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Review

Defining the transcriptional routes controlling lncRNA NEAT1 expression: implications in cellular stress response, inflammation, and differentiation

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Abstract
NEAT1 (Nuclear Enriched Abundant Transcript 1) is a long non-coding RNA playing a critical role in both physiological and pathological settings by directly modulating a variety of biological events, including transcriptional regulation, RNA processing, and chromatin remodeling. Multiple evidence demonstrated that different transcription factors and signaling pathways modulate biological processes by tightly regulating NEAT1 expression. These regulatory mechanisms act at different levels, allowing cells to rapidly modulate NEAT1 expression and dynamically respond to sudden changes in cellular conditions. In this review, we summarize and discuss the transcriptional routes controlling NEAT1 expression, emphasizing recent evidence showing the pivotal role of NEAT1 in regulating important biological processes, such as cellular stress response, inflammation, and cell differentiation.

Keywords Transcription factors · NEAT1 · DNA damage · Cell differentiation · Inflammation

1 Introduction

Long non-coding RNAs (lncRNAs) are a class of untranslated transcripts longer than 200 nucleotides that act as key regulators of gene expression at different levels [1, 2]. Among them, NEAT1 (Nuclear Enriched Abundant Transcript 1), an evolutionarily conserved lncRNA with orthologs in human, mouse, horse and opossum [3, 4], stands out for its critical role in both physiological and pathological contexts by directly participating in a variety of biological processes, including DNA damage response (DDR), cell growth, apoptosis, cell differentiation, and inflammation [5]. *NEAT1* gene is located on chromosome 11 and encodes two overlapping isoforms, namely NEAT1_1 (3.7 kb) and NEAT1_2 (22.7 kb), sharing promoter and 5′-end (Fig. 1a). The two isoforms are generated by alternative transcriptional termination and processing: while the shortest transcript NEAT1_1 follows the canonical polyadenylation and termination steps, NEAT1_2 isoform is transcribed when RNA polymerase II reads through the termination signal and its 3′-end, which is generated by RNase P cleavage, is stabilized by a triple helix structure instead of the classic poly-A tail [6]. Although the two isoforms of NEAT1 are transcribed from the same promoter, their expression pattern does not entirely overlap. The short isoform NEAT1_1 is

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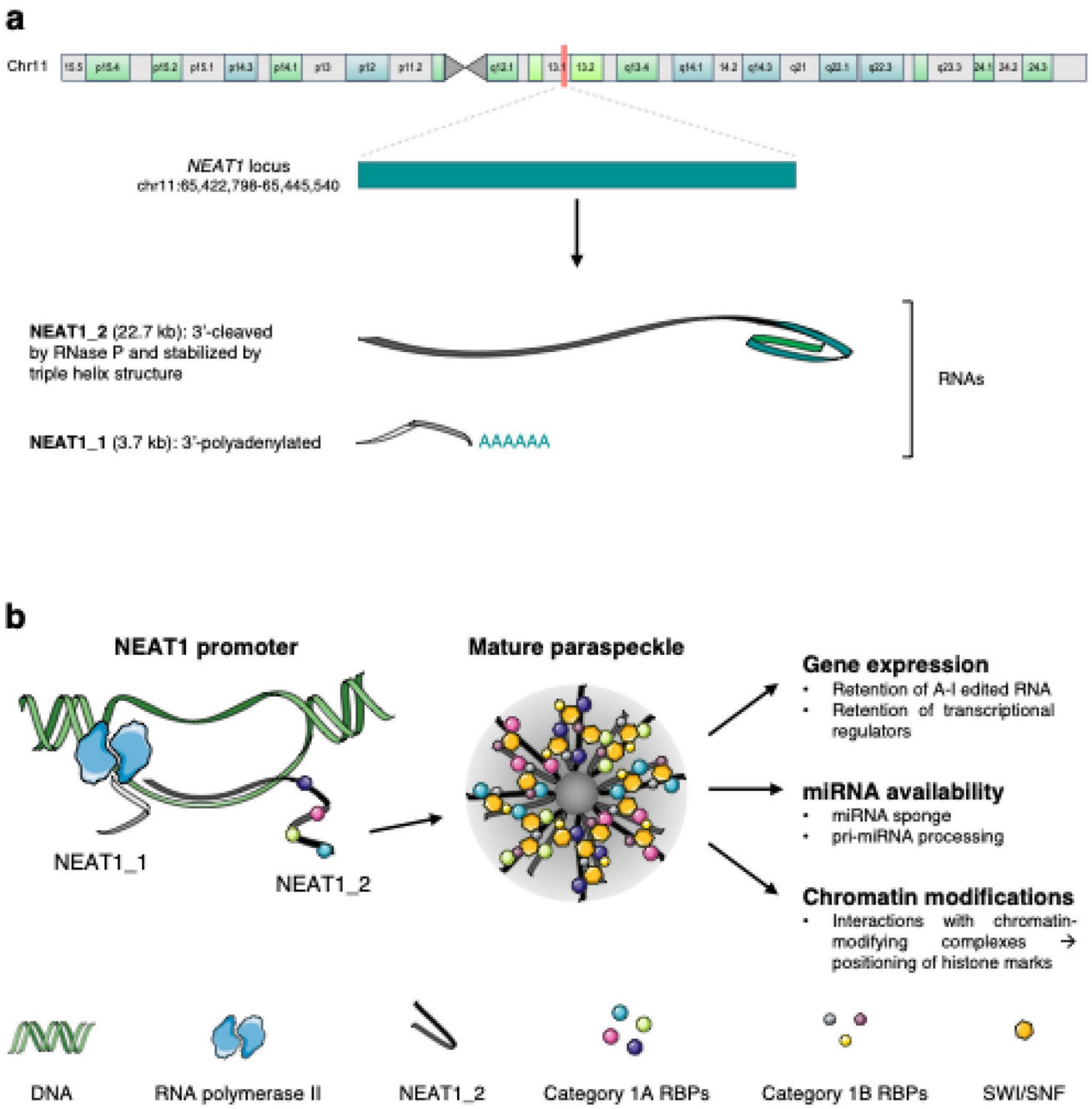

Fig. 1 NEAT1_2 is an essential architectural component of nuclear paraspeckles. **a** *NEAT1* gene located on chromosome 11 encodes 2 overlapping isoforms, simultaneously transcribed by the RNA Polymerase II. **b** The longest isoform, NEAT1_2, acts as a scaffold for Category 1A proteins to initiate paraspeckles biogenesis (Step 1). In Step 2, Category 1B proteins and the chromatin remodeling complex SWI/SNF join the NEAT1_2-RNP complexes formed in the first step, giving rise to mature paraspeckles (*left*). These spheroid nuclear condensates play several key cellular functions (*right*). The figure was drawn in part using and/or modifying images from Servier Medical Art, by Servier (http://smart.servier.com)

present in all tissues and is preferentially expressed in undifferentiated cells [7, 8]. In contrast, the long isoform NEAT1_2 is expressed in specialized tissues or induced in response to various forms of cellular stress. The physiological relevance of NEAT1 isoforms has been elegantly demonstrated through the analysis of isoform-specific knockout mice. Global Neat1 gene deletion results in lactation and fertility defects, along with alterations in DNA damage response and impaired cell growth under oncogenic stress [9, 10]. These defects are absent in NEAT1_1-specific knockout cells [11], suggesting that NEAT1_2 is the most physiologically relevant NEAT1 isoform.

Notably, the longer isoform NEAT1_2 is required for the proper assembly of paraspeckles (PSs) [11, 12], dynamic phase-separated nuclear condensates assembled through the association of NEAT1_2 with several RNA binding proteins (RBPs), generically defined as PSPs (paraspeckles-associated proteins), and chromatin factors [12, 13].

The assembly of the PSs is quite complex and highly dynamic, as it can be induced in response to specific cellular stimuli [12, 14]. Architecturally, different PSPs are recruited on the longer isoform of NEAT1 (*i.e.*, NEAT1_2), which acts as a scaffold to generate a core–shell spheroidal structure. The central region of NEAT1 is embedded within the paraspeckles' core, where it binds several RBPs, while its 5'- and 3'- ends remain in the outer layer. Paraspeckles biogenesis follows an ordered two-step process, in which first, individual NEAT1_2-RNP (ribonucleoprotein) complexes are generated, and then several different complexes assemble into the mature structure of PSs (Fig. 1b). To date, seven key paraspeckle proteins have been identified and classified into Category 1A or 1B, based on whether they function in the first or second phase, respectively. Category 1A comprises Non-POU domain-containing octamer-binding protein (NONO), Splicing factor, proline- and glutamine-rich (SFPQ), RNA binding motif protein 14 (RBM14), and heterogeneous nuclear ribonucleoprotein K (hnRNP K), while Category 1B includes FUS RNA binding protein (FUS), DAZ associated protein 1 (DAZAP1), and heterogeneous nuclear ribonucleoprotein H3 (hnRNP H3) [15, 16]. Another essential component of paraspeckles is the chromatin remodeling complex SWI/SNF that bridges Category 1A and 1B proteins with NEAT1_2, thereby orchestrating the protein–protein interactions necessary for paraspeckle stability [17]. Paraspeckles are crucial for controlling gene expression via different mechanisms (Fig. 1b). First, PS can indirectly influence transcription via A-to-I (Adenine to Inosine) RNA editing mediated by ADAR (adenosine deaminase enzyme RNA specific). Through direct interactions with PSPs such as NONO and SFPQ, the A-to-I edited RNAs are retained within paraspeckles, leading to the inhibition of their translation [18]. Similarly, PSs can sequester proteins involved in gene regulation, such as transcriptional activators or repressors, influencing their ability to bind to their target genes [19, 20]. Second, paraspeckles affect miRNAs availability and biogenesis: PS can either sponge miRNAs to prevent their activity [21] or enhance pri-miRNA processing by the Drosha-DGCR8 Microprocessor complex [22]. Third, paraspeckles are involved in the positioning of specific histone marks around gene promoters that induce or repress transcription by the direct interaction between NEAT1 and several chromatin-modifying enzymes, such as p300/CBP, SWI/SNF or Polycomb Repressive Complex 2 (PRC2) [17, 23–25]. Consistently, NEAT1 is predominantly associated with transcription start sites [26], likely through the formation of sequence-specific RNA:DNA triple helix structures [27].

Given the profound impact of NEAT1 and paraspeckles on a wide range of biological processes, it is not surprising that NEAT1 expression is tightly regulated by multiple transcription factors and signaling pathways [5]. Epigenetic modifications, such as histone acetylation on NEAT1 promoter, provide another layer of regulation, influencing NEAT1 transcription [28]. Additionally, the stability of the NEAT1 transcript is modulated by several factors, including A + U-rich (ARE) binding/degradation factor 1 (AUF1), Hu antigen R (HuR), serine/arginine-rich splicing factor 1 (SRSF1), methyltransferase 3 (METTL3), and miR-140 [29–32]. Finally, NEAT1 expression can be regulated in terms of 3'-end processing. For instance, TAR DNA-binding protein 43 (TDP-43) induces the production of polyadenylated NEAT1_1, thereby inhibiting NEAT1_2 production and reducing paraspeckle formation [8]. In contrast, cleavage and polyadenylation specific factor 6 (CPSF6), nudix hydrolase 21 (NUDT21), and hnRNPK regulate the 3' RNA cleavage and polyadenylation of NEAT1_2, facilitating the formation of nuclear paraspeckles [16].

In this review, we aim to expand the recent view linking NEAT1_2 transcriptional regulation with the activation of cellular differentiation programs [33, 34] by providing a comprehensive perspective on the functional link between NEAT1 transcriptional control and the modulation of key biological processes. We will describe how transcription factors, in response to specific stimuli, modulate the RNA levels of NEAT1, which, in turn, affects the stability, transcription, and localization of its effectors during cellular stress response, inflammation, and cell differentiation.

2 Transcriptional control of NEAT1 during cellular stress response

2.1 p53 and DNA damage response

One of the most well-characterized functions of NEAT1 is related to its role in maintaining cellular homeostasis in response to various stresses, including DNA damage and replication-related injuries [9, 35] (Fig. 2). A crucial molecular pillar of the DDR is the tumor suppressor p53, a transcription factor known as the "guardian of the genome" due to its crucial role in preserving genomic stability. By responding to different stimuli, p53 regulates a wide range of cellular functions, thus determining the cell's fate [36, 37]. In unstressed conditions, p53 protein levels are maintained low by

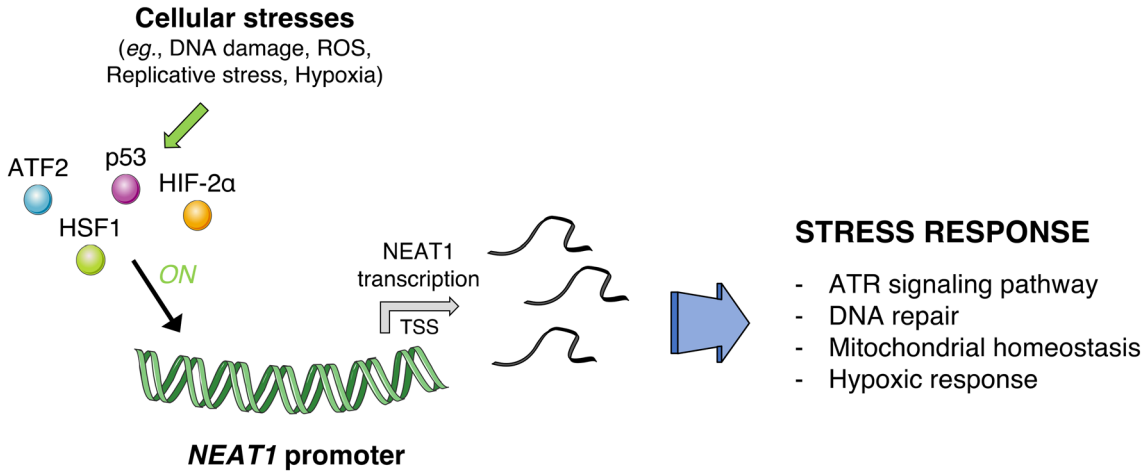

Fig. 2 NEAT1 is induced in response to a variety of cellular insults. The indicated cellular stresses trigger the activation of transcriptional factors (colored spheres) that, in turn, bind the specific DNA consensus motif in the *NEAT1* promoter to induce its transcription. NEAT1-mediated responses to cellular stress are shown. The figure was drawn in part using and/or modifying images from Servier Medical Art, by Servier (http://smart.servier.com)

the E3 ligase MDM2, which induces the p53 proteasome-dependent degradation [38]. In response to a wide range of endogenous and exogenous stresses, including replicative and transcriptional stresses, hypoxia, reactive oxygen species (ROS), ionizing radiation (IR), radio-mimetic drugs, and ultraviolet (UV) light, p53 undergoes a variety of post-translational modifications which dampen its association with MDM2, thereby enhancing its protein stability [39]. Once activated, p53 drives the expression of a subset of transcriptional targets, which ultimately impact cell cycle progression, apoptosis, cell metabolism, or DNA repair, depending on the type and intensity of the stress [39, 40].

Several reports have demonstrated the ability of p53 to induce the expression of NEAT1 in response to DNA damage in different cellular contexts [9, 41–43]. In human and mouse cells treated with different DNA-damaging inducing agents, p53 can induce the transcription of *NEAT1* isoforms by binding a canonical p53 DNA-binding site located in its proximal promoter. The p53-dependent induction of NEAT1 also determines the assembly of paraspeckles, nuclear structures that heavily depend on the expression of the NEAT1_2 transcript (long isoform) [9].

Although the NEAT1-dependent response to cellular stresses and the underlying molecular effectors are still not fully defined, several data suggest that NEAT1 upregulation by p53 might prevent excessive accumulation of DNA damage in response to oncogenic stimuli [9]. Indeed, oncogenic stress, both in vitro and in vivo, induces NEAT1 and the consequent assembly of paraspeckles in a p53-dependent manner, suggesting that NEAT1 might be one of the p53 effectors that modulate the oncogenic stress signaling. In line with this concept, it has been shown that NEAT1 is essential for activating the ataxia telangiectasia and Rad3-related protein (ATR) signaling, a key component of the cellular response to replication-associated damage, such as replication fork stalling and lesions [9]. Lack of NEAT1_2 reduces the cell's ability to respond adequately to damage, decreasing the effectiveness of the ATR signaling pathway [9]. The ability of NEAT1 to modulate replication-associated damage is particularly relevant in pre-neoplastic cells, where oncogene-induced replicative stress generates numerous replication forks, and NEAT1 may contribute to limiting replication stress damage, preventing excessive DNA damage [9].

The increased DNA damage observed in NEAT1-deficient cells upon genotoxic stress could be associated with defects in the DNA repair process. In line with this idea, several data have characterized the involvement of NEAT1 in the DNA damage repair process in different human tumors. In human multiple myeloma cell lines (HMCLs), NEAT1 silencing by LNA-gapmeR induces a marked alteration in the expression of genes and proteins involved in the DNA repair process, particularly those related to homologous recombination (HR) [44, 45]. NEAT1 silencing induces the downregulation of RAD51 recombinase, checkpoint kinase1 and 2 (CHK1, CHK2), replication protein A 32 (RPA32), and breast cancer susceptibility gene 1 (BRCA1), which are DNA repair-related proteins crucial for the recognition and repair of DNA lesions. These molecular events are associated with increased levels of genomic damage, strengthening the role of NEAT1 in maintaining genomic integrity. These results were corroborated in human ovarian cancer cell lines where the NEAT1 targeting approach has been exploited to increase the cytotoxicity of poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi). In detail, upon NEAT1 depletion, human ovarian cancer cells treated with double-strand breaks (DSBs)-inducing

agents significantly reduce RAD51 foci, suggesting a decreased HR repair efficiency. In line with these observations, NEAT1 depletion sensitizes cancer cells to PARPi-induced cell death [46].

A further link between the DNA repair system and the regulation of NEAT1 expression is the ability of BRCA1 to modulate NEAT1 expression in human breast normal and cancer cells, and in murine mammary gland [47]. Besides playing an important role in the DNA-repair processes, BRCA1 is a powerful transcriptional regulator by associating with different transcription factors [48]. BRCA1 binds to the *NEAT1* promoter and represses its transcription in breast cancer cells, likely by recruiting other transcriptional factors [47].

A recent report suggests an additional mechanism by which NEAT1 might modulate DNA damage repair in human cells. During DNA damage response, the methyltransferase METTL3 catalyzes m6A methylation on NEAT1, thus promoting its accumulation at DSBs. Here, NEAT1 colocalizes with P53 Binding Protein 1 (53BP1) and fosters the recruitment of damage response proteins, such as chromodomain helicase DNA binding protein 4 (CHD4), which is released from NEAT1 upon DNA damage and contributes to the regulation of histone acetylation at DNA damage sites [30]. NEAT1 also modulates 53BP1 activity by interacting with the Tudor Interacting Repair Regulator (TIRR), an RBP that interacts directly with 53BP1, restricting its access to DSBs [49]. NEAT1-TIRR interaction (specifically the short NEAT1_1 isoform) destabilizes the TIRR/53BP1 complex, promoting 53BP1's function in specific cell cycle phases.

Altogether, these findings impinge on NEAT1 as a relevant regulator of genomic stability by modulating DDR. However, it is still unclear how NEAT1 activity in the DDR is related to its role as an essential component of the paraspeckles. It is important to emphasize that proteins composing paraspeckles, such as NONO, SFPQ, and RBM14, play a central role in the DNA damage response. In particular, NONO and SFPQ are involved in the DSBs repair, both in the non-homologous end joining (NHEJ) and HR pathways, interacting with key proteins such as KU70/KU80, RAD51, and DNA topoisomerase 2-binding protein 1 (TOPBP1) [50, 51]. Moreover, DNA repair mechanisms involve the activation of proteins such as FUS/TLS and BRM/SWI2-Related Gene 1 (BRG1), which promote homologous recombination and genomic stability. Although this evidence suggests a potential involvement of the paraspeckles in DNA repair, it has also been reported that PSs and several PSs-related proteins (*i.e.*, SFPQ, NONO, and Paraspeckle Component 1 PSPC1) do not co-localize with laser-induced DSBs sites [9]. This contrasting data could be explained by an indirect effect of NEAT1-associated paraspeckles on DSBs repair. A possible explanation could be that paraspeckles regulate the availability of proteins directly involved in DNA repair, such as the phosphatase 2A (PP2A) family [9], by releasing or retaining them according to cellular needs, thereby optimizing the DDR. Alternatively, paraspeckles may act indirectly by sequestering RNA-binding proteins, preventing them from interacting with damage sites and freeing up space for more efficient recruitment of DNA repair complexes. Finally, paraspeckles could represent hubs for post-translational modifications involved in ATR kinase activation during the early response phase. In conclusion, further work is needed to clarify the impact of NEAT1 and paraspeckles on DDR.

2.2 Other transcription factors (TFs) regulating NEAT1 expression during cellular stress response

In addition to p53, other transcription factors regulate NEAT1 expression upon different cellular stresses (Fig. 2). In human mesenchymal stem cells (MSC), Activating Transcription Factor 2 (ATF2), a nuclear TF acting as a sensor of mitochondrial damage, has been identified as a positive regulator of NEAT1 in response to mitochondrial stress induced by treatments like FCCP or oligomycin [52]. The ATF2-dependent regulation of NEAT1 controls the assembly of elongated paraspeckles, which in turn enhance the retention of mRNAs codifying mitochondrial proteins. Remarkably, NEAT1 silencing leads to mitochondrial defects such as alteration of mitochondrial DNA (mtDNA), reduced mitochondrial respiration, and extracellular acidification rate (ECAR), suggesting that NEAT1 and paraspeckles are essential effectors of ATF2-mediated mitochondrial homeostasis [52, 53].

The hypoxia-inducible factors (HIFs) have also been characterized as positive regulators of NEAT1 expression. HIFs are heterodimers containing a regulated HIF-α subunit (HIF-1α, HIF-2α or HIF-3α) and a constitutive β-subunit (HIF-1β) [54]. In the presence of oxygen, HIF-α subunits are targeted for proteasome-dependent degradation by the E3 ubiquitin ligase pVHL, which recognizes HIF-α subunits only when they are hydroxylated by the prolyl hydroxylase domain-containing enzymes (PHD1-3). During hypoxia, the hydroxylation of the HIF-α subunits is impaired, resulting in the accumulation of the HIF-α subunits, which enhance the transcription of a variety of target genes involved in cell metabolism, cell growth, and cellular redox homeostasis [54–56]. Mole's group has identified and characterized *NEAT1* as a novel HIF-2α target gene in human cells [57]. Under hypoxic conditions, HIF-2α promotes *NEAT1* transcription by binding to hypoxia-response elements (HREs) in the *NEAT1* promoter. In turn, induced NEAT1 regulates the cellular response to hypoxia by modulating the stability of the HIF complex and the expression of its target genes. NEAT1 thus acts as an effector of HIF, amplifying the hypoxic response. Since tumor cells face hypoxic environments, NEAT1 inhibition could sensitize tumor

cells to apoptosis and reduce their resistance to treatments, representing a potential therapeutic approach to counteract tumor growth and survival [58, 59].

The heat shock response represents an additional cellular defense mechanism involving NEAT1 transcriptional regulation [60, 61]. This signaling pathway is activated in response to elevated temperatures or electrophilic agents to prevent the cytotoxic effect of misfolded and damaged cellular proteins. The central pillar of the heat shock response is the heat shock transcription factor 1 (HSF1) [62]. Under normal conditions, a multichaperone complex consisting of different heat shock proteins (HSP), such as HSP90, HSP70, HSP40, and T-complex protein Ring Complex (TRiC), inactivates HSF1 [62, 63]. In response to proteotoxic stress, HSF1 undergoes a series of post-translational modifications, which ultimately induce its nuclear accumulation, thus enhancing the transcription of genes involved in the repair and clearance of damaged proteins. In human cells, *NEAT1* has been characterized as a novel target gene of HSF1 [64, 65]. Upon activation of the heat shock response pathway, both *NEAT1* transcription and paraspeckles assembly are induced in an HSF1-dependent manner. Notably, in NEAT1-depleted cells, the expression of HSP70, HSP90, and HSP27 is enhanced, indicating that NEAT1 participates in a feedback mechanism to regulate HSF1 activity [65].

Collectively, these results indicate that key stress-related TFs exploit NEAT1, and likely NEAT1-associated paraspeckles, to finely modulate the cellular response to a variety of different insults. For this reason, NEAT1 could represent not only a potential biomarker but also a therapeutic target for strategies designed to enhance the cytotoxic effect of different therapeutical approaches, mainly in human tumors.

3 Inflammation and NEAT1 expression

The term 'inflammation' refers generically to the body's protective response triggered by host cells' recognition of pathogens or endogenous stress signals (*e.g.,* damaged cells) [66, 67]. Although its physiological targets are injury resolution and tissue repair, non-resolving inflammation is a major contributor to many diseases, from autoimmunity to cancer, infection, and aging [68].

The inflammatory process begins with recognition by pattern recognition receptors (PRRs) of evolutionarily conserved structures derived from pathogens (Pathogen-Associated Molecular Patterns, PAMPs) or damaged tissues (Damage-Associated Molecular Patterns, DAMPs). The engagement of PRRs triggers a cascade of cytokines, the release of acute phase proteins, and the progressive infiltration of various immune cells into the tissue. Under physiological conditions, timely removal of the initial stimuli leads to a gradual spontaneous resolution of inflammation and restoration of homeostasis [67]. A dysregulated innate immune response is a primary cause of chronic, unresolved inflammation [68]. Several studies characterized NEAT1 as a key lncRNA in immune cell regulation and inflammation (Fig. 3) [69].

Evidence of the importance of NEAT1 in innate immune response coordination came from a study on myocardial infarction pathogenesis [70]. Transcriptome analysis of PBMCs from post-myocardial infarction patients revealed a strong downregulation of NEAT1 expression with an altered chemokines profile. A subsequent phenotypical and RNA-seq analysis of splenocytes and bone marrow-derived macrophages (BMDMs) from a *Neat1*-KO mouse model reported similar alterations. Both splenocytes and BMDMs exhibited altered responses to lipopolysaccharide (LPS), with impaired cytokine production [70].

In murine macrophages, Zhang and colleagues showed that Neat1 is involved in the proper activity of inflammasomes, protein complexes that activate inflammatory caspases, thus promoting cytokines maturation and pyroptosis [71]. Upon activating signals, paraspeckles disassemble, and Neat1 translocates into the cytoplasm, fostering the assembly of several caspase-1-associated inflammasomes, including NLR family CARD domain-containing protein 4 (NLRC4), absent in melanoma 2 (AIM2), and NLR family pyrin domain containing 3 (NLRP3). Within these macromolecular complexes, Neat1 stabilizes caspase-1 tetramers, thus increasing their proteolytic activity and inducing pyroptosis [71]. The transcriptional activation of Neat1 upstream of inflammasome assembly depends on the specific inflammatory signal.

In LPS-induced murine dendritic cell (DC) maturation, Neat1 expression is regulated by the transcriptional repressor E2F1, which hinders H3K27 acetylation. Accordingly, in mature DCs, the binding of E2F1 to the *Neat1* promoter is significantly reduced. Silencing of Neat1 expression in DC cells is associated with the development of tolerogenic DCs and altered inflammasome activation, thus impairing DCs' pro-inflammatory function [28].

During hypoxia, a well-known inflammasome activator, HIF-1α induces the activation of *Nlrp3* and interleukin (*Il)-1β* genes, while *Neat1* transcriptional activation by HIF-2α is necessary for paraspeckles expansion and correct activation of inflammasomes [71]. HIF-2α-dependent transcription of *NEAT1* may also be involved in Sepsis-Associated Encephalopathy (SAE), a condition in which hypoxia is often present [72]. In murine models of SAE, the increase of Neat1 in neurons during

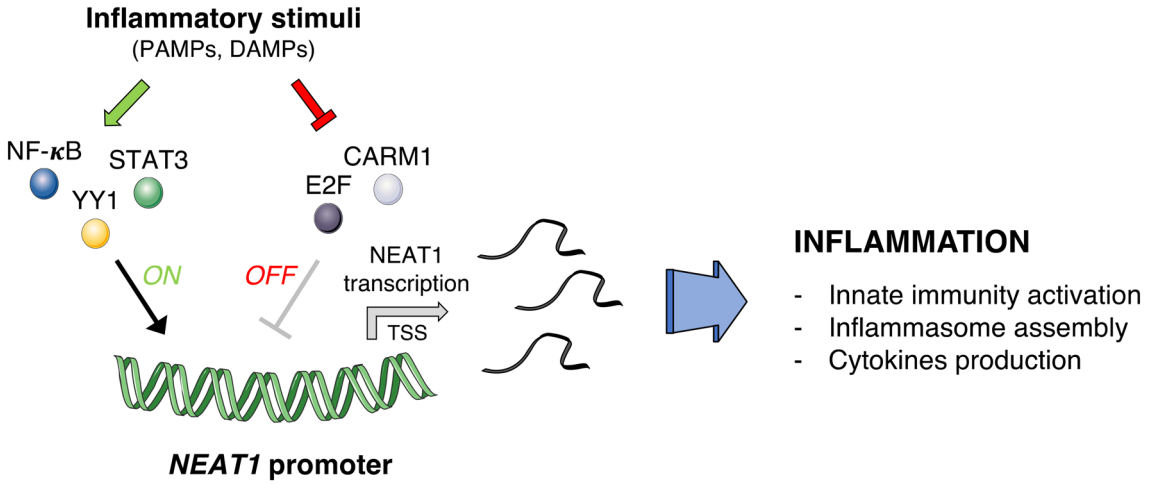

Fig. 3 Inflammation stimuli modulate NEAT1 expression. Inflammatory stimuli activate positive regulators of NEAT1 transcription while suppressing negative regulators. This transcriptional network leads to an increase in NEAT1 RNA levels, which in turn drives inflammation-related outcomes. The figure was drawn in part using and/or modifying images from Servier Medical Art, by Servier (http://smart.servier.com)

sepsis has been associated with impaired neuronal synapse formation due to dysregulation of the interplay between Postsynaptic Density Protein 95 (PSD-95) and Hemoglobin subunit beta (Hbb) [72]. Neat1 inhibits Hbb ubiquitination, leading to its stabilization. The increased levels of Hbb are associated with decreased expression of PSD-95, a master regulator of synaptic plasticity, with a consequent reduction in the number of dendritic spines [72].

In rat microglial cells, the transcription factor Yin Yang 1 (YY1) has been proposed to be responsible for Neat1 upregulation induced by oxygen–glucose deprivation/reoxygenation (OGD/R), a condition that mimics the inflammatory damage associated with ischemic stroke [73]. Although OGD/R does not affect YY1 expression, silencing or mutagenesis of the YY1 binding site on the *Neat1* promoter is sufficient to abrogate Neat1 upregulation. According to the authors, Neat1 promotes the release of proinflammatory cytokines (e.g., TNF-α, IL-1β, and IL-6) via activation of the Wnt/β-catenin pathway [73].

As previously described, a key step in inflammation is the recognition of pathogens or altered host molecules by specific receptors, *i.e.*, Toll-like receptors (TLRs). The increase of NEAT1 levels represents an early event following the activation of TLR3 or TLR4, which detects intracellular double-stranded RNA (dsRNA) and bacterial LPS, respectively [74]. In lung adenocarcinoma, it has been found that TLR4 activation by LPS or Galectin-3 induces NEAT1 expression, and the effect is mediated by the direct binding of NF-κB to *NEAT1* promoter [75]. In acute kidney injury (AKI), inflammasome activation relies on TLR4 triggering [76], and in murine kidney tubular cells, LPS treatment induces Neat1 upregulation by TLR4/NF-κB signaling through direct binding of the p65 subunit of NF-κB to the *Neat1* promoter. Moreover, the translocation of Neat1 from the nucleus to the cytoplasm and its interaction with RACK1 contributes to NLRP3 stabilization. In in vivo murine models, Neat1 knockdown ameliorated kidney injury by reducing proinflammatory IL-6 and CCL2 cytokines and infiltration of immune cells [76]. Similarly, NEAT1 was highly expressed in the plasma of a cohort of sepsis-induced acute respiratory distress syndrome (ARDS) patients and human lung epithelial cells after LPS treatment, thus confirming its pro-inflammatory role. In CLP-induced septic mice, the in vivo silencing of Neat1 increased animal survival, reduced the content of primary inflammatory cytokines (TNF-α, IL-6, and IL-1β), and increased the expression of proliferation markers in lung tissues [77].

Although TLR3 activation requires a completely different stimulus with respect to TLR4, it still induces NEAT1 upregulation, strengthening the concept that NEAT1 modulation represents a key step in the intricate pathways regulating the recognition of pathogens. In detail, both transfection with dsRNA poly I:C and viral infection (with herpes simplex virus 1 (HSV-1) or influenza virus) lead to TLR3/p38-dependent transcriptional activation of *NEAT1* and paraspeckle accumulation. The downstream consequence is the sequestration in the paraspeckles of the SFPQ repressor by NEAT1, thus enabling the expression of many antiviral genes, mainly *IL-8* [20]. Although the transcriptional regulation of *NEAT1* is not fully explained, the involvement of NF-κB or IFNs signaling is excluded, as stimulation with either IFN-α or IFN-β is not sufficient to induce the lncRNA expression [20]. Interestingly, it was recently shown that transfection of poly I:C into HeLa cells reduces the occupancy of coactivator associated arginine methyltransferase 1 (CARM1) co-repressor

on *NEAT1* promoter, mediating NEAT1 increase. The silencing of CARM1 is sufficient to induce NEAT1 transcription at similar levels to those obtained by dsRNA transfection [78]. Signal transducer and activator of transcription 3 (STAT3) has been proposed as the TF responsible for the NEAT1 induction during HSV-1 infection, in which paraspeckles play a pro-viral role by interacting with the viral genome and promoting its replication [79]. Accordingly, STAT3 silencing is sufficient to abrogate the lncRNA increase during HSV-1 infection, and both NEAT1_2 and STAT3 siRNA healed the skin lesions caused by HSV-1 in vivo [79].

In autoimmune uveitis, STAT3-mediated induction of NEAT1 is linked to the pathological role of Th17 cells. Th17 cells rely heavily on IL-23, which acts partially through STAT3 activation. The resulting upregulation of NEAT1 supports the expression of pro-inflammatory IL-17 and IL-23R in two ways: i) by binding NONO in paraspeckle, thus preventing transcriptional repression of *IL-17* and *IL-23R* genes; ii) through the regulation of miR-128-3p/ Nuclear factor of activated T-cells 5 (NFAT5) axis, which allows the expression of RAR-related orphan receptor (ROR)-γ, the master TF for *IL-17* and *IL-23R* [80]. In addition, in rheumatoid arthritis it has been shown that NEAT1 prevents STAT3 ubiquitination [81], possibly further increasing NEAT1 levels in a positive feedback loop.

Collectively, these data indicate that NEAT1 transcriptional modulation is a common event during the inflammatory process. However, although we extensively know about the downstream mechanisms of NEAT1, much remains to be done regarding its transcriptional regulation. Despite the diversity of activating stimuli, NEAT1 plays a unique role in innate immune response coordination due to its ability to act as a scaffold for several proteins and miRNAs. From this perspective, NEAT1 offers a great therapeutic opportunity for autoimmune, inflammatory, and viral diseases, as demonstrated for HSV-1-induced lesions where local inhibition of NEAT1 expression was sufficient to reduce the extent of skin sores [79].

4 NEAT1 and cell differentiation

Cellular differentiation is a tightly regulated process by which pluripotent stem cells acquire specialized functions essential for tissue development, maintenance, and repair. This transition involves intricate changes in gene expression orchestrated by transcription factors and regulatory networks. Among these regulatory mechanisms, the transcriptional control of lncRNAs expression has emerged as a pivotal modulator of cellular fate. In this context, multiple pieces of evidence have elucidated the impact of NEAT1 on cellular differentiation in various biological settings (Fig. 4). Treatment of acute promyelocytic leukemia (APL) cells with all-trans retinoic acid (ATRA) triggers myeloid differentiation in concomitance with NEAT1 induction. Remarkably, ATRA-induced myeloid differentiation is attenuated by NEAT1 inhibition, suggesting that ATRA-induced upregulation of NEAT1 is critical for the proper activation of the APL cell differentiation program. In line with these data, the expression of Promyelocytic leukemia protein (PML)/ Retinoic acid receptor (RAR)α fusion

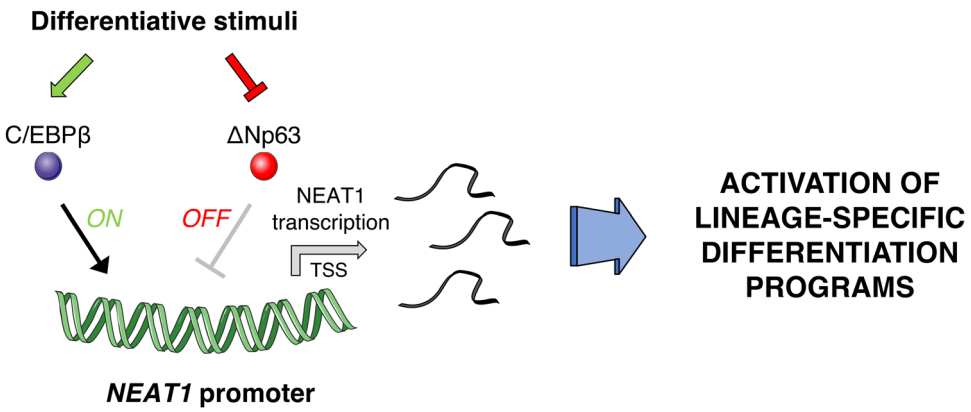

Fig. 4 NEAT1 expression is modulated during cell differentiation. In response to differentiation stimuli, the activation or repression of specific transcription factors ensures NEAT1 upregulation to drive the lineage-specific differentiation programs. In detail, the C/EBPβ-dependent regulation of NEAT1 expression allows the proper activation of the myeloid differentiation program. In human keratinocytes, ΔNp63 recruits the histone deacetylases HDAC1/2 on NEAT1 promoter to repress NEAT1 transcription. Upon differentiation stimuli, ΔNp63 transcriptional repression is released allowing the efficient transcription of NEAT1, which, in turn, promotes the expression of epidermal differentiation genes. Green arrows indicate activation, while red T-shaped lines indicate inhibition. "ON" and "OFF" indicate the transcriptional activation or repression, respectively. TSS = transcription start site. The figure was drawn in part using and/or modifying images from Servier Medical Art, by Servier (http://smart.servier.com)

protein, an oncogenic event impacting myeloid differentiation, suppresses the expression of NEAT1 [82]. At the molecular level, NEAT1 induction upon ATRA treatment is mediated by the transcription factor CCAAT/enhancer-binding protein β (C/EBPβ), which directly binds to the *NEAT1* promoter [83]. C/EBPβ likely operates in synergy with other transcription factors, including PU.1, specificity protein 1 (SP1), GATA-1, STAT6, and Rel p50, forming an intricate regulatory network that controls NEAT1 transcription during the activation of the myeloid differentiation program.

NEAT1 is also involved in the differentiation of other cell types, including muscle cells, glial cells, and spinal cord neural progenitor cells (SC-NPCs) [84–86]. In SC-NPCs, the overexpression of miR-124 enhances NEAT1 levels, likely in an RXRα-dependent manner, promoting neuronal maturation, migration, and apoptosis suppression through the Wnt/β-catenin signaling pathway [84]. Conversely, NEAT1 knockdown disrupts these processes, highlighting its indispensable role in neural differentiation.

Further insights into NEAT1's functions on cell differentiation came also from our studies in keratinocytes. We demonstrated that ΔNp63, a master regulator of epidermal development [87–91], represses NEAT1 expression in basal keratinocytes through HDAC1/2-mediated histone deacetylation on the *NEAT1* promoter [33]. As keratinocyte differentiation progresses, ΔNp63 levels decrease, leading to NEAT1 accumulation and activation of the epidermal differentiation program. Notably, using a combination of NEAT1 trans genomic profiling by ChIRP assay and RNA-sequencing data in human primary keratinocytes (HEKns), we showed that NEAT1 associates with the proximal promoter of key epithelial differentiation markers, sustaining their expression during epidermal differentiation [33]. The involvement of NEAT1 in the transcriptional activation of highly expressed genes has been corroborated by additional studies in breast and prostate cancer cells [26, 92].

Since dysregulation of the cell differentiation program is often associated with the pathogenesis of human diseases, it is not surprising that NEAT1 expression might also influence pathological events. Dysregulation of NEAT1 expression has been found in skin diseases such as ichthyosis or psoriasis, which are characterized by alteration of the proliferation/differentiation balance [33]. In a mouse model of pancreatic carcinogenesis, Mello and colleagues demonstrated that Neat1 acts as a tumor suppressor by inhibiting the acinar-to-ductal metaplasia (ADM) dedifferentiation process [43]. Genetic deletion of *Neat1* inhibits the expression of several pancreatic differentiation markers, suggesting that Neat1 can preserve the terminal differentiation of pancreatic cells [43].

Although it is not completely clear how NEAT1's function in the paraspeckles assembly and cell differentiation are functionally related, several evidence indicated the involvement of NEAT1-associated paraspeckles in cellular differentiation. For instance, both in vitro and in vivo studies have shown that NEAT1_2 long isoform promotes the early differentiation program of embryonic stem cells (ESCs) by sequestering TDP-43 into the paraspeckles [8]. This sequestration prevents TDP-43 from enhancing the polyadenylation of the short isoform of Neat1, suppressing paraspeckles assembly, and the transcripts encoding pluripotency factors (*e.g.,* SOX2), thus promoting the exit from pluripotency. Loss of NEAT1_2 and the consequent absence of paraspeckles disrupt these regulatory mechanisms, leading to inefficient patterning during gastrulation [8]. The impact of NEAT1-associated paraspeckles during early mammalian development has also been established by additional studies. In particular, an elegant study demonstrated that in the mouse embryo at the 2- to 4-cell stage transition, paraspeckles are induced and associated with the methyltransferase CARM1 [93]. Loss of Neat1 during these stages results in arrest at the 16- to 32-cell stage associated with elevated expression of homeobox protein CDX2, a master regulator of differentiation of the first extra-embryonic lineage [93].

The absence of NEAT1-associated paraspeckles has been also linked to defects in the corpus luteum formation [10]. In *Neat1*-KO mice, the absence of paraspeckles hinders the sequestration of SFPQ, leading to its accumulation in the nucleoplasm. This prevents the activation of the steroidogenic acute regulatory protein (*Star*), a gene involved in steroidogenesis, ultimately affecting progesterone production and impairing corpus luteum development [10]. These alterations are also responsible for developmental defects observed in the mammary glands, including impaired ductal elongation and branching, which limits the ability of *Neat1*-KO female mice to nourish their offspring [94].

NEAT1-associated paraspeckles play a pivotal role in bone formation and remodeling as well. Liu and colleagues showed that Neat1-deficient mice exhibit severe impairments in osteoblast differentiation, a consequence of Neat1's failure to sequester the E3 ubiquitin ligase Smad Ubiquitination Regulatory Factor 1 (SMURF1) into paraspeckles [95]. This results in elevated Smurf1 levels, leading to the proteasomal degradation of Runt-related transcription factor 2 (RUNX2), a critical transcription factor in osteogenesis. A recent study conducted by Nakagawa's lab demonstrated that Neat1 and paraspeckles also play a key role in beige adipocyte differentiation, a process critical for thermogenesis in response to cold exposure [34]. This further emphasizes NEAT1's broad influence across various differentiation processes.

Collectively, these data indicate that NEAT1 is a critical regulator of cellular differentiation, orchestrating a variety of biological processes from hematopoiesis and osteogenesis to neural differentiation and adipogenesis. Its role in

the formation and function of paraspeckles is especially significant, as it fine-tunes key developmental pathways by sequestering proteins that would otherwise impede differentiation. These findings position NEAT1 as a promising target for therapeutic interventions aimed at modulating cellular differentiation, tissue regeneration, and disease progression. Further exploration of its molecular mechanisms will be essential for uncovering its full potential in clinical applications.

5 Conclusions

Over the last decade, multiple pieces of evidence have clearly established the pivotal role of the lncRNA NEAT1 in different physiological and pathological processes. One of the most well-characterized functions of NEAT1 (mainly the long isoform NEAT1_2) is related to its ability to act as an essential component of the paraspeckles, subnuclear structures whose assembly is finely tuned in response to sudden changes in cellular conditions.

Parallel to paraspeckles assembly, NEAT1 expression itself is finely regulated in response to changes in the cellular conditions. In this review, we discussed recent evidence functionally linking NEAT1 transcriptional control to the regulation of various biological processes, such as DDR, inflammation, and cell differentiation (see Table 1). One picture stemming from our vision is that NEAT1 acts as a cellular effector of specific transcription factors (*e.g.*, p53, STAT3, HIF-2α), which are master regulators of the cellular response to different insults (*e.g.*, DNA damage) or stress conditions (*e.g.,* inflammation, heat shock). These TFs directly drive the expression of NEAT1 by binding to specific DNA consensus sequences located on the *NEAT1* genomic locus. The tight regulation of NEAT1 expression under different cellular stresses might represent an additional mechanism of how higher eucaryotes face different endogenous and exogenous insults by modifying the nuclear architecture for the complex regulation of gene expression.

Besides its roles in stress response, NEAT1 is also a key modulator of cellular differentiation, influencing the transcription of key lineage-specific genes [96]. NEAT1 expression has been shown to vary across cell types and developmental stages, suggesting its involvement in regulating cell fate decisions [8, 93].

Although the NEAT1-dependent biological outcome may vary and may be context-dependent, it ultimately depends on its ability to impinge upon gene expression. For instance, NEAT1 binds to the promoters of highly transcriptional active genes, favoring their efficient expression as described in the context of keratinocyte differentiation or prostate cancer progression. Along the same line, during DDR, NEAT1 regulates the expression of DNA repair genes, even though the underlying molecular mechanisms have not been clarified. NEAT1 regulates transcription by modulating the sequester of specific epigenetic factors in the paraspeckles, a mechanism that ultimately impacts the expression of specific genes.

The strong dependency of paraspeckle assembly on NEAT1_2 suggests that its impact on various biological processes may largely rely on its function within paraspeckles. In line with this view, the effects of NEAT1 on epidermal differentiation and DNA damage response are closely linked to its paraspeckle-dependent role [9, 33]. However, examples of paraspeckle-independent functions of NEAT1_2 and NEAT1_1 have been reported [71, 97]. For instance, upon inflammatory stimuli, the decrease in the abundance of paraspeckles-associated protein (*e.g.* Pspc1) causes paraspeckles disassembly, NEAT1 release, and its export to the cytoplasm. Here, NEAT1 stabilizes the inflammasome structure [71].

Given the profound impact of NEAT1 and paraspeckles on a wide range of biological processes, it is not surprising that its dysregulation has been implicated in various pathological conditions, including tumorigenesis and neurodegenerative diseases. In different cancer types, multiple evidence has highlighted the ability of NEAT1 to act as an oncogene regulating tumor progression, metastasis, and resistance to chemotherapy [43, 92, 98]. However, in other tumor settings, NEAT1 can be considered a tumor suppressor, as its inhibition accelerates tumor progression, as described in a mouse model of pancreatic cancer. These contrasting data suggest that the role of NEAT1 on cancer progression might be context dependent.

In neurodegenerative diseases such as Parkinson's and amyotrophic lateral sclerosis (ALS), aberrant NEAT1 expression has been linked to disease pathogenesis, underscoring its potential role in neuronal dysfunction and cell death [99–101]. Given its involvement in these critical diseases, NEAT1 is emerging as a promising biomarker for early diagnosis and prognosis. Furthermore, targeting NEAT1, by either modulating its expression or disrupting paraspeckle formation, holds promise as a therapeutic strategy to address the molecular defects underlying these conditions [102]. Ongoing research into NEAT1's functional roles and regulatory mechanisms may pave the way for novel diagnostic and therapeutic approaches, offering new opportunities for intervention in different diseases.

Table 1 Summary table of the transcription factors regulating NEAT1 expression for each biological process, along with their specific DNA binding sites on NEAT1 promoter

Factor	Regulation	Binding site	Motif	Process	Refs
ATF2	Positive	– 543 to – 536	TGACGTCA	Mitochondrial stress	[42]
HIF2α	Positive	Upstream of NEAT1 promoter	n.a	Hipoxia	[57]
p53	Positive	– 1497 to – 1478	GAGCAAGCCTGGGCTTGCCA	Replication stress, DNA damage	[9, 41, 43]
HSF1	Positive	– 445 to – 431	GGAATTTTCCAGATG	Heat shock	[65]
YY1	Positive	– 1220 to – 1215	GCCATT	Inflammation	[73]
NF-κB	Positive	– 1468 to – 1459 – 445 to – 436	TGGGCTTGCC TGGAATTTTC	Inflammation	[75]
CARM1	Negative	n.a	n.a	Inflammation	[78]
STAT3	Positive	– 657 to – 667 – 1411 to 1402	CTGCCAGGAAC TTCCGAGAA	Cardiovascular Diseases Inflammation	[103]
E2F1	Negative	– 172 to – 156	CTTTCCCGCAATTTAAT	Inflammation	[28]
C/EBPβ	Positive	– 1453 bp region – 54 bp region	CGGGGTACCGCAGTGAAGACTCCTCCATTGG CGGGGTACCTTCGCCTCCCAAATGTCACCTT	APL cells differentiation	[83]
C/EBPα	Positive	– 1453 bp – 54 bp region	CGGGGTACCGCAGTGAAGACTCCTCCATTGG CGGGGTACCTTCGCCTCCCAAATGTCACCTT	APL cells differentiation	[104]
ΔNp63	Negative	– 1497 to – 1478	GAGCAAGCCTGGGCTTGCCA	Skin differentiation	[33]
BRCA1	Negative	About – 1400	CTCGGTTG	DNA repair	[47]
RXRa	Positive	– 597 to – 499	TGACGTCA	SC-NPCs differentiation	[105]

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Declarations

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