loops
D)
NEAT1
miR-485-5p
ABCB8
Oxidative stress
Chemotherapeutic resistance
Activation / Up-regulation
Inhibition / Down-regulation
Proposed/indirect activation
Proposed/indirect inhibition

Figure 3

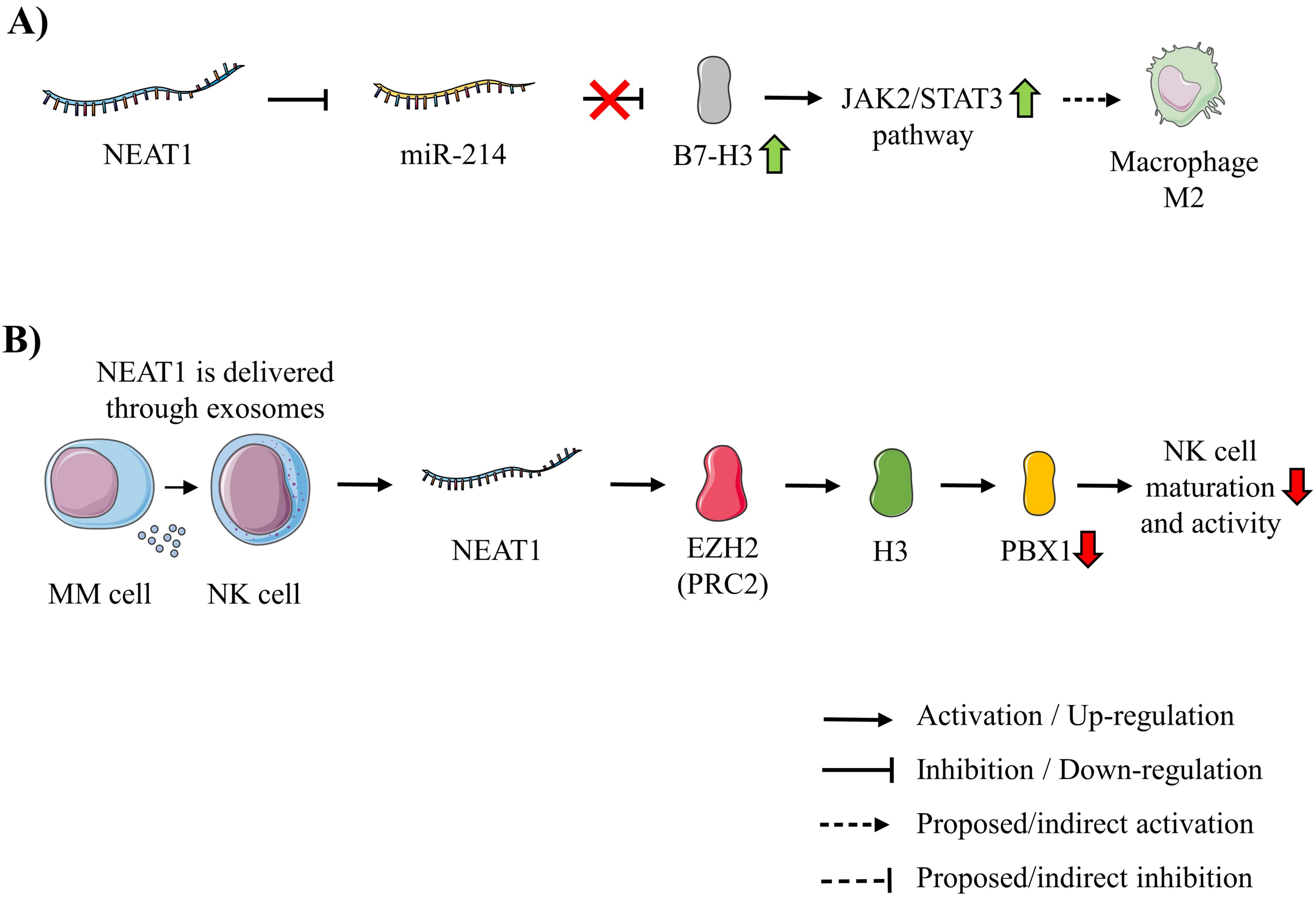
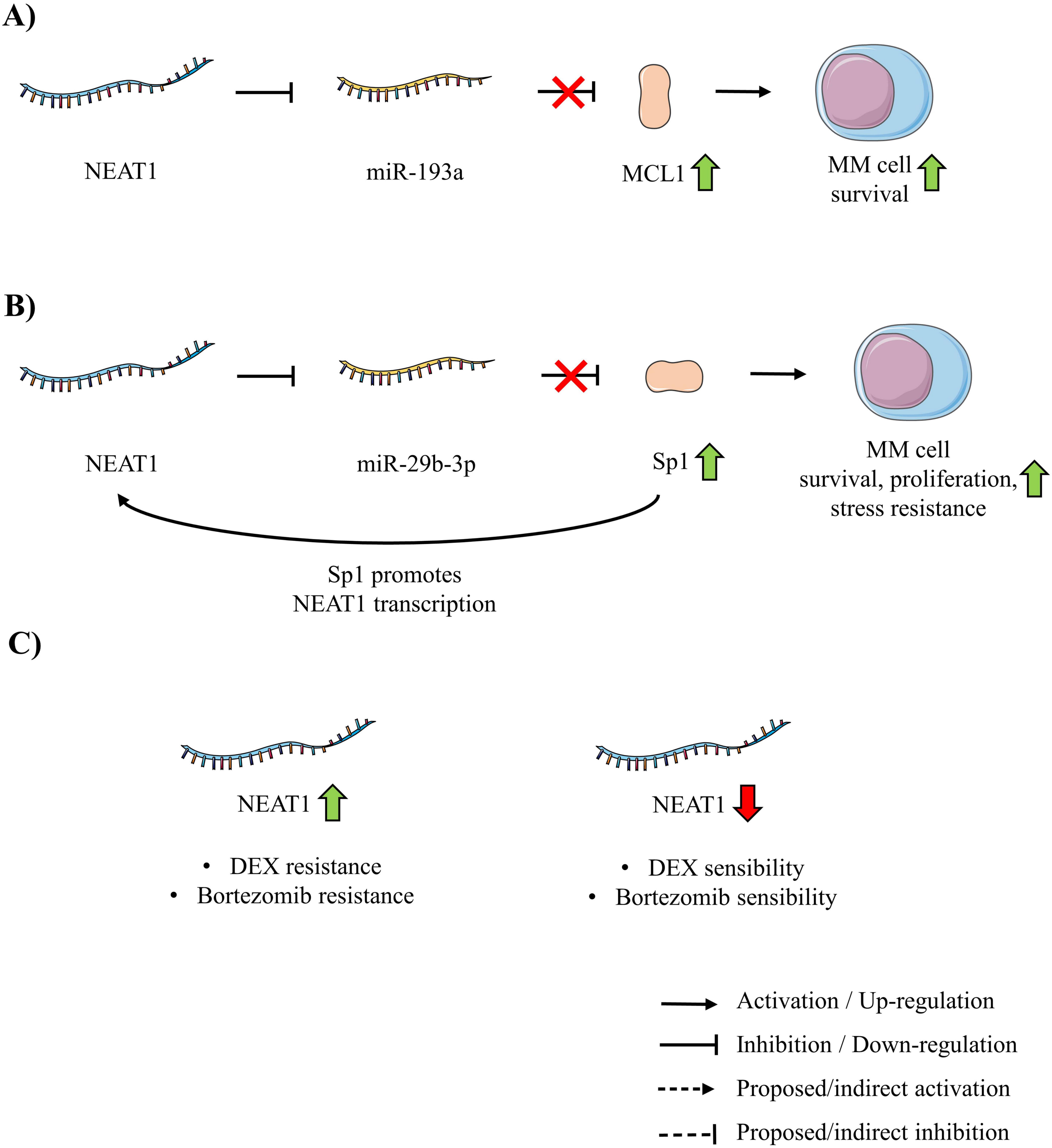

A)
NEAT1
miR-214
B7-H3
JAK2/STAT3 pathway
Macrophage M2
B)
NEAT1 is delivered through exosomes
MM cell
NK cell
NEAT1
EZH2 (PRC2)
H3
PBX1
NK cell maturation and activity
Activation / Up-regulation
Inhibition / Down-regulation
Proposed/indirect activation
Proposed/indirect inhibition

Figure 4


A)
NEAT1
miR-193a
MCL1
MM cell survival
B)
NEAT1
miR-29b-3p
Sp1
MM cell survival, proliferation, stress resistance
Sp1 promotes NEAT1 transcription
C)
NEAT1
• DEX resistance
• Bortezomib resistance
NEAT1
• DEX sensibility
• Bortezomib sensibility
Activation / Up-regulation
Inhibition / Down-regulation
Proposed/indirect activation
Proposed/indirect inhibition