



Review Article

MIAT lncRNA: A multifunctional key player in non-oncological pathological conditions

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ABSTRACT

The discovery of non-coding RNAs (ncRNAs) has unveiled a wide range of transcripts that do not encode proteins but play key roles in several cellular and molecular processes. Long noncoding RNAs (lncRNAs) are a specific class of ncRNAs that are longer than 200 nucleotides and have gained significant attention due to their diverse mechanisms of action and potential involvement in various pathological conditions. In the current review, the authors focus on the role of lncRNAs, specifically highlighting the Myocardial Infarction Associated Transcript (MIAT), in a non-oncological context. MIAT is a nuclear lncRNA that has been directly linked to myocardial infarction and is reported to control post-transcriptional processes as a competitive endogenous RNA (ceRNA) molecule. It interacts with microRNAs (miRNAs), thereby limiting the translation and expression of their respective target messenger RNA (mRNA) and regulating protein expression. Yet, MIAT has been implicated in other numerous pathological conditions such as other cardiovascular diseases, autoimmune disease, neurodegenerative diseases, metabolic diseases, and many others. In this review, the authors emphasize that MIAT exhibits distinct expression patterns and functions across different pathological conditions and is emerging as a potential diagnostic, prognostic, and therapeutic agent. Additionally, the authors highlight the regulatory role of MIAT and shed light on the involvement of lncRNAs and specifically MIAT in various non-oncological pathological conditions.

1. Introduction

Through the advancement of transcript mapping and RNA sequencing technologies, it has been discovered that although the human genome is extensively transcribed, only a minor percentage of RNAs (around 2%) are responsible for encoding proteins and a significant portion of the remaining RNAs exhibit noncoding functions [1]. The latest developments in next-generation technologies and RNA-based techniques have contributed to the identification of non-coding RNAs (ncRNAs), a class of transcripts that do not code for proteins [2–5].

These ncRNAs are often classified as housekeeping transcripts or

regulatory transcripts. The length of housekeeping ncRNAs is typically from 50 to 500 nucleotides [6–8], and regulatory ncRNAs are classified into two broad categories: long non-coding RNAs (lncRNAs), that include more than 200 nucleotides in length [9–11], and small non-coding RNAs (sncRNAs), that include less than 200 nucleotides in length [12–15].

MicroRNAs (miRNAs) have been extensively studied as potential biomarkers and therapeutic targets for several diseases [3,16–21], however, the focus has now shifted to lncRNAs [22–27]. Genomes undergo extensive transcription, resulting in the generation of lncRNAs [28]. These lncRNAs are classified based on their localization, which is

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typically either nuclear or cytoplasmic [29]. lncRNAs are still considered novel class of ncRNAs [30]. lncRNAs are produced from two genomic regions: the opposite strand of protein-coding genes, such as natural antisense transcripts, or from intergenic regions of the genome, such as large intergenic ncRNAs [31]. lncRNAs control gene expression by binding to chromatin regulators and interfering RNAs, which can influence the response of cells [32,33]. Aberrant expression of lncRNAs has been correlated to numerous oncological and non-oncological pathological conditions [34–36].

Myocardial Infarction Associated Transcript (*MIAT*) is a nuclear lncRNA. *MIAT* was originally linked to an increased risk of myocardial infarction (MI) in genome-wide association studies [37,38]. *MIAT* has been reported to control post-transcriptional processes, particularly as a competitive endogenous RNA (ceRNA) molecule [11,39]. Indeed, growing research suggests that a real battle between mRNAs and *MIAT* for the binding of distinct miRNAs. Overall, *MIAT* either directly binds to target mRNAs or directly bind to the 3' untranslated regions (3' UTRs) of the mRNA. This, in turn, limits translation and the production of end product, hence controlling protein expression [40,41].

MIAT has been implicated in a variety of cellular processes and pathological conditions [42]. *MIAT* can influence different types of oncological conditions such as gastric cancer, hepatocellular carcinoma, colorectal cancer, esophageal cancer, pancreatic cancer, cholangiocarcinoma, ovarian cancer, breast cancer, cervical cancer, renal cell carcinoma, prostate cancer, lung cancer, and thyroid cancer [43]. Apart from cancer, *MIAT* plays a crucial role in other non-oncological conditions, including MI [44,45], paranoid schizophrenia [46], microvascular dysfunction [47], diabetes mellitus [48], multiple sclerosis [49], neurogenic commitment [50], ischemic stroke [51], osteoarthritis [52], and nuclear body formation [53]. In this review article, the authors will mainly focus on the modulatory vital roles of lncRNAs with a specific emphasis on the role of *MIAT* in non-oncological conditions.

2. What are lncRNAs and how they work?

lncRNAs are produced from two genomic regions: the opposite strand of protein-coding genes, such as natural antisense transcripts, or from intergenic regions of the genome, such as large intergenic ncRNAs [31]. While lncRNAs do not encode proteins, they share certain similarities with mRNAs in terms of their biology. Similar to mRNAs, the majority of lncRNAs are transcribed by RNA polymerase II (Pol II) and undergo processes such as capping and polyadenylation [54]. It was believed at first that lncRNAs are not stable, however, this is the case for only a small portion of lncRNAs [55]. The majority of lncRNAs find stability through polyadenylation [55,56], whereas non-polyadenylated lncRNAs can be made stable by secondary structures like triple-helical structures at their 3' ends [57].

These 3' sequence features not only play a stabilizing role but also aid in an efficient nuclear export [58]. Due to extensive alternative splicing, the number of potential isoforms for the vast majority of lncRNAs dramatically increased [59]. Different studies have shown that although lncRNA splicing efficiency is lower than that of mRNAs [60], lncRNAs are considerably more alternatively spliced than mRNAs [61, 62].

lncRNA expression levels are generally lower than those of mRNAs [63]. However, they exhibit stronger tissue-specific expression patterns, indicating their crucial involvement in cell type-specific processes [60, 64]. Unlike mRNAs, lncRNAs are not highly conserved in terms of sequence among species. Although this makes it more challenging to assess lncRNA function, it can provide valuable insights into the roles that lncRNAs have evolved to play in different species. Nonetheless, some subsets of lncRNAs exhibit sequence or genomic position conservation and may function similarly across species [65,66].

A recent investigation by Guo et al. [67] found that some lncRNAs exhibit sequence and positional conservation between human and

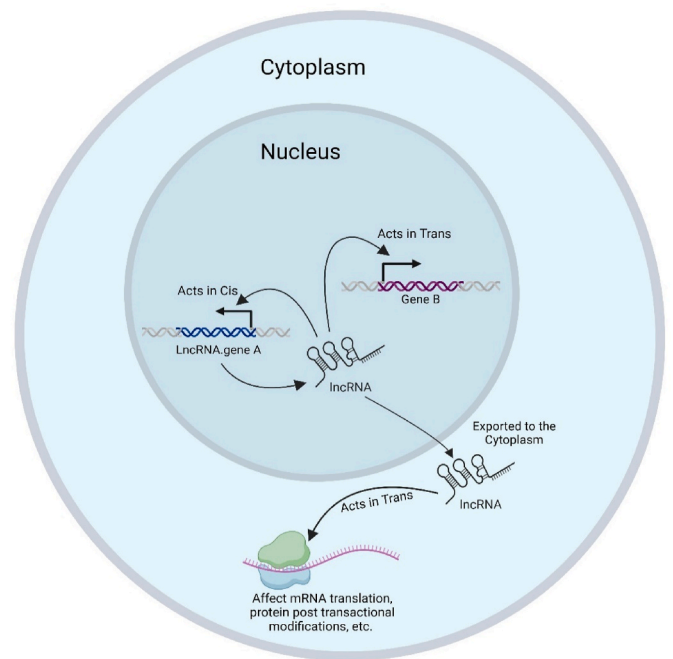


Fig. 1. lncRNAs modes of Actions. lncRNAs mode of action; they can be strictly localized in the nucleus in cis or localized in the nucleus and function in trans. Additionally, they can be localized and function in the cytoplasm.

mouse embryonic stem cells. However, these lncRNAs are processed differently, leading to their localization in different subcellular compartments and ultimately serving distinct functions in mouse and human cells. In contrast, conserved mRNAs showed similar localization patterns in both species. Hence, lncRNA sequence conservation does not always indicate conserved functional roles, and lncRNA processing and binding partners significantly impact subcellular distribution and function. A study by Chen L.L [68], brought attention to the importance and impact of lncRNA localization on their function.

Certain lncRNAs are recognized as important regulators of nuclear functions and exhibit unique patterns of nuclear localization [69,70], while others must be transported to the cytoplasm to carry out their regulatory function. To better understand the relationship between lncRNA localization and function, lncRNAs can be classified based on their subcellular localization. These classifications include those that are strictly localized in the nucleus in cis, those that are primarily localized in the nucleus and function in trans, and those that are predominantly localized and function in the cytoplasm (Fig. 1) [68].

The past decade has witnessed extensive research focusing on lncRNAs due to their intriguing nature and diverse mechanisms of action [30]. These RNA molecules have been found to exert their functions through various means [71]. For instance, they can modulate transcription, epigenetic modifications, protein and RNA stability, translation, and post-translational modifications by interacting with DNA [72–74], RNAs [75–78], and proteins as previously reviewed [30, 79–81]. Recently, it was also discovered that lncRNAs can directly interact with signaling receptors [82].

An increasing number of lncRNAs have been discovered and have gained recognition for their pivotal involvement in various cellular processes such as cell cycle [8,83], metabolism [84,85], differentiation [86–88], and their association with several diseases [89–91] including malignant and non-malignant disorders [92]. In this review, the authors will focus on the role of lncRNAs in multiple non-oncological illnesses.

3. lncRNAs as central players in different pathological conditions

lncRNAs play a crucial role in several physiological and pathological processes [93–96]. A database of experimentally verified lncRNA-related pathological conditions has been created by compiling data from over 500 publications. This database has listed 321 lncRNAs that are associated with 221 diseases. It is worth noting that lncRNAs have been identified to have a robust link with diverse types of pathological conditions where cardiovascular diseases and neurodegenerative disorders were ranked as highest two categories of diseases associated with lncRNAs after cancer [97].

In oncology, 6 lncRNAs have been identified in prostate cancer, with three being highly specific to the prostate: prostate cancer-associated lncRNA transcript 1 (*PCAT1*), prostate cancer gene expression marker 1 (*PCGEM1*), and prostate cancer antigen 3 (*PCA3*) [98]. HOX antisense intergenic RNA (*HOTAIR*) lncRNA is implicated in multiple cancers, such as breast cancer, gastric adenocarcinoma, and colorectal cancer. The colon cancer associated transcript 1 (*CCAT1*) lncRNA has been found to enhance long-range chromatin looping between the myelocytomatosis oncogene (*MYC*) promoter and its enhancers. Additionally, an increasing number of cancer-associated lncRNAs are being identified [99].

In cognitive abilities, lncRNAs play a significant role as well, given that the brain is the second most prevalent organ that expresses many lncRNAs. Moreover, several lncRNAs are exclusive to primates and mammals, indicating their potential importance in cognitive functions [100,101]. When the natural antisense lncRNA β -site amyloid precursor protein cleaving enzyme 1 (*BACE1*)-antisense transcript (*BACE1-AS*) is upregulated, it enhances the stability of *BACE1*, resulting in sustained high levels of the *BACE1* enzyme. This, in turn, could potentially contribute to the pathophysiology of Alzheimer's disease [102].

In immune response processes, lncRNAs have been found to play a keystone role. For instance, the long noncoding-interleukin-7 receptor α -subunit gene (*lnc-IL7R*) overlaps with the 3'-UTR region of the interleukin-7 receptor α -subunit gene. When this lncRNA is repressed, it leads to a reduction in trimethylation of H3K27 at the proximal promoter regions of inflammatory mediators, thereby decreasing lipopolysaccharide (LPS)-induced inflammatory responses [103]. Additionally, lncRNAs can bind to the signal transducer and activator of transcription 3 (*STAT3*) in the cytoplasm and promote *STAT3* phosphorylation, which is crucial for dendritic cell differentiation and T cell activation [104].

In growth and development medical conditions, the lncRNA *IPW*, imprinted gene in the region of the Prader-Willi syndrome, is typically transcribed from chromosome 15 specifically from the paternal allele. It interacts with histone lysine methyltransferase to preserve the trimethylation of Histone H3 at Lysine 4 (H3K9me3) state at the *DLK1-DIO3* region on chromosome 14, which helps to suppress maternally expressed genes (MEGs) [105]. The abnormal upregulation of MEGs could potentially contribute to the manifestation of Prader-Willi phenotypes.

4. lncRNAs as potential theranostic agents (diagnostic, prognostic, and therapeutic agents)

The discovery of ncRNAs has sparked a new field in biomarker research [106]. This is mainly attributed to the prominent abundance of ncRNAs in various cellular compartments, participating in multiple cellular functions [18]. They have been detected in cells, tissues, or biological fluids [4]. lncRNAs exhibit distinctive expression patterns and functional versatility across a range of diseases, making them valuable in the fields of theranostics (diagnosis, prognosis, and therapy) for multiple pathological conditions [107].

HOXA Cluster Antisense RNA 3 (*HOXA-AS3*) is implicated in several non-oncological conditions such as atherosclerosis, pulmonary arterial

hypertension, and mesenchymal stem cell (MSC) lineage commitment. In atherosclerosis, *HOXA-AS3* contributes to endothelial inflammation and influences angiogenesis progression. In pulmonary arterial hypertension, *HOXA-AS3* promotes cell proliferation and migration while suppressing apoptosis. Regarding MSC lineage commitment, *HOXA-AS3* plays a role in the differentiation of MSCs into adipocytes and osteoblasts. These findings emphasize the significance of *HOXA-AS3* in the pathogenesis and advancement of non-cancerous diseases. *HOXA-AS3* abnormal expression and functional roles also position it as a potential biomarker and therapeutic target for both cancers and non-cancerous diseases [108].

In cardiovascular diseases (CVDs), several lncRNAs show promise as diagnostic and prognostic markers. For instance, lncRNA *LIPCAR* (long intergenic noncoding RNA predicting cardiac remodeling) is a potential biomarker for atherosclerosis. Furthermore, Antisense Noncoding RNA in the *INK4* Locus (*ANRL*) is linked to atherosclerosis susceptibility, in-stent restenosis, and ventricular dysfunction post-MI. Other lncRNAs such as growth arrest specific 5 (*GAS5*), non-coding repressor of NFAT (*NRON*), myosin heavy chain associated RNA Transcripts (*MHRT*), *MIAT*, uc004cov.4, and uc022bqu.1 are also being explored as potential biomarkers in several pathological conditions [109]. Furthermore, the deregulation of lncRNAs in CVDs indicated that they might be therapeutic targets. Modulating lncRNA expression levels using recombinant plasmids, viruses, small nucleotide molecules, and gene-editing techniques has shown potential in animal models, improving cardiac dysfunction and related gene expression [109].

lncRNAs play a crucial role in autophagy regulation and are associated with neurological diseases. While some lncRNAs contribute to the development of neurological diseases, others can slow their progression. Understanding the involvement of lncRNAs in autophagy regulation holds promise for identifying therapeutic targets and biomarkers for neurological diseases. lncRNAs function through diverse mechanisms, such as interacting with miRNAs, influencing autophagy-related signaling pathways, and modulating the expression of autophagy-related genes [110]. Notably, in specific neurological disorders such as Alzheimer's disease, lncRNA *17A* enhances autophagy by increasing the expression of the Gamma-Aminobutyric Acid Type B Receptor Subunit 2 (*GABABR2*) gene, leading to elevated secretion of β -amyloid peptides [111]. In Parkinson's disease, lncRNA nuclear enriched abundant transcript 1 (*NEAT1*) stabilizes the PINK1 protein, thereby promoting autophagy and safeguarding dopaminergic neurons [112]. In ischemic stroke, lncRNA *H19* activates autophagy by regulating the dual-specificity phosphatase 5 (*DUSP5*)- extracellular signal-regulated kinase 1/2 (*ERK1/2*) axis, potentially worsening cerebral ischemia-reperfusion injury [113]. In epilepsy, lncRNA Metastasis Associated Lung Adenocarcinoma Transcript 1 (*MALAT1*) inhibits the phosphoinositide 3-kinase (*PI3K*)/protein kinase B (*AKT*)/mammalian (or mechanistic) target of rapamycin (*mTOR*) signaling pathway, triggering autophagy and contributing to the degeneration of hippocampal neurons [114]. In glioma, lncRNA Maternally Expressed Gene 3 (*MEG3*) suppresses the *PI3K/AKT/mTOR* signaling pathway, activating autophagy and suppressing cell proliferation and migration [115].

5. Myocardial Infarction Associated Transcript (*MIAT*)

5.1. *MIAT* discovery, structure and chromosomal location

lncRNA *MIAT* is the main focus of the current review due to its recent involvement in several malignant and non-malignant conditions and their prominent role in modulating several signaling cascades simultaneously. *MIAT* is a nuclear lncRNA with four splicing variants. In 2000, *MIAT* was discovered [116] and then found to be located at 22q12.1 with a length of 30,051 base pairs. A susceptible locus for *MIAT* has been revealed through a massive case-control association research study using 52,608 haplotype-based single nucleotide polymorphism (SNP) markers. Within this locus, scientists extracted a complete cDNA

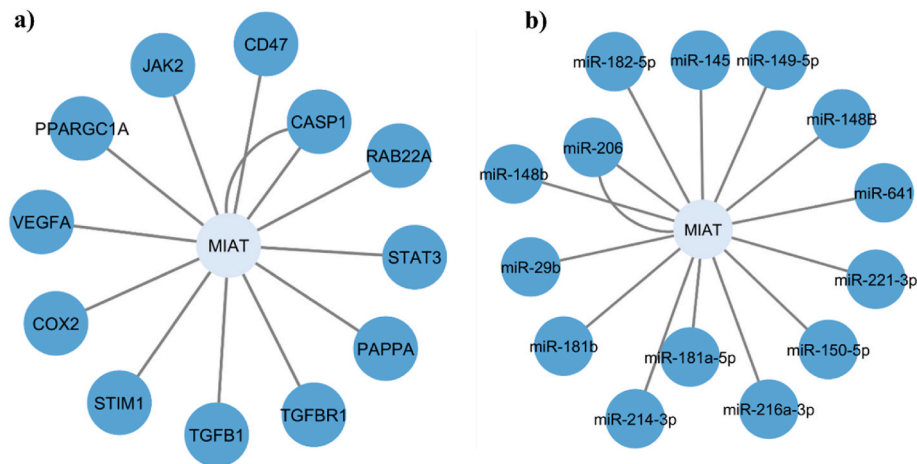


Fig. 2. *MIAT*-mRNA and *MIAT*-miRNA regulatory networks in non-oncological disorders. *MIAT*-mRNA and *MIAT*-miRNA regulatory networks in non-oncological disorders generated from LncTarD and LncRNA2Target databases. (a) Network plot for *MIAT* encompassing 12 lncRNA-mRNA interactions. (b) Network plot for *MIAT* encompassing 14 lncRNA-miRNA interactions.

of a novel gene, which they named *MIAT* [44]. *MIAT* is also known as GomaFu in humans or Rncr2 in mice [44,117,118].

MIAT gene is composed of five exons and all its splice junctions are believed to adhere to the fundamental GT/AG rule [119,120]. Despite the finding that typical sequence alignment searches identified no orthologous *MIAT* genes in non-mammals [118], a search indicated that putative *MIAT* was orthologous to *Xenopus tropicalis* and chick [121]. Remarkably, every orthologous gene's largest exon had many clustered sequence repetitions of the sequence (ACUAACC), with five to eight repeats detected within each transcript [122]. This repeat sequence contains the (ACUAAY) consensus recognition site for the RNA binding protein Quaking that controls RNA subcellular stability and distribution [123,124]. *MIAT*, compared to additional nuclear-retained lncRNAs such as antisense of *IGF2R* non-protein coding RNA (*AIRN*) and X-inactive specific transcript (*XIST*), is strongly linked with the nuclear matrix rather than chromatin [118].

MIAT is a potentially important functional lncRNA. It influences cellular processes such as apoptosis, proliferation, and invasion across multiple medical conditions and its abnormal expression has a strong association in several diseases' progression. *MIAT* expression is altered in various diseases as it is upregulated in some conditions such as MI, cardiomyopathy, cataract, ischemic stroke, non-small-cell lung cancer, and prostate cancer. In contrast, it is downregulated in other pathological conditions such as bone diseases, schizophrenia, and diabetic nephropathy [121]. In this review, the authors will shed the light on such paradoxical expression profile of *MIAT* in several non-oncological pathological conditions such as neurological conditions, cardiovascular-related diseases and metabolic disorders and linking it with respective molecular signaling pathways tuned by *MIAT*.

5.1.1. *MIAT* regulatory networks for non-oncological disorders

Several ncRNA databases have been reported to store curated data across multiple domains including genome annotation, molecular interaction, expression profiles, as well as therapeutic insights for related diseases [125]. RNAcentral and miRbase are versatile ncRNA database that various tissues and species, as well as serve as primary databases that harness huge data collection from other resources for up-to-date ncRNA specifications [126,127].

Moreover, LncTarD and LncRNA2Target are two lncRNA databases that include potential lncRNA interactions across oncological and non-oncological samples collected from all published lncRNA studies [128, 129]. Cytoscape v.3.10 was used to construct lncRNA regulatory networks using mentioned data.

It is worth noting that similar to most of lncRNAs, *MIAT* has been

associated with competing endogenous RNA (ceRNA) hypothesis that suggests that ncRNAs and mRNAs communicate by competing for binding to shared miRNAs, which accordingly modulate targets' gene expression [130]. Following screening of *MIAT* lncRNA on both databases, our results revealed 60 *MIAT*-mRNA-miRNA interactions, where non-oncological disorders showed 12 *MIAT*-mRNA interactions, as well as 14 *MIAT*-miRNA ones across different tissues and disease states.

Our in-silico results showed that *MIAT*-mRNA regulatory network revealed that STAT3, RAB22A, CASP1, CD47, JAK2, PPARGC1A, VEGFA, COX2, STIM1, TGFB1, TGFB1, and PAPP genes have significant interaction with *MIAT*, while in *MIAT*-miRNA regulatory network, miR-182-5p, miR-145, miR-149-5p, miR-148B, miR-641, miR-221-3p, miR-150-5p, miR-216A-3p, miR-181a-5p, miR-214-3p, miR-181b, miR-29b, miR-148b, and miR-206 were regulated by *MIAT* as shown in Fig. 2.

Experimentally, it has been also validated that *MIAT* is involved in several pathological conditions through the ceRNA regulatory network. Investigations have reported that *MIAT* acts as a ceRNA for miR-150-5p [47,131], miR-24 [132], miR-22-3p [133], and miR-150 [134]. Moreover, *MIAT* can also activate a variety of signaling pathways through regulating various proteins such as Nrf2 (nuclear factor erythroid 2-related factor 2), which is critical in high glucose-induced renal tubular epithelial injury [135], and SRSF1 (serine/arginine-rich splicing factor 1), which contributes to the pathophysiology of schizophrenia [136]. *MIAT* also creates a positive feedback regulatory loop with its transcriptional regulator octamer-binding transcription factor 4 (OCT4) in malignant mature B cells to enhance cellular proliferation [137].

5.2. Neurological diseases

5.2.1. Multiple sclerosis (MS)

MS stands as the most predominant inflammatory and demyelinating disease impacting the central nervous system (CNS), with a higher prevalence among young adults, especially women. According to the Atlas of MS, approximately 2.9 million individuals are affected globally, and its incidence has been on the rise since 2013 [138]. It can be categorized under neuropathological condition as well as autoimmune diseases [139].

Immunotherapies have shown promise in halting the progression and relapse of MS, but their efficacy appears to be more pronounced in the early stages of the disease compared to the later, progressive stages [140,141]. The complex pathophysiology of MS involves demyelination, neurodegeneration, immune-mediated processes, and inflammation. Although the exact causative factors remain unidentified, research indicates that genetic, environmental, infectious, nutritional, and

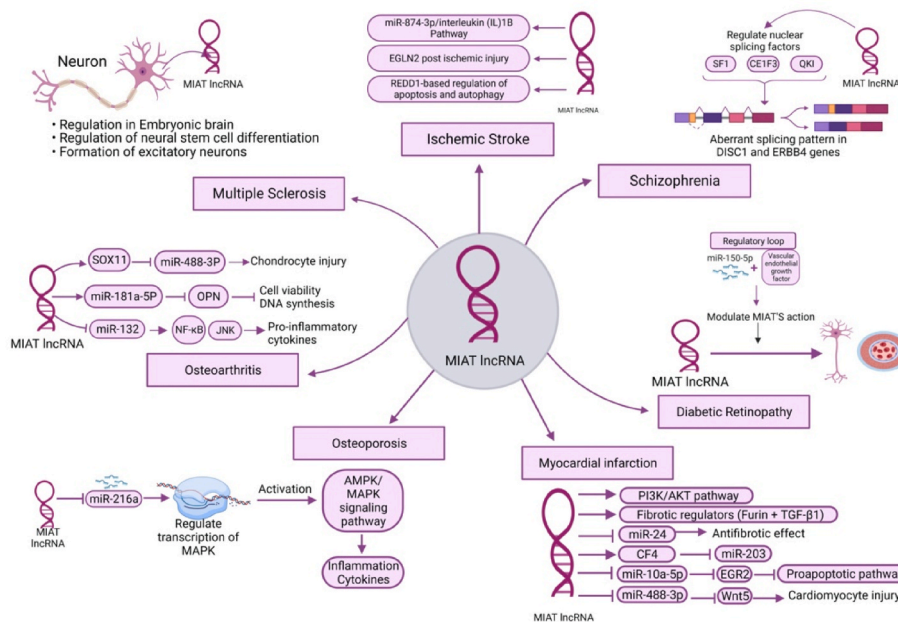


Fig. 3. Role of lncRNA *MIAT* in several pathological diseases.

epigenetic components play a role in the development of MS [142–144]. The onset of MS is believed to be linked to autoimmune responses involving adaptive T- and B-lymphocytes targeting the CNS [145]. Therefore, there is a crucial need to comprehend the underlying mechanisms driving MS and develop effective therapies to combat this neuropathological condition.

The dysregulation of lncRNAs has been implicated in the causes of various neurological diseases including MS [146]. lncRNAs play a role in regulating gene expression and controlling immune system responses [147,148]. Several lncRNAs, including *MIAT*, have been associated with the pathogenesis, prognosis, and diagnosis of MS [147–150]. *MIAT* has also been linked to the induction of inflammatory responses. Further research into the role of *MIAT* and other lncRNAs may provide valuable insights into the molecular mechanisms underlying MS and potential therapeutic targets.

5.2.1.1. Exploring the role of *MIAT* in MS: expression profile, signaling pathways and potential implications. *MIAT* is predominantly expressed in neuronal cells, particularly in the nucleus of post-mitotic neurons [151, 152]. The physiological functions of *MIAT* in CNS have been extensively discussed in the literature. It is known that *MIAT* is involved in the regulation of several processes in the embryonic brain, such as the regulation of neural stem cell differentiation and the formation of excitatory neurons as shown in Fig. 3 [153,154]. *MIAT*-deficient mice did not show developmental abnormalities but resulted in hyperactive behavior [151]. These findings highlight the significance of *MIAT* in neuronal development and functioning. Further research is needed to fully elucidate its precise mechanisms of action in the CNS and its potential implications for neurological disorders.

In recent studies, *MIAT* expression in the peripheral blood of MS patients has been investigated, revealing controversial findings. One study reported a significantly higher expression of *MIAT* in MS patients compared to controls [49]. In contrast, another study found down-regulation of *MIAT* in peripheral blood mononuclear cells (PBMCs) of MS patients compared to controls; however, validation on a different cohort did not show significant differences in *MIAT* expression between the two groups [155]. This could be attributed to age differences between cohorts and different ethnic groups.

Given the conflicting results, further research is warranted to fully understand the role of *MIAT* in the context of MS. It is crucial to

determine whether *MIAT* expression correlates with MS prognosis, diagnosis, or the potential for therapeutic targeting. These investigations hold promise for advancing our understanding of MS pathogenesis and may have implications for the development of targeted interventions to improve patient outcomes.

5.2.2. Schizophrenia (SZ)

Schizophrenia (SZ) is a complex psychiatric condition that affects around 24 million individuals worldwide, particularly young adults [156]. It exerts a profound impact on normal life functioning and has a high mortality and suicidal rates [157]. The development of SZ is believed to be influenced by a combination of environmental, genetic, and epigenetic factors, ultimately resulting in neural and glial cells abnormalities [158–160]. However, the precise mechanisms through which genetic and epigenetic factors contribute to the pathophysiology of the disease remain unclear.

5.2.2.1. Exploring the role of *MIAT* in SZ: expression profile, signaling pathways and potential implications. Alternative splicing, the process that generates multiple protein isoforms from a single gene, has been implicated as a significant contributor to genetic dysregulation in SZ [161,162]. Among the genes affected are disrupted in schizophrenia 1 (*DISC1*) and v-Erb A erythroblastic leukemia viral oncogene homolog 4 (*ErbB4*), which show aberrant splicing patterns in SZ [161,162]. Notably, lncRNAs have been found to influence gene transcription by modulating the alternative splicing of their target genes [163]. In this context, *MIAT* has been shown to regulate nuclear splicing factors like Splicing Factor 1 (*SF1*), EBF Transcription Factor 3 (*EBF3*), and QKI, KH Domain Containing RNA Binding (*QKI*) as shown in Fig. 3, which, in turn, alter the splicing patterns of *DISC1* and *ErbB4* in a manner similar to that observed in SZ [164–166].

In the pursuit of understanding the potential link between *MIAT* dysregulation and SZ, researchers conducted a study on the Chinese Han population to identify specific SNPs in SZ patients compared to controls [167]. Among the 485 SNPs examined within *MIAT*, only one SNP was found to be associated with paranoid SZ [167]. This intriguing finding suggests that certain SNPs within the *MIAT* gene might contribute to the vulnerability to SZ, providing valuable insights for further research into the genetic underpinnings of this complex psychiatric disorder.

Recent studies have shed light on the expression of *MIAT* in the brain

tissues of SZ patients. One investigation found that *MIAT* expression in the brains of SZ patients was lower compared to controls [166]. Additionally, data from the PsychEncode Consortium revealed that *MIAT* was among the downregulated genes in a SZ cohort that included post-mortem brain samples from patients with various psychiatric conditions and controls [168,169]. These intriguing findings suggest the potential involvement of *MIAT* in the pathophysiology of SZ and provide valuable insights into its role in susceptibility to the disorder.

The lack of blood-based biomarkers and the high heterogeneity of the disease among patients present significant hurdles to SZ diagnosis and treatment efficacy [170]. Due to the predominant presence of lncRNAs in PBMCs and their high transcriptomic resemblance to lncRNAs expressed in the brain, researchers are actively investigating the potential of lncRNAs as diagnostic non-invasive biomarkers for SZ [171,172]. In a small study conducted on a Chinese Han cohort, researchers examined the expression of *MIAT* in PBMCs and observed that *MIAT* was overexpressed in SZ patients compared to controls [173]. These findings were inconsistent with previous results obtained from post-mortem brain cohorts. The authors discussed potential reasons for such contradictory outcomes. Furthermore, the study indicated that treatment with anti-psychotics led to a further increase in *MIAT* expression; however, this increase did not correlate with improved disease progression for SZ patients [173].

Another study, involving a small cohort of 50 SZ patients and 50 normal individuals, found no statistically significant differences in *MIAT* expression levels between the two groups [174]. However, the study reported that the diagnostic accuracy of the *MIAT* gene to differentiate between SZ patients and controls was 68% [174]. On the other hand, transcriptome profiling of amygdala tissues from SZ patients and controls revealed no differences in *MIAT* expression between both groups [175]. Furthermore, another study using mouse models of SZ showed significantly lower *MIAT* expression in the brains of SZ-induced mice, but *MIAT* was not detected in peripheral blood samples taken from the same mice [176].

Another study revealed that *MIAT* expression was reduced in the brains of fear-conditioned mice.

Furthermore, knocking down *MIAT* in mice led to increased anxiety-like behavior and higher expression of Crystallin Beta B1 (*Crybb1*), a gene associated with SZ. The mechanism behind the upregulation of *Crybb1* was also found to occur through the interaction of *MIAT* with BMI1 Proto-Oncogene, Polycomb Ring Finger (*BMI1*), a component of the polycomb repressive complex. Under normal circumstances, this interaction would repress *Crybb1* expression. However, when *MIAT* was repressed through knocking down experiments or due to fear conditioning in mice, the interaction between *MIAT* and *BMI1* was disrupted, leading to the de-repression of *Crybb1* [177].

The controversy surrounding *MIAT*'s expression in SZ patients and its potential as a possible diagnostic and prognostic non-invasive biomarker emphasizes the necessity for further research on its expression in the blood of SZ patients. These investigations are crucial in determining its validity as a potential biomarker in liquid biopsies of SZ patients. It is also worth noting that to ensure consistency between different studies, it is essential to establish standardized protocols for quantifying *MIAT* from blood samples, thus minimizing discrepancies.

5.2.3. Ischemic stroke (IS)

Ischemic strokes (IS) are a widespread global health concern, affecting 15 million people annually, according to the WHO [178]. They are associated with high morbidity and mortality rates, with approximately 67% of stroke sufferers experiencing death or permanent disability [178]. As strokes are more prevalent in individuals older than 40 years, the absolute number of cases continues to rise due to the increasing aging population [178].

High blood pressure and smoking are the main causative factors of stroke. IS is the most common type, accounting for 62.4% of all strokes, as estimated in 2019 [179]. IS occurs due to insufficient blood supply to

the brain, leading to neuronal death and severe neurovascular damage [180]. Treatment options for IS include plasminogen activating therapy or mechanical thrombectomy. Plasminogen activating therapy is currently the only FDA-approved treatment for IS and is most effective when administered within the first few hours after the onset of the stroke [181,182].

In terms of diagnostics, there is an urgent need for improvement as the current methods rely heavily on clinical examination and imaging techniques, making the detection of small infarcts challenging and lengthy in terms of duration [183]. Therefore, the discovery of new targets and biomarkers for IS remains crucial to combating the high mortality rate associated with such disease.

5.2.3.1. Exploring the role of MIAT in IS: expression profile, signaling pathways and potential implications. lncRNAs have been implicated in the pathophysiology of IS and are currently under investigation as potential diagnostic biomarkers. Among these lncRNAs, *MIAT* comes on top of the list. *MIAT* has been found to be upregulated in the blood of IS patients and showed positive correlations with the National Institutes of Health Stroke Scale (NIHSS), high-sensitivity C-reactive protein, and infarct volume [184]. Notably, *MIAT* was identified as a potential prognostic marker for IS, as patients with higher *MIAT* expression exhibited increased mortality rates [184]. Multivariate analysis demonstrated that *MIAT* independently predicted the outcome and death in IS patients [184]. Additionally, *MIAT* was observed to possess diagnostic value for IS patients [184]. To fully realize the promising potential of *MIAT* as a diagnostic and prognostic biomarker for IS, further clinical trials on larger cohorts are imperative to validate these findings. By advancing our understanding of *MIAT*'s role in IS, we may pave the way for improved patient management and targeted therapeutic interventions in the future.

A comprehensive investigation was conducted to examine the potential involvement of *MIAT* in the pathogenesis of IS through the miR-874-3p/IL-1 β pathway as shown in Fig. 3 [185]. Zhang et al. observed that the expression of *MIAT* and IL-1 β in serum was upregulated in IS patients, while miR-874-3p was downregulated [185]. To further explore this pathway, the researchers performed *in-vivo* experiments, demonstrating that knockdown of either *MIAT* or IL-1 β reduced neuronal apoptosis and inflammatory factors in the brains of mice, resulting in alleviated brain damage [185]. Remarkably, the mice exhibited improved neurological functions and behaviors [185].

Another study utilizing middle cerebral artery occlusion models discovered that *MIAT* increased the stability of Egl-9 Family Hypoxia Inducible Factor 2 (*EGLN2*) post-ischemic injury [186]. This increased stability reduced *EGLN2* degradation, which had a detrimental effect on the volume of the infarct and neuronal apoptosis [186].

Additionally, an interaction between *MIAT* and Regulated in Development and DNA Damage Responses 1 (*REDD1*) was revealed in another study as shown in Fig. 3 [187]. *REDD1* plays crucial regulatory roles in autophagy and apoptosis in stressed neurons [187]. The study observed increased *MIAT* and *REDD1* levels in the brains of IS-induced mice, along with augmented infarct volumes [187]. Intriguingly, knocking down of *MIAT* resulted in the downregulation of *REDD1*, decreased apoptotic markers, and reduced infarct volumes [187]. The interaction between *MIAT* and *REDD1* was further confirmed through RNA-pulldown and RIP assays [187].

These findings collectively suggest that *MIAT* plays a pivotal role in the progression of IS and hold promising potential as a therapeutic target as well as promising diagnostic and prognostic biomarker for IS. The in-depth exploration of the *MIAT*-mediated molecular pathways in IS opens new avenues for potential interventions to combat the detrimental effects of such neuropathological condition.

5.3. Cardiovascular diseases

5.3.1. Myocardial infarction (MI)

Cardiovascular diseases are the leading cause of global mortality, with coronary heart disease (CHD) accounting for the largest proportion [188]. Among CHD complications, MI is the predominant one, and is more prevalent in the elderly (>60 years) [188]. MI is an ischemic heart disease resulting from inadequate blood flow, leading to reduced oxygen supply, cell death in the ischemic region, and activation and proliferation of cardiac fibroblasts, contributing to cardiac fibrosis [189–191]. The deterioration of functional cardiomyocytes with fibrotic tissue worsens cardiac function, especially in the left ventricle (LV), ultimately leading to irreversible heart failure [192]. Cardiomyocytes are terminally differentiated cells lacking the ability to divide, limiting the heart's regenerative capacity in adult mammals [193]. As a result, the replacement of deceased cardiomyocytes with new functional ones becomes a formidable challenge, significantly impacting the severity of MI and its potential long-term effects on cardiac function [193]. Despite improved clinical outcomes for MI, CHD remains a leading cause of death worldwide. This emphasizes the urgent need to identify new therapeutic targets and potential stable biomarkers to reduce the chances of myocardial injuries in MI.

5.3.1.1. Exploring the role of *MIAT* in MI: expression profile, signaling pathways and potential implications. In the 2000s, researchers identified a SNP within *MIAT* that was highly prevalent in MI patients, suggesting its potential involvement in MI pathogenesis [194]. This finding was further validated in a larger cohort in 2006 [195]. In a subsequent clinical trial focusing on the expression of specific lncRNAs in MI, Vausort et al. observed moderate expression of *MIAT* in PBMCs of MI patients compared to controls [196].

Interestingly, when analyzing the two subtypes of MI, namely ST-segment-elevation MI (STEMI) and non-ST-segment-elevation MI (NSTEMI), Vausort et al. found that *MIAT* levels were lower in STEMI patients relative to NSTEMI patients [196]. Moreover, *MIAT* expression was negatively correlated with cardiac biomarkers such as troponin T [196]. Another study focusing on acute MI also reported similar findings, with *MIAT* expression being lower in STEMI compared to NSTEMI [197]. Furthermore, Vausort et al. found that *MIAT* expression showed positive correlations with cardiovascular risk factors, including hypertension and smoking [196]. Additionally, *MIAT* levels were positively correlated with the percentage of lymphocytes and negatively correlated with neutrophils and platelets [196]. The study also indicated that *MIAT* was a weak predictor of LV dysfunction, a condition commonly associated with MI [196].

In another study, researchers investigated whether *MIAT*'s expression could serve as a diagnostic biomarker for MI. They found that plasma levels of *MIAT* in MI patients were significantly higher than in controls [198]. Furthermore, the expression of *MIAT* showed a positive correlation with cardiac markers, including creatine kinase-MB and troponin T [198]. Similar investigations in animal models also demonstrated a similar trend, with increased *MIAT* levels in MI-induced rats compared to controls. Knocking down experiments further revealed *MIAT*'s involvement in cardiomyocyte apoptosis [199]. Similar findings were also reported by Wang et al., where *MIAT* was found to be more highly expressed in MI patients, although its expression was not positively correlated with cardiac biomarkers [200]. Additionally, a more recent clinical study conducted on a Chinese population also observed higher *MIAT* expression in MI patients compared to normal individuals [201]. These collective findings provide valuable insights into the potential utility of *MIAT* as a diagnostic biomarker in the context of MI.

In mouse models of MI, *MIAT* expression in MI hearts was significantly higher compared to controls. Interestingly, *MIAT* knockdown was found to prevent cardiac fibrosis, likely achieved by inhibiting *MIAT*'s effects on collagen production, leading to improved cardiac function

[202]. *MIAT*'s involvement in heart failure models has been linked to the activation of the PI3K/AKT/mTOR signaling pathway, both in *in-vivo* and *in-vitro* settings, and its role in collagen production was once again validated, indicating its potential contribution to promote cardiac fibrosis [203].

Additionally, *MIAT* upregulation was associated with increased expression of fibrotic regulators, including furin and transforming growth factor (TGF- β 1), and downregulation of miR-24 that is known for its role in mediating anti-fibrotic effects [202]. This suggests that the interplay between *MIAT*, miR-24, and fibrotic regulators contributes to the pathogenesis of MI as shown in Fig. 3.

It is well-established that exercise can significantly improve the quality of life for MI patients and reduce mortality [204]. In light of this, a recent study sought to investigate the impact of exercise on the expression of lncRNAs in rats [205]. The researchers conducted experiments in rats to demonstrate that moderate exercise indeed had positive effects on the progression of MI [205]. They observed improvements in LV function and a reduction in fibrosis and apoptosis of cardiomyocytes. Interestingly, the expression of *MIAT* was found to be downregulated in mice after the exercise regimen [205]. This intriguing finding, combined with the previously mentioned pro-fibrotic effects of *MIAT*, suggests that the reduction of fibrosis post-exercise may be attributed to the repression of *MIAT* expression levels. However, further investigations are required to validate the potential of *MIAT* as a therapeutic target for managing MI. These findings offer valuable insights into the potential therapeutic benefits of exercise in the context of MI and highlight the need for continued research to better understand the underlying mechanisms involved.

Another study demonstrated an interplay between miR-203, *MIAT*, and mitochondrial coupling factor 6 (CF6) in MI, where *MIAT* and CF6 were upregulated but miR-203 was downregulated in mouse myocardial tissues following MI [206]. CF6 is known to aggravate MI, and knocking down of *MIAT* led to downregulation of CF6 expression, suggesting *MIAT* and CF6 as downstream players of miR-203 in MI pathogenesis [206].

Furthermore, *MIAT* was found to interact with miR-10a-5p, downregulating its expression [207]. This repression of miR-10a-5p had repressive effects on Early Growth Response 2 (EGR2) expression, a factor associated with activating pro-apoptotic pathways [207]. The study demonstrated that *MIAT* silencing contributed to cardio protection in MI by modulating the miR-10a-5p/EGR2 axis as shown in Fig. 3 [207].

In another study, a distinct role of *MIAT* in MI was uncovered, involving its interaction with a mitochondrial membrane protein in cardiac cells known as Translocator protein (TSPO) [208]. TSPO plays a crucial role in regulating mitochondrial membrane potential and is involved in various signaling cascades, including apoptosis [208]. The study revealed that the interaction between *MIAT* and TSPO had significant consequences on mitochondrial membrane integrity in the infarct zone [208]. This interaction appeared to have detrimental effects on mitochondrial function and energy production within cardiac cells, leading to impaired contractile function of the heart [208]. Knocking down of *MIAT* not only represses TSPO levels but also rescues mitochondrial damage and reduced apoptosis [208]. To investigate further, the researchers initially examined the expression of *MIAT* in the hearts of MI mouse models and cultured neonatal mouse ventricular cells (NMVCs) after being subjected to hypoxic insult [208]. They observed that *MIAT* was significantly more highly expressed in both the induced-MI models and the NMVCs compared to their respective controls [208]. These findings provide valuable insights into the molecular mechanisms underlying MI-induced cardiac damage and could potentially pave the way for future therapeutic strategies aimed at targeting *MIAT* or TSPO to mitigate the detrimental effects of MI on the heart's contractile function. Such interventions may hold promise for improving the prognosis and quality of life for individuals affected by this devastating condition.

In a recent model of hypoxia-induced cardiomyocyte injury, another regulatory network governed by *MIAT* was unveiled. *MIAT* was found to suppress miR-488-3p, a miRNA known for its cardioprotective effects on cardiomyocyte injury, particularly through the downregulation of Wnt family member 5A (Wnt5A) [209]. The Wnt- β -catenin signaling pathway has been extensively discussed in the pathogenesis of MI [209]. This suggests that the *MIAT*-miR-488-3p-Wnt5 axis may also play a role in the pathogenesis of MI, highlighting the importance of normalizing the expression of *MIAT* in MI patients.

In another study exploring the cardioprotective properties of the phytochemical lutein in a mouse model of isoprenaline-induced MI, researchers found that treatment with lutein led to the suppression of *MIAT* expression [210]. These findings suggest that targeting *MIAT* could potentially offer cardiovascular benefits to MI patients.

These findings add to the growing body of evidence supporting the multifaceted role of *MIAT* in cardiac pathophysiology, particularly in heart failure and MI. The identification of these regulatory networks provides valuable insights into potential therapeutic targets for managing cardiac fibrosis and improving outcomes in patients with heart failure and MI. Further research is warranted to fully elucidate the mechanisms underlying *MIAT*'s molecular pathways and explore its potential as a theranostic agent in cardiovascular diseases.

5.3.2. Coronary artery disease (CAD)

Coronary artery disease (CAD) is a prevalent condition stemming from atherosclerotic processes occurring in the coronary arteries. This disorder may exhibit no symptoms or lead to life-threatening situations. Notably, CAD stands as the primary cause of mortality in CHD [211]. Atherosclerosis is recognized as a gradually advancing inflammatory state wherein oxidative, hemodynamic, and biochemical factors impair the functionality of endothelial cells [212]. Subsequent changes in endothelial cell permeability, the accumulation of macrophages, the release of inflammatory substances, and the activation of smooth muscle cells represent additional stages in the progression of atherosclerosis [213,214].

5.3.2.1. Exploring the role of *MIAT* in CAD: expression profile, signaling pathways and potential implications. Tan et al. [215] conducted a study with the objective of uncovering the clinical significance of *MIAT* expression in predicting CAD. In pursuit of this goal, the researchers evaluated the serum levels of *MIAT*, tumor necrosis factor- α (TNF- α), and interleukin-6 (IL-6) in 102 CAD patients and 89 healthy controls. The findings indicated that the expression of *MIAT* was approximately three times higher in CAD patients compared to healthy donors. Corroborating this observation, linear correlation analysis demonstrated a positive association between *MIAT*, IL-6, and TNF- α in CAD. Furthermore, the results of multivariate analysis highlighted that, apart from hypertension, diabetes, and HDL-C, serum *MIAT* stood out as an independent risk factor for CAD. Considering these outcomes, the authors concluded that serum *MIAT* may serve as a potential biomarker for both diagnosing and prognosticating CAD. However, it is crucial to note that this study did not delve into the potential correlation between serum *MIAT* and coronary risk factors, such as hypertension, hyperlipidemia, diabetes, sex, and age.

Toraih et al. [216] further supported and expanded upon this concept by examining the circulating levels of *MIAT* in 110 stable CAD patients and 117 control volunteers using qPCR. They then correlated the expression of *MIAT* with both clinical and laboratory data. The results revealed a striking 12-fold increase in the median *MIAT* level in patients compared to controls. These compelling findings led the authors to suggest that *MIAT* holds diagnostic significance in CAD patients. However, the regulatory role of *MIAT* in the pathogenesis of atherosclerosis of coronary arteries is still needs further investigations.

5.3.3. Cardiac hypertrophy (CH)

Cardiac hypertrophy (CH) primarily arises as a response to heightened preload or afterload, aiming to maintain cardiac output. Infrequently, it may result from genetic mutations or exposure to growth factors. When confronted with increased workload, CH leads to enhanced contractility, initially reduces LV wall stress through increased wall thickness, accordance with Laplace's law, and induces alterations in gene expression. This, in turn, brings about modifications in heart metabolism, contractility, and the survival of cardiomyocytes. The classification of CH includes physiological and pathological forms. Despite their differences, both conditions involve the enlargement of cardiomyocytes and represent adaptive responses to cardiac stress [217].

5.3.3.1. Exploring the role of *MIAT* in CH: expression profile, signaling pathways and potential implications. Multiple studies employing various animal models have demonstrated the role of *MIAT* in the progression of CH. The findings from these investigations unanimously converge on the conclusion that *MIAT* functions as a growth stimulator, promoting hypertrophic changes in the heart. The initial study, conducted by Zhu et al. [218] investigated a mouse model of CH induced by Angiotensin II (AngII) and utilized an *in-vitro* model with rat heart-derived H9c2 cells. In both the *in-vivo* and *in-vitro* models, a substantial 5–6-fold increase in *MIAT* was observed in CH. Upon silencing of *MIAT* levels, it markedly mitigated the upregulation of hypertrophic biomarkers including atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and beta-myosin heavy chain (β -MHC) in H9c2 cells. Additionally, it significantly reduced the increase in cell surface area and protein synthesis induced by AngII. In a ceRNA manner, overexpression of *MIAT* in H9c2 cells resulted in the downregulation of miR-150 expression, while knockdown of *MIAT* upregulated it. Furthermore, forced expression of miR-150 inhibited the expression of hypertrophic marker genes and suppressed hypertrophic phenotypes, aligning with other studies that demonstrate the anti-hypertrophic action of this miRNA [219].

Later, another study was conducted to unravel the underlying mechanism through which *MIAT* regulates the development of CH. In their findings, *MIAT* and miR-93 exhibited contrasting expression patterns in AngII-treated cardiomyocytes; *MIAT* showed high expression, while miR-93 displayed low expression levels. These reciprocal changes prompted the researchers to establish the targeting relationship between *MIAT* and miR-93, employing a combination of qPCR, luciferase assays, and RNA immunoprecipitation (RIP) techniques. The results confirmed *MIAT* as a ceRNA of miR-93, subsequently regulating Toll-like receptor 4 (TLR4) expression. Consequently, their data suggest that *MIAT* knockdown exerts inhibitory effects on CH through the miR-93/TLR4 pathway [220].

In another experimental work, researchers affirmed the pro-hypertrophic nature of *MIAT* in both a mouse model of CH induced by intraperitoneal isoproterenol (ISO) and a cellular model of cardiomyocyte hypertrophy involving neonatal rat ventricular myocytes (NRVMs) [221]. Their findings demonstrated a significant 4.5-fold increase in *MIAT* transcripts upon ISO stimulation, observed both *in-vivo* and *in-vitro*. Again this study showed that knocking down of *MIAT* resulted in decreased expression levels of hypertrophic marker genes and a reduction in cell surface area. Furthermore, they presented evidence supporting *MIAT*'s capability to inhibit miR-150 and extended their investigation to identify P300, an acetyltransferase and transcriptional coactivator known to promote cardiac growth and drive CH [222], as a target gene for miR-150. Subsequently, they established that *MIAT* reduces P300 expression by sequestering miR-150.

Yet another research team detailed their investigation into the impact of berberine, an effective natural supplement compound derived from various plants, on CH. They conducted experiments using a rat model with abdominal aorta constriction and H9C2 cells stimulated with AngII to induce cardiomyocyte hypertrophy [223]. Their findings

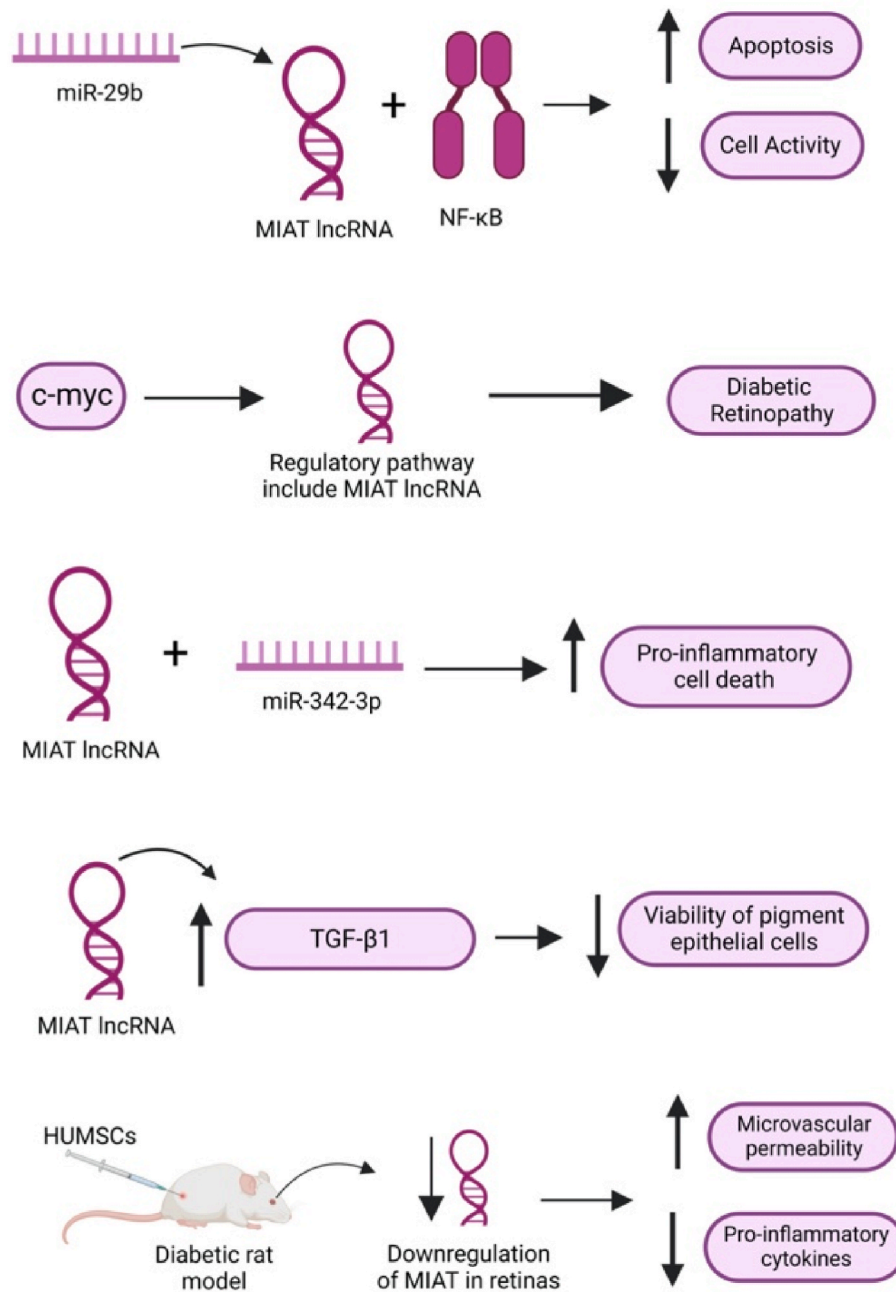


Fig. 4. MIAT as a regulator of multiple pathways in diabetic retinopathy.

indicated that berberine significantly alleviates CH, reduces cardiomyocyte enlargement, and diminishes the expression of hypertrophy marker proteins. Notably, berberine also suppresses the expression of *MIAT* in CH. Additionally, berberine downregulates phosphorylated mTOR, phosphorylated adenosine monophosphate-activated protein kinase (AMPK), and microtubule-associated proteins 1A/1B light chain 3B (LC3), while simultaneously upregulating autophagy-related genes. Despite concluding that berberine exerts beneficial effects on CH by decreasing *MIAT* expression and enhancing autophagy, the authors did not establish a connection between *MIAT* and autophagy, nor did they clarify the mechanism through which berberine suppresses the expression of *MIAT* [224].

5.4. Metabolic disorders

5.4.1. Diabetes mellitus (DM)

Diabetes mellitus (DM) is a highly prevalent disease, affecting approximately half a billion people worldwide according to the International Diabetes Federation Atlas in 2021 [225]. It is a cluster of metabolic disorders characterized by chronic hyperglycemia stemming from defects in insulin secretion, insulin action, or both [226–228]. This condition leads to elevated blood sugar levels, resulting in severe complications that often cause dysfunction or impairment in various organs. The heart, eyes, nerves, kidneys, and blood vessels are particularly susceptible to damage or adverse effects due to chronic DM, contributing to the high morbidity and mortality associated with the disease [225].

DM is categorized into type 1 and type 2, both influenced by several genetic, epigenetic, and environmental factors [226]. Type I DM is an autoimmune disease affecting individuals younger than 30 years and

accounts for only 5–10% of all DM cases. On the other hand, type II DM is the most prevalent, affecting individuals over the age of 40 and is often associated with obesity [225,226].

5.4.1.1. Exploring the role of MIAT in DM: expression profile, signaling pathways and potential implications. Numerous studies have highlighted the significant roles of lncRNAs in the pathogenesis, prognosis, and complications of DM. In this context, *MIAT* has drawn particular attention due to its potential implications for type 2 DM. Several investigations have demonstrated elevated *MIAT* expression in the blood of patients with type 2 DM compared to controls [229,230]. One study identified a positive correlation between *MIAT* expression and markers of cardiac remodeling, suggesting its potential as a prognostic or diagnostic factor for type 2 DM [230]. Another study focusing on PBMCs in type 2 DM also found upregulation of senescent and pro-inflammatory markers, along with a positive correlation between *MIAT* expression and poor glycemic control and insulin resistance [229]. Although direct links between *MIAT* expression and downstream effects on senescent and proinflammatory markers require further exploration, such investigations could yield valuable insights into the underlying mechanisms of *MIAT*'s impact on type 2 DM [229].

Moreover, the intriguing VITA cohort study investigated lncRNA expression in non-diabetic older adults and conducted a follow-up after 7.5 years to correlate lncRNA expression with the incidence of type 2 DM [231]. Consistent with previous findings, *MIAT* was found to be upregulated in patients who developed type 2 DM during follow-up [231]. Furthermore, its expression was correlated with both baseline and follow-up glycated hemoglobin levels, indicating that *MIAT*'s expression in the blood may predict the development of diabetes even before disease onset, suggesting a potential role for *MIAT* in the progressive loss of glucose homeostasis over time [231]. These studies highlight the importance of *MIAT* in the context of type 2 DM and warrant further research to elucidate its precise mechanisms and potential implications as a diagnostic or prognostic biomarker in DM.

In a recent study investigating the expression of ncRNAs in type 1 DM, *MIAT* was also identified as one of the upregulated differentially expressed genes in such metabolic disorder [232]. Notably, the differentially expressed genes also encompassed crucial pathways relevant to DM, including the phosphatidylinositol signaling system and the insulin signaling pathway [232]. While these findings indicate the potential involvement of *MIAT* in the pathogenesis of type 1 DM, further investigations are necessary to validate its role and significance in disease development and diagnosis.

The role of *MIAT* in the pathogenesis of DM has been extensively explored in a study conducted by Yan et al. In their project, they discovered that *MIAT* plays a significant role in microvascular complications that lead to diabetic retinopathy (DR) [233]. To gain deeper insights into the underlying mechanisms of *MIAT*'s contribution to DM pathogenesis, the researchers uncovered a regulatory loop involving vascular endothelial growth factor (VEGF) and miR-150-5p [233]. This regulatory loop was found to modulate *MIAT*'s actions on neural and vascular cell functions [233].

Moreover, Zhou et al. investigated the role of *MIAT* in hyperglycemia-induced renal tubular epithelial injury in diabetes-induced rats [234]. Their findings suggested that *MIAT* may exacerbate diabetic kidney dysfunction, potentially contributing to the progression of diabetic nephropathy [234].

These studies collectively shed light on the diverse roles of *MIAT* in the pathogenesis of DM and its related complications. Unraveling the underlying molecular mechanisms holds promise for potential therapeutic interventions by targeting *MIAT* to ameliorate the microvascular and organ-specific complications associated with DM. Further investigations are warranted to fully comprehend *MIAT*'s multifaceted impact on DM pathogenesis and its potential as a therapeutic target.

5.4.1.2. Novel crosstalk between MIAT and diabetic retinopathy (DR). A recent study studied the utility *MIAT* as a diagnostic marker for DR, a serious complication of DM that can lead to visual impairment and blindness [235]. However, no association was found between *MIAT* and DR disease progression in this study [235]. Yet, Biswas et al. conducted further investigations and confirmed that *MIAT* was upregulated in the serum of DR patients [236]. Moreover, another recent study linked the expression of a specific variant of *MIAT* to DR prognosis and its ability to predict a poor response to aflibercept treatment [237].

These findings collectively suggest the potential value of *MIAT* as a blood-based biomarker for DR. However, to establish its clinical utility, further validation studies on larger cohorts are required. Additionally, standardizing the protocol for *MIAT* quantification is essential to ensure consistent and reliable results as previously mentioned.

On both *in-vitro* and *in-vivo* levels, DR-induced rats and retinal Müller cells exhibited higher levels of *MIAT* expression compared to control groups [238]. Hyperglycemia induced an interaction between *MIAT* and nuclear factor- κ B (NF- κ B), leading to increased apoptosis and reduced cell activity, which were reversed upon knockdown of *MIAT* as shown in Fig. 4 [238]. In this regulatory network, miR-29b was also found to be involved in the regulation of *MIAT* [238]. A recent study indicated that *MIAT* is part of a pathway regulated by c-myc, which subsequently triggers the release of proinflammatory cytokines from retinal Müller cells, contributing to the pathogenesis of DR [239].

Furthermore, in another study using primary human retinal pericytes, *MIAT* was found to be upregulated and was observed to interact with miR-342-3p as shown in Fig. 4 [240]. This interaction was associated with increased proinflammatory cell death, providing additional insights into the role of *MIAT* in the inflammatory processes contributing to DR [240]. In adult retinal pigment epithelial cells, another study revealed that *MIAT* upregulates TGF- β 1 signaling, leading to a reduction in the viability of pigment epithelial cells [241]. These findings offer further understanding of the diverse impact of *MIAT* in various cellular contexts related to the development and progression of DR.

In an interesting study, the impact of human umbilical-cord mesenchymal stem cells (HUMSCs) on diabetic rat models was investigated [242]. The study revealed that post-injection of HUMSCs, *MIAT* expression in the retinas of diabetic rats was downregulated [242]. This downregulation was associated with enhanced microvascular permeability and a reduction in the levels of pro-inflammatory cytokines known to play a role in DR [242]. The findings of this study established a correlation between *MIAT* expression and proinflammatory cytokines in DR, shedding the light onto the potential role of *MIAT* in regulating these cytokines (Fig. 4) [242]. These results underscore the importance of further investigations to explore the precise mechanisms by which *MIAT* influences the inflammatory processes in DR, potentially paving the way for innovative therapeutic interventions.

5.4.1.3. Novel crosstalk between MIAT and diabetic cardiomyopathy (DCM). Diabetic cardiomyopathy (DCM) is a serious complication of DM that can lead to severe manifestations such as heart failure and arrhythmias [243]. However, treatment options for DCM are limited, highlighting the need to understand the underlying mechanisms driving this condition.

In the context of DCM, *MIAT* has emerged as a potential key player, as a study indicated its over-expression in DCM rats compared to controls. Notably, *MIAT* has been linked to the over-expression of IL-17, a proinflammatory cytokine with significant roles in cardiac fibrosis, thereby contributing to the pathogenesis of DCM [244]. This effect on IL-17 is mediated through the repressive impact of *MIAT* on miR-214-3p [244]. These findings underscore the importance of the *MIAT*/miR-214-3p/IL-17 regulatory pathway as a crucial contributor to cardiac fibrosis in DCM [244].

Another significant pathway involved in promoting pyroptosis of cardiomyocytes in rat models of DCM was reported, where *MIAT* was

found to downregulate miR-214-3p and upregulate caspase 1 [245]. These findings strongly implicate MIAT in the pathogenesis of DCM and emphasize the need for further studies to investigate targeting this pathway and validate its role as an upstream regulator of cardiac fibrosis.

Despite these compelling findings, studies analyzing the levels of MIAT in the blood of DCM patients are still lacking. Correlating the expression of MIAT with pro-fibrotic and pro-apoptotic markers is also essential to unravel the true role of MIAT in DCM. Such investigations will provide critical insights into the potential use of MIAT as a diagnostic and/or prognostic biomarker for DCM and may shed light on its therapeutic potential in combating the detrimental effects of DCM.

5.4.2. Osteoporosis (OP)

Osteoporosis (OP) is a chronic metabolic disease characterized by an imbalance in bone formation and resorption, leading to impaired bone mass and an increased risk of fractures [246]. The impact of OP is substantial, with an alarming frequency of bone fractures worldwide, as estimated by the International Osteoporosis Foundation, where a bone breaks every 3 s due to this condition [247]. With an estimated 500 million affected individuals globally, OP poses a significant health burden, particularly in the aging population [247]. Among postmenopausal women, 30% experience postmenopausal OP, which remains challenging to manage due to limited treatment options [248, 249]. Therefore, there is a pressing need to delve into research aimed at identifying therapeutic targets and gaining a deeper understanding of the mechanisms contributing to this debilitating condition. Such research endeavors hold the key to developing more effective treatments and interventions to combat the detrimental impact of OP on bone health and overall quality of life.

5.4.2.1. Exploring the role of MIAT in OP: expression profile, signaling pathways and potential implications. In a recent study, researchers investigated the levels of MIAT in the blood of postmenopausal OP patients [250]. The findings revealed that MIAT, along with IL-6, TNF- α , and p38 mitogen-activated protein kinases (p38MAPK) were upregulated in PBMCs of postmenopausal OP patients compared to healthy controls [250]. Furthermore, the study identified that MIAT acts as a repressor of miR-216a expression in PBMCs, thereby regulating the transcription of p38MAPK [250]. This regulation of p38MAPK is crucial for AMPK/MAPK signaling activation, which, in turn, influences the secretion of inflammatory cytokines [250]. These unique insights suggest that MIAT could serve as a promising predictive biomarker for postmenopausal OP and may be involved in the underlying pathogenesis of the condition. However, it is essential to conduct future studies on larger cohorts to validate these findings and fully elucidate the intricate pathways through which MIAT regulates OP. Such investigations may open up new avenues for understanding the mechanisms involved in OP development and potentially lead to the development of targeted therapeutic regimens for managing such debilitating condition.

Jin et al. investigated the role of MIAT in the osteogenic differentiation of human adipose-derived stem cells (hASCs) [251]. It is known that hASCs possess self-renewal capabilities, indicating their potential for bone tissue engineering [251]. Despite their promise, the precise mechanisms underlying hASCs' contribution to osteogenic differentiation remain poorly understood [251]. The study revealed a crucial regulatory role for MIAT in osteogenic differentiation [251]. During the process of osteogenic differentiation, MIAT expression was found to be downregulated [251]. Knockdown experiments demonstrated that reduced MIAT levels led to increased differentiation of osteoblasts [251]. Remarkably, MIAT knockdown effectively rescued the inhibition of osteogenesis induced by TNF α -mediated inflammation [251]. These findings propose a mechanism that contributes to the differentiation of hASCs, which holds particular significance for future clinical applications in tissue engineering. Understanding the role of MIAT in osteogenic

differentiation may pave the way for improved strategies to harness the therapeutic potential of hASCs in bone regenerative medicine. Further investigations are warranted to fully elucidate the intricate molecular pathways involved in this process.

5.5. Bone diseases

5.5.1. Osteoarthritis (OA)

Based on the Global Burden of Disease systemic analysis in 2019, approximately 500 million people worldwide are afflicted by osteoarthritis (OA) [252]. OA is an autoimmune diseases that profoundly impacts daily life functions due to its association with joint pain and disability [253]. While it is more prevalent in the older population (over 55), it can also affect younger individuals [253]. The primary features of OA encompass the progressive depletion of cartilage and the remodeling of the subchondral bone. Treatment options for OA are quite limited, leaving patients with joint replacement surgery as their primary recourse [254]. Additionally, drug therapy primarily focuses on alleviating pain, as there is a scarcity of drugs available that effectively slow down or reverse joint damage in OA [255]. This emphasizes the importance of identifying biomarkers and diagnostic targets that can help mitigate joint damage in OA.

5.5.1.1. Exploring the role of MIAT in OA: expression profile, signaling pathways and potential implications. In a study involving 60 participants in China, the expression of MIAT in knee cartilage tissues was found to be significantly higher in individuals with OA compared to those with normal knee conditions [256]. Additionally, this study identified miR-488-3p and SRY-Box Transcription Factor 11 (SOX11) as targets for MIAT. Previous research has established a link between SOX11 and OA, as it plays a crucial role in the regulation of proinflammatory cytokines [256]. To investigate the relationship between MIAT expression, miR-488-3p, and SOX11, the researchers employed a cell model of OA in their study [256]. The results revealed a positive correlation between MIAT expression and SOX11 levels, which was attributed to the downregulation of miR-488-3p [256]. This correlation was also found to be associated with the potentiation of chondrocyte injury, indicating a potential mechanism by which MIAT impacts OA pathogenesis.

Previous studies have reported on osteopontin (OPN)'s function as a regulator of various factors related to OA, affecting chondrocyte proliferation and apoptosis [257–259]. In human chondrocytes isolated from OA cartilage, MIAT has been associated with its role as an upstream regulator of miR-181a-5p and OPN [260]. Notably, MIAT was found to be upregulated in OA cartilage tissue [260]. When targeted in chondrocytes, it led to increased expression of miR-181a-5p, which, in turn, inhibited OPN overexpression [260]. This resulted in reduced cell viability, decreased DNA synthesis, and promoted apoptosis in human chondrocytes [260]. Another study using a cell model of OA revealed that MIAT was involved in inducing apoptosis and the release of pro-inflammatory cytokines through the regulation of NF- κ B and c-Jun N-terminal kinases (JNK) by inhibiting the expression of miR-132 [261]. These findings suggest that MIAT acts as an upstream regulator within several networks contributing to the pathogenesis of OA.

5.6. Conclusion and future perspectives

In the current review, the authors have unveiled the significance of lncRNAs in various physiological and pathological conditions. LncRNAs have distinct expression patterns and versatile functions across different diseases. Accordingly, disease-associated lncRNAs can be utilized as diagnostic and prognostic biomarkers and/or therapeutic targets tailoring a personalized medicine approach for patients with rare complex diseases. This review was mainly concerned about the non-oncological pathological conditions where lncRNAs were found to be implicated in neurological diseases, cardiovascular diseases, metabolic

Table 1
Expression status of *MIAT* in multiple pathological diseases.

Disease	Expression Profile	Validated Target Genes/Signaling pathway	References
Multiple Sclerosis	Controversial	SF1 CE1F3 QKI	[49,155,166,168,169,176]
Schizophrenia	Controversial	BMI1 Crybb1	[174,177]
Ischemic stroke	Upregulated	miR-874-3p/IL-1 β pathway EGLN2 REDD1	[185] [186] [187]
Myocardial infarction	Upregulated	involvement in cardiomyocyte apoptosis Activation of the PI3K/Akt signaling pathway miR-24/furin/TGF- β 1 miR-203 miR-10a-5p/EGR2 axis. TSPO modulating mitochondrial membrane integrity in the infarct zone Wnt- β -catenin signaling pathway	[189,198] [203] [202] [206] [207] [208] [209]
Coronary artery disease	Upregulated	chemokine signaling pathways NOD-like receptors	[215,216]
Cardiac hypertrophy	Upregulated	ANP BNP β -MHC miR-93/TLR4 PI3K/Akt/mTOR pathway miR-150/P300	[218,219] [220] [222]
Diabetes mellitus	Upregulated	N/A	[229,230]
Diabetic retinopathy	Upregulated	NF- κ B miR-342-3p TGF- β 1 signaling pathway	[238] [240] [241]
Diabetic cardiomyopathy	Upregulated	miR-214-3p/IL-17 miR-214-3p-CASP1 axis in pyroptosis of cardiomyocytes	[244] [245]
Osteoporosis	Upregulated	miR-216a/p38MAPK signaling pathway	[250]
Osteoarthritis	Upregulated	miR-488-3p/SOX11 miR-181a-5p/OPN miR-132/NF- κ B	[256]

disorders and some bone diseases. In particular, *MIAT* lncRNA was reported to be involved in most of previously mentioned categories of non-oncological pathological conditions. The authors cast the light upon the controversial studies regarding the expression profile, diagnostic and prognostic potential of *MIAT* in several diseases as summarized in (Table 1). Nonetheless, a snapshot of all validated signaling pathways drawn downstream *MIAT* lncRNA in non-oncological conditions have been highlighted in the current review.

It is also worth noting the *MIAT* lncRNA also show high therapeutic potential in several conditions highlighting a great promise in preclinical studies. However, further research is needed to fully elucidate the underlying molecular mechanisms and evaluate their effectiveness and safety in clinical settings. Future research should focus on comprehensive functional studies to uncover the specific roles of *MIAT* in different diseases. Exploring the interactions between lncRNAs and other ncRNAs, such as miRNAs, may reveal complex regulatory networks and therapeutic opportunities. Developing innovative technologies for accurate detection and quantification of lncRNAs will be crucial for their clinical use. In summary, lncRNAs have the potential to revolutionize the diagnosis, prognosis, and treatment of various non-oncological diseases. Continued research efforts and interdisciplinary collaborations are necessary to unlock the full potential of lncRNAs as diagnostic biomarkers, therapeutic targets, and interventions in the era of personalized medicine.

CRedit authorship contribution statement

Yousra Zeinelabdeen: Writing – original draft, Methodology, Investigation, Data curation. **Tasneem Abaza:** Writing – original draft, Validation, Methodology, Data curation. **Montaser Bellah Yasser:** Data curation, Formal analysis, Methodology, Software. **Noha M. Elemam:** Writing – review & editing, Validation, Methodology, Formal analysis. **Rana A. Youness:** Writing – review & editing, Writing – original draft,

Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

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