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Puzzling out the role of *MIAT* LncRNA in hepatocellular carcinoma

Rawan Amr Elmasri [a], Alaa A. Rashwan [a,b], Sarah Hany Gaber [a], Monica Mosaad Rostom [c], Paraskevi Karousi [d], Montaser Bellah Yasser [e], Christos K. Kontos [d], Rana A. Youness [a,*]

[a] *Molecular Genetics Research Team (MGRT), Biology and Biochemistry Department, Faculty of Biotechnology, German International University (GIU), New Administrative Capital, 11835, Cairo, Egypt*
[b] *Biotechnology Graduate Program, School of Sciences and Engineering, The American University in Cairo (AUC), 11835, Cairo, Egypt*
[c] *Pharmacology and Toxicology Department, Faculty of Pharmacy and Biotechnology, German University in Cairo (GUC), 11835, Cairo, Egypt*
[d] *Department of Biochemistry and Molecular Biology, Faculty of Biology, National and Kapodistrian University of Athens, Panepistimiopolis, 15701, Athens, Greece*
[e] *Bioinformatics Group, Center for Informatics Sciences (CIS), School of Information Technology and Computer Science (ITCS), Nile University, Giza, Egypt*

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ABSTRACT

A non-negligible part of our DNA has been proven to be transcribed into non-protein coding RNA and its intricate involvement in several physiological processes has been highly evidenced. The significant biological role of non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) has been variously reported. In the current review, the authors highlight the multifaceted role of myocardial infarction-associated transcript (*MIAT*), a well-known lncRNA, in hepatocellular carcinoma (HCC). Since its discovery, *MIAT* has been described as a regulator of carcinogenesis in several malignant tumors and its overexpression predicts poor prognosis in most of them. At the molecular level, *MIAT* is closely linked to the initiation of metastasis, invasion, cellular migration, and proliferation, as evidenced by several *in-vitro* and *in-vivo* models. Thus, *MIAT* is considered a possible theranostic agent and therapeutic target in several malignancies. In this review, the authors provide a comprehensive overview of the underlying molecular mechanisms of *MIAT* in terms of its downstream target genes, interaction with other classes of ncRNAs, and potential clinical implications as a diagnostic and/or prognostic biomarker in HCC.

1. Introduction

Following the completion of "The Human Genome Project" in 2003, the classification of the genome and its elements has been a challenge and the focus of all molecular scientists [1,2]. One of the broad classifications of the genome is categorizing it into protein-coding and non-protein-coding genes [3]. The protein-coding regions of the DNA were once thought to be the most fundamentally functional segment, and as a result, must make up the majority of the DNA [4,5]. Surprisingly, less than 3 % of the genome's transcribed region is translated into proteins [6,7]. Given this, non-coding RNAs (ncRNAs), or non-protein producing RNA, which were previously assumed to be the result of "junk DNA", attracted attention as it became clear that they do serve a purpose [8,9]. According to databases such as Human GENCODE and NONCODEV5, the major class of ncRNAs are long non-coding RNAs (lncRNAs), with over 100,000 members. Yet to be determined is the precise number of functional lncRNAs [10–14]. Members of this class have transcripts larger than 200 nucleotides and are important regulators [15,16]. LncRNAs can also be divided into subclasses [17,18]. According to one of these classifications, the genomic location of ncRNAs can result in intergenic, intronic, sense, and antisense lncRNAs [9,19,20], as shown in Fig. 1.

2. Roles and functions of lncRNAs

Alternatively, lncRNAs can be classified according to their functional role [17]. As already indicated, lncRNAs have a significant regulatory function, modulating the activity of genes, RNAs, proteins, organelles, and nuclear condensates [21,22]. More specifically, lncRNA functions include one or more of the following: chromatin remodeling, histone modification, RNA-DNA-DNA triplex formation through direct pairing with the DNA, gene silencing, transcriptional regulation of genes through silencing or enhancing respective mRNA expression, nuclear condensate formation, post-transcriptional modifications exerted by direct protein-binding, miRNA sponging, and mRNA stabilization.

* Corresponding author. Molecular Genetics Research Team (MGRT), Biology and Biochemistry Department, Faculty of Biotechnology, German International University (GIU), New Administrative Capital, 11835, Cairo, Egypt.
E-mail addresses: rana.youness@giu-uni.de, rana.youness21@gmail.com (R.A. Youness).

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Abbreviations

ABCG2 ATP Binding Cassette subfamily G member 2
ACE Angiotensin-converting enzyme gene
ADGRL2 adhesion G protein-coupled receptor L2
ANRIL Antisense Non-coding RNA in the INK4 Locus
ASO Antisense Oligonucleotide
ATG7 autophagy related 7
ATM Ataxia Telangiectasia Mutated
BANCR BRAF-Activated Non-Protein Coding RNA
CASP1 Caspase 1
CCAT1 Colon Cancer-Associated Transcript 1
CCND1 Cyclin D1
CD8 Cluster of Differentiation 8
CDC16 Cell division cycle protein 16 homolog
CDKN1A Cyclin Dependent Kinase inhibitor 1A
CDKN2B Cyclin-Dependent Kinase 4 inhibitor B
CEP170 Centrosomal Protein 170
CK2 Checkpoint Kinase 2
c-Met Mesenchymal-Epithelial Transition factor
CORO1C Coronin-like actin-binding protein 1C
CREBRF CREB3 Regulatory Factor
CTLA4 Cytotoxic T-Lymphocyte Antigen 4
CTNNB1 catenin beta 1
DAPK2 Death-associated protein kinase 2
DDX5 DEAD box polypeptide 5
Derlin-1 Degradation in Endoplasmic Reticulum protein 1
DLG3 Disks large homolog 3
DUSP7 Dual Specificity Phosphatase 7
EGFR Epidermal Growth Factor Receptor
EMT Epithelial-Mesenchymal Transition
ENCORI Encyclopedia of RNA Interactomes
eNOS Endothelial nitric oxide synthase
EPHA2 Erythropoietin-Producing Hepatocellular receptor A2
EZH2 Enhancer of Zest Homolog 2
FASTKD5 FAST kinase domains 5
FOXP3 Forkhead Box P3
GAPDH Glyceraldehyde-3-Phosphate Dehydrogenase
GAS5 Growth arrest-specific 5
GDI2 GDP Dissociation Inhibitor 2
GENCODE Human GENCODE database
GEO Gene Expression Omnibus
GO Gene Ontology
GZMK Granzyme K
HAVCR2 hepatitis A virus cellular receptor 2
HCC Hepatocellular Carcinoma
HDAC4 Histone Deacetylase 4
HEIH HCC-specific lncRNA Enhancer of Invasion and Migration
HIF1A Hypoxia Inducible Factor 1 Subunit Alpha
HOTAIR HOX Transcript Antisense RNA
HOXA5 Homeobox A5
HSC hepatic stellate cell
IER2 Immediate Early Response 2
IL-17 Interleukin 17
IPO7 Importin 7
IST1 IST1 factor associated with ESCRT-III
JAG1 Jagged canonical Notch ligand 1
JAK2 Janus Kinase 2
JNK Jun *N*-terminal kinase
KCND1 Potassium Voltage-Gated Channel Subfamily D Member 1
KCNQ1 Potassium Voltage-Gated Channel Subfamily Q member 1
KCNQ1OT1 KCNQ1 Overlapping Transcript 1
LAG3 Lymphocyte-Activation Gene 3
LASP1 LIM And SH3 Protein 1
LDB1 LIM Domain-Binding protein 1
LincRNA-p21 Long Intergenic Non-coding RNA-p21
LINGO1 Leucine Rich Repeat And Ig Domain Containing 1
LIPCAR Long Intergenic Non-Protein Coding RNA for Cardiac Regeneration
lncRNA Long Non-coding RNA
LncRNA-ATB Long Non-coding RNA Activated by TGF-β
LncRNA-LET Long Non-coding RNA Low Expression in Tumor
LONP2 Lon peptidase 2, peroxisomal
LOXL2 Lysyl oxidase homolog 2
LUCAT1 Lung Cancer-Associated Transcript 1
MALAT1 Metastasis-Associated Lung Adenocarcinoma Transcript 1
MEG3 Maternally expressed 3
MEGF8 Multiple Epidermal Growth Factor-like Domains 8
MEIS3 Meis Homeobox 3
MIAT Myocardial Infarction-Associated Transcript
MIR34A MicroRNA 34a
miRNA MicroRNA
MLF2 Myeloid Leukemia Factor 2
MMP14 Matrix metalloproteinase-14
MTCH1 Mitochondrial carrier homolog 1
MYO1B Myosin IB
NAD Nicotinamide Adenine Dinucleotide
NBR2 Neighbor Of BRCA1 LncRNA 2
ncRNA Non-coding RNA
NEAT2 Nuclear Enriched Abundant Transcript 2
NF-κB Nuclear Factor kappa B
NLM National Library of Medicine
NO Nitric Oxide
NONCODEV5 NONCODE database version 5
NONO Non-POU Domain Containing Octamer Binding
NORAD Non-Coding RNA Activated By DNA Damage
Notch1 Neurogenic locus notch homolog protein 1
PANDAR Promoter of CDKN1A Antisense DNA Damage Activated RNA
PCAT-1 Prostate cancer associated transcript-1
PCDH1 Protocadherin 1
PD-1 Programmed Cell Death 1
PDCD1 Programmed cell death protein 1
PD-L1 Programmed Death-Ligand 1 (CD274 molecule)
PFN1 Profilin 1
PGC-1a Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K Phosphatidylinositol 3-Kinase
PLAGL2 Pleomorphic adenoma gene like-2
PRODH Proline Dehydrogenase 1
PTENP1 Phosphatase and Tensin homolog Pseudogene 1
PVT1 Plasmacytoma Variant Translocation 1
RAN Ras-related Nuclear protein
Rfam RNA Families database
RIN1 Ras and Rab Interactor 1
RPL13 Ribosomal Protein L13
RPL23A Ribosomal Protein L23a
RPLP1 ribosomal protein lateral stalk subunit P1
RPS3 Ribosomal Protein S3
SART3 Spliceosome Associated factor 3
SCHLAP1 SWI/SNF Complex Antagonist Associated With Prostate Cancer 1
SF-1 Steroidogenic Factor 1
SGK1 Serum/Glucocorticoid regulated Kinase 1
siRNA small interfering RNA
SIRT1 Sirtuin 1
SIX1 Sine oculis homeobox homolog 1
SLC6A6 Solute Carrier Family 6 Member 6
SNPs Single Nucleotide Polymorphisms
SOX4 SRY-Box Transcription Factor 4

SP1	Specificity Protein 1
SPHK2	Sphingosine Kinase 2
STAT3	Signal Transducer and Activator of Transcription 3
STAU1	Staufen-1
TCF20	Transcription Factor 20
TCGA	The Cancer Genome Atlas
TGF-β2	Transforming Growth Factor beta 2
TIM3	T-cell Immunoglobulin and Mucin-domain containing 3
TME	Tumor Microenvironment
TMEM147	Transmembrane Protein 147
TP53	Tumor Protein p53
TRAF6	TNF Receptor Associated Factor 6
TTC37	Tetratricopeptide repeat domain 37
TUBA1B	Tubulin Alpha 1B
UBA2	Ubiquitin-Like Modifier-Activating Enzyme 2
VEGF	Vascular endothelial growth factor
VELUCT	Viability Enhancing in Lung cancer Transcript
WNT9A	Wnt Family Member 9A
XIST	X-linked X-inactive-specific transcript
YAP1	Yes-associated protein 1
YBX1	Y-box binding protein 1
YWHAE	Tyrosine 3-Monooxygenase/Tryptophan 5-Monooxygenase Activation Protein Epsilon
ZEB1	Zinc finger E-box binding homeobox 1

Additionally, lncRNAs may affect mitochondrial function, intercellular exosomal transport, and cell regulation [12,20,23,24]. Table 1 lists functional roles played by lncRNAs.

3. LncRNAs as potential theranostic agents (biomarkers and/or therapeutic agents)

The functional roles of lncRNAs unravel their crucial role in various aspects of cellular homeostasis [39]. Moreover, lncRNAs have the potential to serve as non-invasive prognostic markers, diagnostic markers, and/or potential therapeutic agents/targets in a variety of diseases, such as cancer, diabetes, and genetic diseases which perfectly classifies them as theranostic agents with great potential in several malignant and non-malignant contexts [12,14,40,41].

Specifically, several lncRNAs have been characterized as non-invasive biomarkers quantifiable in liquid biopsies [42]. LncRNAs show tissue-specific expression patterns, which aid in the traceability of different cancer types [43]. Additionally, they are abundant in plasma samples, enabling their easy detection. Although it is still unclear whether exosomal or free lncRNAs contribute more to the detectable fraction, exosomal lncRNAs are known to be stable in biological fluids, due to their resistance and stability against RNases [42,44,45].

Exosomal lncRNAs constitute promising candidates for therapeutic intervention in various diseases since they are increasingly recognized as key players in intercellular communication, controlling cellular functions, and affecting disease states. These characteristics also raise the possibility of employing non-oncogenic exosomal lncRNAs therapeutically for internalization and cell-specific effects after a disease mechanism has been thoroughly elucidated [42,45]. Other hypotheses have been put forth in which lncRNAs act as the therapeutic targets rather than the therapeutic agents [6,15].

LncRNAs that foster neovasculature, drug resistance, or cancer cell-to-cell communication could constitute promising targets [45]. Similarly, by identifying the binding domains of an oncogenic lncRNA that is responsible for triggering a certain signaling pathway, a complimentary chemical can be synthesized and delivered to block that lncRNA and subsequently inhibit its tumor-promoting action. Although such an approach has merit, it currently has the challenge of inadequate motif structural knowledge [12,46–48]. Additionally, lncRNAs were demonstrated to be the less toxic and more potent biological alternatives to proteins [12]. Jiang et al. highlighted how current technology can be used to pave the path for the usage of lncRNAs as therapeutic agents [12,49].

Metastasis-associated lung adenocarcinoma transcript 1 *(MALAT1)* [14,15,18], HOX transcript antisense RNA (*HOTAIR)* [41,50], H19 imprinted maternally expressed transcript (*H19)* [16,22], colon cancer associated transcript 1 (*CCAT1)* [13,21], and hepatocellular carcinoma up-regulated EZH2-associated long non-coding RNA (*HEIH)* [7] are some of the well-known lncRNA members with the potential to serve as biomarkers or therapeutic agents/targets for several malignancies such as breast, liver, and brain tumors, while *LIPCAR*, CDKN2B antisense RNA 1 (*ANRIL)*, and KCNQ1 opposite strand/antisense transcript 1 (*KCNQ1OT1)* are well-studied lncRNAs in terms of non-malignant disorders such as cardiovascular diseases [42,51,52].

4. LncRNAs in oncology

Focusing on the role of lncRNAs in cancer, several studies have identified and correlated many lncRNAs to a diverse range of malignancies. LncRNAs are pivotal regulators in the complex landscape of oncology. Aberrant expression of lncRNAs is associated with various cancers (Table 2). In addition to the ones that were before listed, *HEIH* and *sONE* act as significant breast cancer regulators [7,53,54]. LncRNA activated by TGF-β (*LNCRNA-ATB*) and NPTN intronic transcript 1 (*LNCRNA-LET*) are associated with HCC. *CCAT1*, as its name suggests, is linked to colorectal cancer, while promoter of CDKN1A antisense DNA damage activated RNA (*PANDAR)* and colon cancer associated transcript 2 (*CCAT2)* are two examples of lncRNAs important for lung cancer progression and prognosis [20,55]. Lung cancer-related transcript 1 (*LUCAT1*), is involved in breast cancer, ovarian cancer, thyroid cancer, and renal cell carcinoma [56], as well as *H19*, plays a role in breast cancer, colorectal cancer, and lung cancer [20,34,51,55].

Remarkably, lncRNAs have the potential to be used as biomarkers and therapeutic agents if they are tumor-suppressive, or as therapeutic targets if they are oncogenic. Their potential to serve as therapeutic targets and diagnostic markers holds promise for improving early detection and treatment options in oncology. Fig. 2 represents a graphical presentation of the lncRNAs and their possible association with several solid malignancies. Each lncRNA has distinct effects mediated through different signaling pathways in each cancer context. This proposes a complexity in the mechanisms and interrelated functions of lncRNAs and their subsequent effect.

5. Methodology

In the current review, the authors aimed at exploring the role of *MIAT* in HCC. The authors screened the National Library of Medicine (PubMed). To search databases, the descriptors or keywords used were: "*MIAT*", "myocardial infarction-associated transcript" "*MIAT* LncRNA", "HCC", "Hepaticellular carcinoma", and "Oncology", "LncRNAs" to cover as many articles as possible in the literature. Relevant publications with detailed information were included including research articles, review articles, and book chapters; These selected references were evaluated and summarized in order to fulfill the purpose of this review article.

6. Myocardial infarction associated transcript (*MIAT*)

Myocardial infarction-associated transcript (*MIAT*) is a novel lncRNA that has recently been reported to have a fundamental role in several oncological contexts [13,41]. *MIAT* is located on chromosome 22q12.1 as shown in Fig. 3 [79]. *MIAT* gene length is around 30 Kb.

MIAT is transcribed from the sense strand of the genome, producing a structure with 5 exons and several introns with multiple combinations of single nucleotide polymorphisms (SNPs), and a polyadenylated tail, as shown in Fig. 3. Post-transcriptional splicing gives rise to 4 different variants of spliced lncRNA [80–83]. As indicated by its name, it is predicted that it has a role in cardiovascular diseases such as atherosclerosis, and coronary artery diseases. However, it has been discovered that not only does it influence these diseases, but it also plays a key role in several solid malignancies such as lung cancer, hepatocellular carcinoma, and breast cancer among countless others [20,60,84,85]. The biogenesis of *MIAT*-like all other lncRNAs is dependent on the cell type and stage, as previously reviewed [17]. Collectively, research studies focusing on *MIAT* shed light on its complex function and offer a possible path for therapeutic interventions, as discussed below. Different functional mechanisms of *MIAT* have been described, so far; moreover, this lncRNA has been described to decoy several microRNAs (miRNAs) and thus altering the downstream array of critical signaling pathways dictating cellular proliferation, apoptosis, and inflammation (Fig. 4).

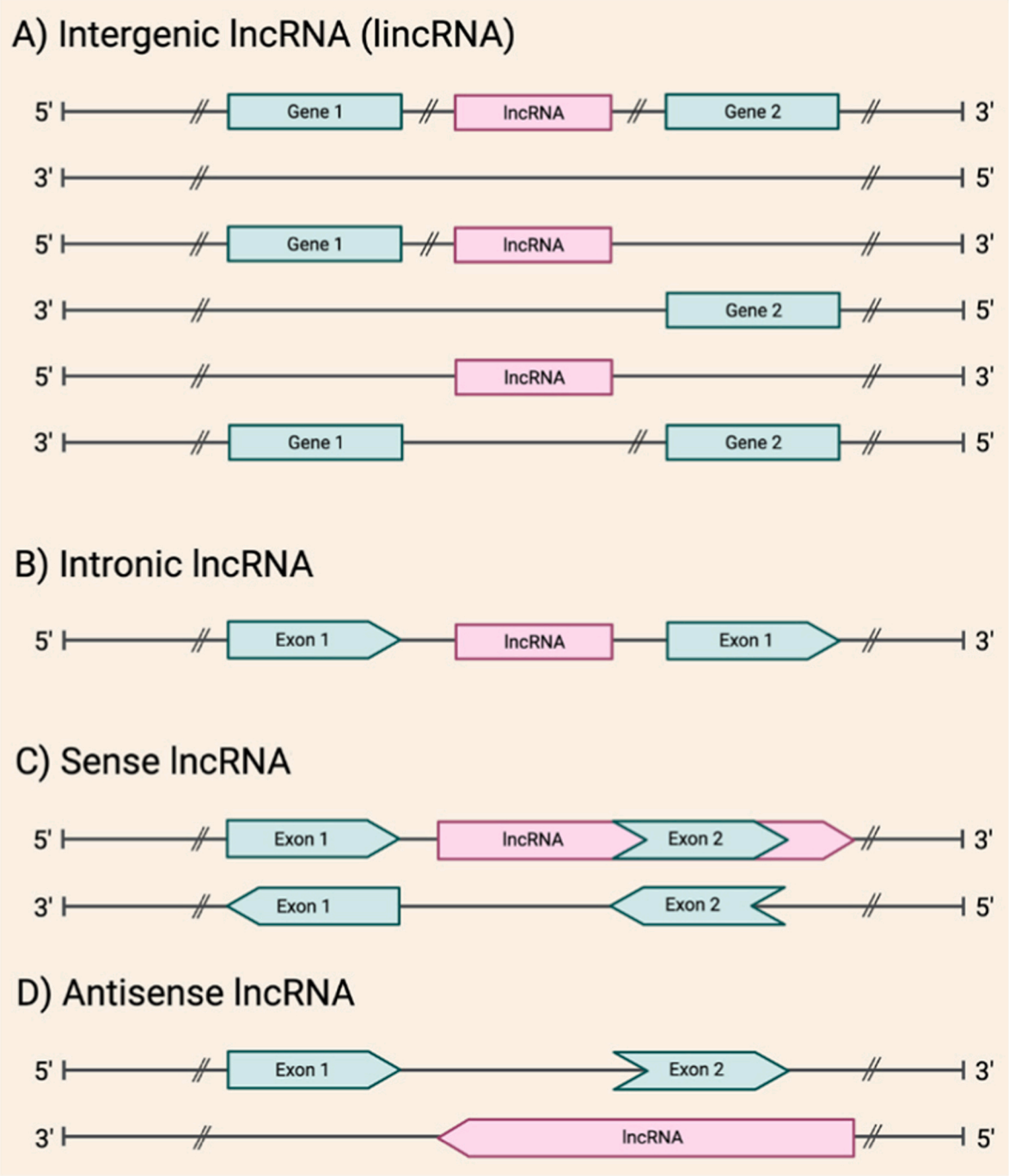

Fig. 1. The possible genomic locations of lncRNAs. Protein-coding genes and their exons are represented by green segments, while lncRNAs and their introns are represented by pink segments. (A) An intergenic lncRNA, transcribed from either DNA strand between two protein-coding genes. (B) An intronic lncRNA, transcribed from protein-coding gene introns. (C) A sense lncRNA, transcribed from the sense strand of protein-coding genes, overlapping with part (or entirely) of a protein-coding sequence and one or more introns. (D) An antisense lncRNA, transcribed from the antisense strand of protein-coding genes, overlapping with a part (or entirely) of a protein-coding sequence and 1 or more introns. (*) Sense and Antisense lncRNAs are subcategories of a larger class called genic lncRNAs.

Table 1
Molecular and functional roles of lncRNAs.

Molecular role	Functional role	References
Epigenetic regulation	Chromatin remodeling	[25]
	Histone modification	[26]
	Gene silencing	[27]
	Triplex formation	[28]
Transcriptional regulation	Promotion via promotor regions and/or transcription factor modulation	[29,30]
	Suppression via promotor regions and/or transcription factor modulation	[31]
Post-transcription regulation	Protein binding	[32]
	mRNA stabilizing activity	[33]
	miRNA sponging (lncRNAs function as competing endogenous RNA)	[34,35]
Nuclear scaffolding and condensates	–	[12]
Organelle regulation	Mitochondrial modulation of apoptosis, metabolism, and nucleus crosstalk	[36,37]
	Exosomal release	[38]

6.1. MIAT cellular localization and single nucleotide polymorphisms (SNPs)

The subcellular localization of *MIAT* is the nucleus, as demonstrated by a nuclear/cytosol fractionation assay that showed that it is mostly expressed in the nucleus of cardiomyocytes [86]. *MIAT* is known for its multiple SNPs that are strongly associated with increased susceptibility to myocardial infarction [87]. The fully elucidated sequence and SNP variations of lncRNA *MIAT* are present in multiple databases, including GeneCaRNA, Rfam, and the National Library of Medicine (NLM) gene dataset. For instance, in the Chinese Han population, the promoter polymorphisms in the *MIAT* gene Rs5752375 and Rs9608515 were found to be associated with acute myocardial infarction [83]. Furthermore, many different SNPs of *MIAT* have been shown to have different diverse effects as shown in Fig. 3. For instance, Rs1894720 *MIAT* polymorphism has been found to increase susceptibility to age-related loss of hearing by tuning the miR-29 b-3p/SIRT1/PGC-1α axis [88]. Another study demonstrated a notable correlation between Rs1894720 in *MIAT* and paranoid schizophrenia within the Chinese Han population [89].

Table 2
Potential oncogenic and tumor-suppressive lncRNAs in several malignant contexts.

LncRNA	Cancer Type	Signaling pathway	Expression profile	Impact	Hallmark involved	Reference
H19	Colorectal cancer	Sponging miR-141, thus activating the β-catenin pathway	Upregulated	Oncogenic	Cancer cell stemness and chemoresistance	[57]
	Hepatocellular cancer	Exosomal release increases the expression of endothelial factors	Upregulated	Oncogenic	Angiogenesis	[58]
HOTAIR	Non-small cell lung cancer	Suppression of matrix metalloproteinases and HOXA5 protein	Upregulated	Oncogenic	Cell invasion and metastasis	[59]
MIAT	Lung cancer	Promotor methylation of the *MIR34A* gene leads to decreased expression and subsequent activation of the PI3K/AKT signaling pathway	Upregulated	Oncogenic	Drug resistance	[60]
	Glioma	Promotor of proliferation, migration, and metastasis of brain cancer cells	Upregulated	Oncogenic	Cancer progression	[61]
PTENP1	Bladder cancer	Exosomal release acts as a miR-17 decoy to regulate PTEN expression	Downregulated	Tumor-suppressive	Cancer progression	[62]
GAS5	Non-small cell lung cancer	Suppression of miR-23a	Downregulated	Tumor-suppressive	Cancer tissue growth and apoptosis	[63,64]
MALAT1 (also known as *NEAT2*)	Non-small cell lung cancer	MALAT1 promoting activation through Specificity Protein 1 (SP1)	Upregulated	Oncogenic	Cancer cell growth and invasion	[65,66]
	Breast cancer	Exosomal	Upregulated	Oncogenic	Cell proliferation	[67]
	Esophageal squamous cell carcinoma	ATM-CHK2 dephosphorylation leading to unregulated G2/M cell cycle checkpoint	Upregulated	Oncogenic	Cancer cell proliferation, invasion, and metastasis	[68]
CCAT1	Non-small cell lung cancer	CCAT1/miR-130a-3p/SOX4 axis, boosting ABCG2-mediated drug efflux	Upregulated	Oncogenic	Cancer cell chemoresistance	[69]
MEG3	Non-small cell lung cancer	Suppressive action on WNT/b-catenin pathway through TP53, b-catenin, and survivin	Downregulated	Tumor-suppressive	Cancer cell cycle regulation and chemoresistance	[70]
		LC3 cleavage downregulation, suppressing intracellular components autophagy	Downregulated	Tumor-suppressive	Cancer cell chemoresistance	[71]
XIST	Non-small cell lung cancer	LC3 autophagy-factor cleavage promotion and overexpression of ATG7 through miR-17/autophagy axis	Upregulated	Oncogenic	Cancer cell chemoresistance	[72]
	Pancreatic cancer	Compound action of a multitude of pathways, primarily by sponging miRNAs: EGFR/miR-133a, iASSP/miR-140/miR-124, YAP/miR-34a, ZEB1/miR-429, TGF-β2/miR-141–3p, and Notch1/miR-137 pathways	Upregulated	Oncogenic	Cancer cell growth, invasion, and migration	[73]
NEAT1	Triple-negative breast cancer	*SOX2* mRNA downregulated expression	Upregulated	Oncogenic	Cancer cell stemness and chemoresistance	[74,75]
	Hemangioma	Sponging of miR-33a-5p enhances NF-κB signaling thus increasing the expression of the *HIF1A* gene	Upregulated	Oncogenic	Cancer cell proliferation, invasion, and metastasis	[75,76]
	Acute myeloid leukemia	Negative feedback on miR-338-39, potentiating CREBRF	Downregulated	Tumor-suppressive	Cancer cell proliferation, invasion, and metastasis	[75,77]
sONE	Triple-negative breast cancer	Suppression of MYC and enhancement of *TP53* thus increasing the concentration of several downstream tumor suppressive mRNAs, including miR-34a, miR-15, miR-16, and let-7a. Additionally, NO production modulator via eNOS posttranscriptional regulation.	Downregulated	Tumor-suppressive	Cancer cell proliferation, invasion, and metastasis	[54,78]

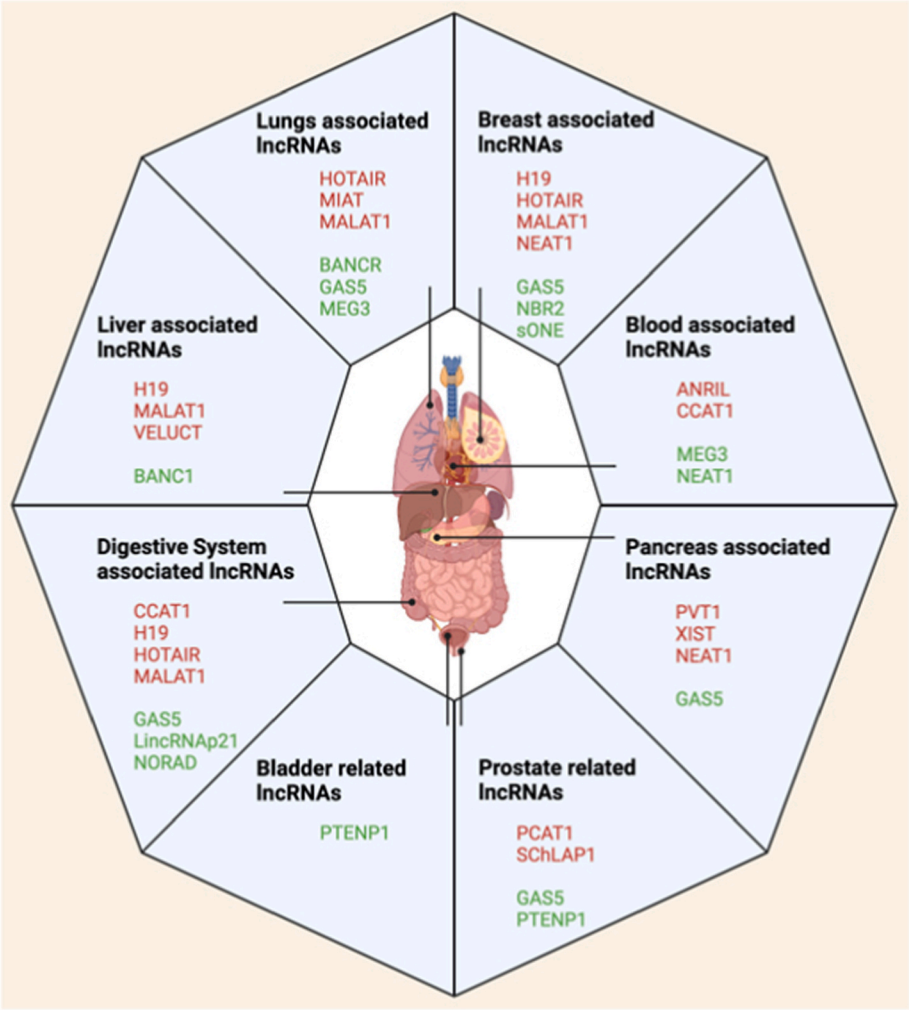

Fig. 2. Graphical representation of human tumors and related lncRNAs. Red labels indicate oncogenic lncRNAs, while green labels indicate tumor-suppressive lncRNAs.

6.2. *MIAT-mRNA and MIAT-miRNA networks*

Recent progress in high-throughput sequencing technologies has led to the identification of novel ncRNAs as well as an understanding the regulatory mechanisms for their co-expression including protein-coding genes and ncRNA molecules [90]. Databases are categorized into various classifications depending on their role in storing, displaying, and also analyzing data for ncRNAs.

RNAcentral is one of the most comprehensive databases for ncRNAs, where since its launch in 2014 about 10.2 million ncRNA sequences were identified, sequenced and recorded in it, thus providing invaluable information for subsequent recognition of ncRNAs once sequenced [91]. Also, RNAcentral integrates other ncRNA databases into one platform to allow accessible search for ncRNAs of interest.

NONCODE and LNCipedia are two of about 12 databases that integrate with RNAcentral, particularly to provide in-depth information regarding lncRNAs as well as tRNAs and rRNAs [92,93]. RNAcentral allows sequence similarity search, text search, and genome browsing of ncRNAs which aids in the identification of novel ncRNAs in different species as well as providing GO (Gene ontology) annotations for miRNAs and lncRNAs using RNAcentral identifiers.

LncTarD is a lncRNA-specific database that provides comprehensive information regarding lncRNA functions, regulatory mechanisms, as well as lncRNA-target insights following data retrieval from GEO (gene expression omnibus) database of NCBI as well as PubMed [94]. Another lncRNA database that provides lncRNA-target gene information is LncRNA2Target which includes curated data for both human and mice samples across different pathologies in order to display insightful results through combined analysis of stored lncRNA data in tabular format [95].

ENCORI (The Encyclopedia of RNA interactomes) is also a robust database that is particularly useful for understanding how RNA molecules integrate following results from high throughput sequencing data stored in the database. LncRNA-lncRNA, lncRNA-gene, miRNA-gene, and miRNA-ncRNA are useful integration techniques provided by ENCORI in order to understand how lncRNAs, miRNAs, and protein-coding genes interact together, particularly in cancer contexts [96].

Following *in-silico* analysis of *MIAT*-mRNA and *MIAT*-miRNA interactions using ENCORI, LncTarD, and LncRNA2Target databases, results revealed a comprehensive list of protein-coding genes and miRNAs that directly interact with *MIAT* in different pathological conditions. *MIAT*-mRNA network was constructed using Cytoscape software (v.3.10) and revealed 45 interaction nodes with *MIAT* at different disease states as listed in Table 3, where tumor protein p53 (TP53), transmembrane protein 147 (*TMEM147*), importin 7 (*IPO7*), mitochondrial carrier homolog 1 (*MTCH1*), LIM domain-binding protein 1 (*LDB1)*, ubiquitin-like modifier-activating enzyme 2 (*UBA2)*, coronin-like actin-binding protein 1C (*CORO1C)*, IST1 factor associated with ESCRT-III (*IST1)*, and proline dehydrogenase 1 (*PRODH)* were highlighted in later annotation using gene ontology Fig. 4. Also, *MIAT*-

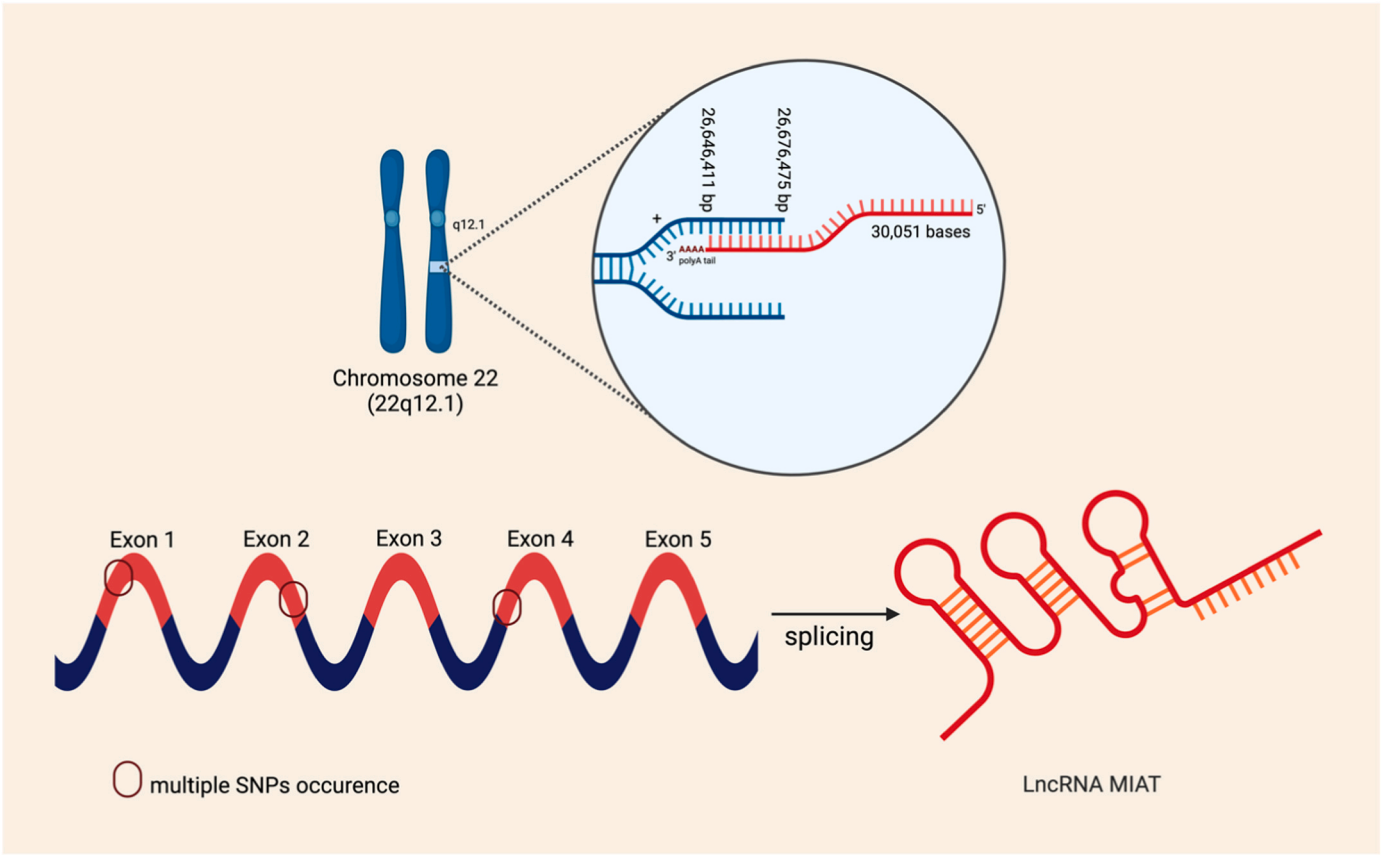

Fig. 3. Chromosomal locations and Single Nucleotide Polymorphisms (SNPs) in *MIAT*. *MIAT* is located on chromosome 22, band q12.1. A simplified view of *MIAT* is also illustrated with its exons with various splicing combinations and SNPs.

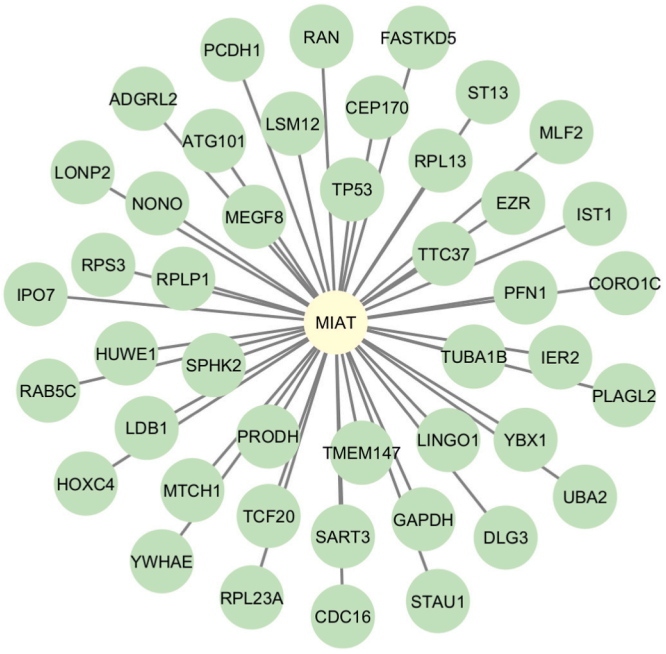

Fig. 4. *MIAT*-mRNA interaction network. A network plot representing *MIAT*-mRNA regulatory network. Data was retrieved from the ENCODE database.

miRNA interaction resulted in the detection of 9 miRNAs; miR-150, miR-145, miR-148 b, miR-206, miR-181 b, miR-149–5p, miR-214–3p, miR-641, and miR-181a-5p (**Table 3**); which could provide further understanding of *MIAT* role in HCC following further analysis. Moreover, gene ontology annotation of *MIAT*-mRNA interactions revealed several biological processes in which *MIAT* acts as a regulator of their action through suppressing the top 10 processes which *MIAT*-related protein-coding genes (n = 45) are directly regulating via GO scoring

Table 3
MIAT-mRNA and *MIAT*-miRNA selected interactions[a] reported in non-coding RNA databases.

mRNA or miRNA	Database	Reference
CORO1C *IPO7* *IPO7* *IST1* *LDB1* *MTCH1* *PRODH* *TMEM147* *TP53* *UBA2*	ENCORI	[96]
miR-145 miR-148 b miR-149–5p miR-150 miR-181a-5p miR-181 b miR-206 miR-214–3p miR-641	LncTarD/LncRNA2Target	[94,95]

[a] *MIAT*-mRNA and *MIAT*-miRNA interactions across multiple pathological conditions using ENCORI, LncTarD, and LncRNA2Target databases. Results were retrieved using search API tool identifier for *MIAT*-related interaction on the mentioned databases.

(Fig. 5), which explains the interconnection between all *MIAT*-related genes and subsequent GO functions following construction using R programming language (v. 4.0).

6.3. Role of MIAT in solid malignancies

Recently, it has been experimentally reported that *MIAT* has distinct roles in the tumorigenesis and progression of distinct types of cancer. Briefly, *MIAT* has been shown to have a pro-tumorigenic activity against the following types of cancer including HCC, breast cancer, non-small cell lung cancer, colorectal cancer, pancreatic cancer, ovarian cancer, gastric cancer, cholangiocarcinoma, and renal cell carcinoma. Mainly, *MIAT* contributed to the previous types of cancers via increasing the proliferation, the invasion, and the migration. In addition to this, the sponging or interacting activity of *MIAT* with an array of miRNAs reveals how *MIAT* up-regulation could increase the cancerous activity of tumor cells via the downstream target genes/proteins of these miRNAs as shown in Fig. 6. We and others have extensively reported the direct involvement of miRNAs and lncRNAs in the hepatocarcinogenesis process [97–103]. The following section will discuss the role of *MIAT* as a puzzling lncRNA in HCC with its pro-tumorigenic or anti-tumorigenic nature, its mechanism of action in terms of the downstream target genes including their possible signaling pathways, crosstalk between different classes of ncRNAs and lastly, its clinical eligibility to be a predictive diagnostic and/or prognostic marker.

7. Hepatocellular carcinoma (HCC)

HCC is considered one of the most lethal solid malignancies with high relapse rates and poor prognosis [97,98]. A myriad of factors could be listed under the etiology of the disease, as these factors have a profound impact on the initiation and progression of the disease. For instance, many research studies have revealed that unhealthy diet, alcohol, smoking, hepatitis C virus, and aflatoxin are the drivers for inflammation–causing conditions that eventually cause HCC. Although there are considerable scientific records for the causative reasons for the pathogenesis of HCC, there is still a gap that needs to be filled regarding how the non-coding part of our genome could have a non-negligible role in the aggravation of this disease.

7.1. Role of MIAT in chronic liver diseases

Chronic liver diseases (CLD), including cirrhosis, fibrosis, alcoholic liver disease, and chronic hepatitis, are important precursors of HCC. A recent study showed that elevated *MIAT* expression during liver fibrosis is linked to increased hepatic stellate cell (HSC) proliferation and collagen expression, while *MIAT* knockdown demonstrated a marked suppression of fibrosis progression and collagen accumulation *in vivo*. *MIAT* acts as a sponge for miR-3085–5p, showing a negative correlation with miR-3085–5p levels in cirrhotic patients and activated HSCs. The study underscores the role of *MIAT* in HSC activation through the miR-3085–5p/*YAP1*, where *MIAT* inhibition leads to reduced yes-associated protein 1 (YAP1) levels and subsequent suppression of the epithelial-to-

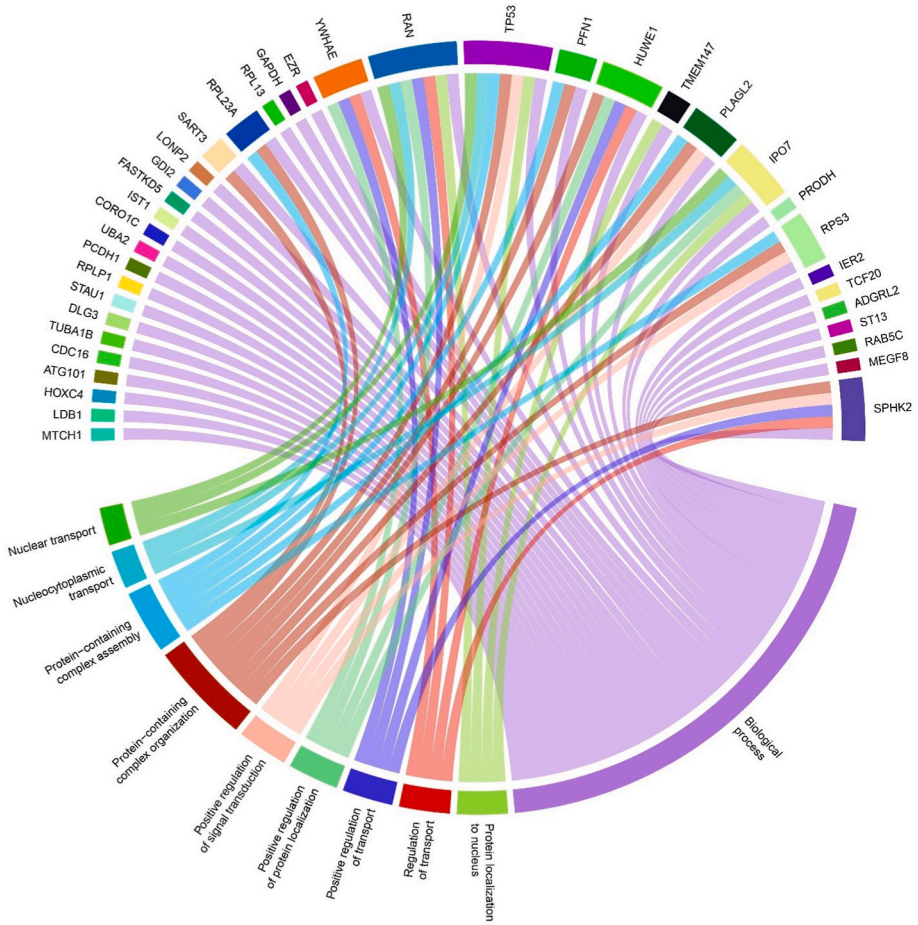

Fig. 5. Chord diagram for *MIAT* gene-function network using GO and ENCORI databases; this diagram describes the top GO expressed biological functions for the 45 genes interacting with *MIAT*. Results showed that *SPHK2*, *RPS3*, *IPO7*, *TP53*, *RAN*, and *YWHAE* are highly expressed genes from *MIAT*-based network and are directly interacting with higher of functions compared to the other genes.

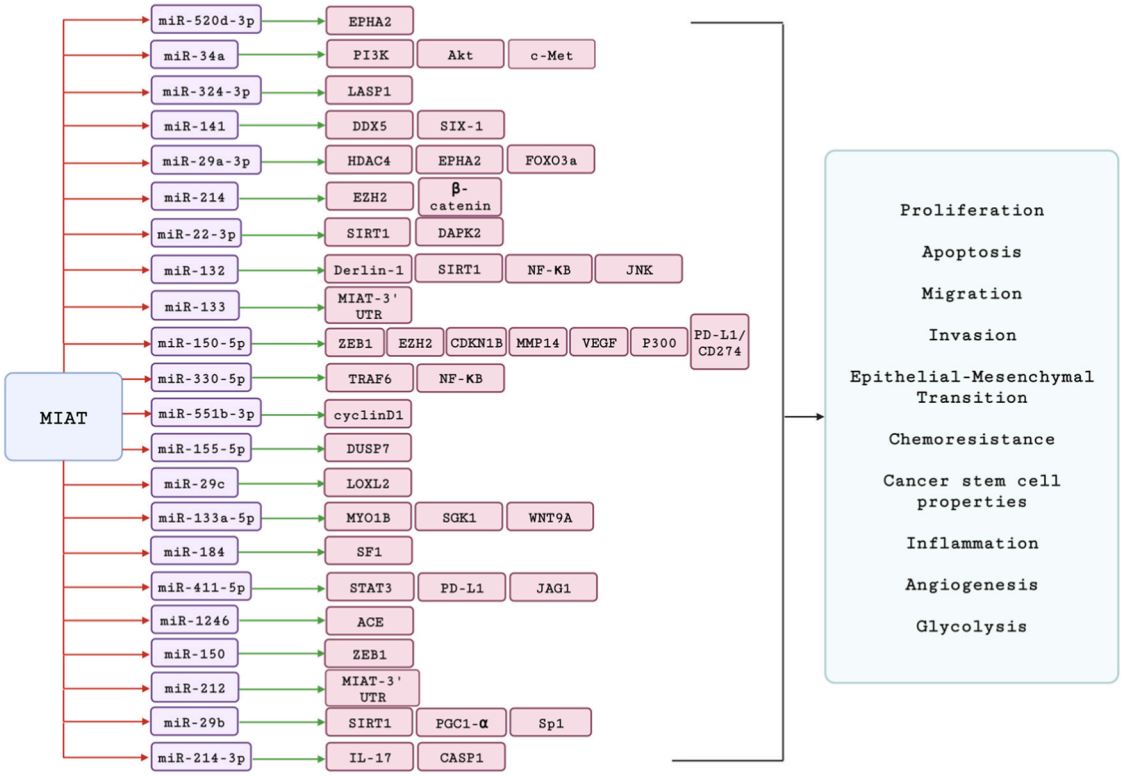

Fig. 6. Validated *MIAT* lncRNA-miRNAs-mRNAs interaction network in carcinogenesis. Crosstalk between *MIAT* lncRNA, its microRNA prey and their respective targets, and the cancer hallmarks that are altered due to these interactions, in different malignant contexts. The potential of some microRNAs, such as miR-133 and miR-212, to target *MIAT*, is also highlighted. Red arrows signify downregulation effect mediated by lncRNA *MIAT* on the several microRNAs. Green arrows signify upregulation effect on the downstream targets, subsequent to the respective microRNA suppression.

mesenchymal transition (EMT) process [104]. While the detailed function of *MIAT* in alcoholic liver disease and chronic hepatitis has not yet been investigated, to the best of our knowledge, given its role in fibrosis and cirrhosis there is potential for a similar influential role in other forms of CLD. Going beyond merely acting as precursors to HCC, these observations imply that *MIAT* could contribute to the pathogenesis of HCC through inflammation, fibrosis, and other aspects inherent to CLD. Hence, understanding the role of *MIAT* in CLD could provide useful insights into the molecular mechanism of hepatocellular carcinogenesis.

7.2. Role of MIAT in HCC pathogenesis

As indicated in the literature, a unanimous consensus across multiple studies underscores the robust correlation between *MIAT* presence and the onset of HCC. A study focusing on lncRNAs associated with epithelial-mesenchymal transition (EMT) in HCC presented *MIAT* on top of the list of lncRNAs that were both differentially expressed in HCC and positively correlated with EMT in HCC. On the molecular level, it was reported that *MIAT* plays an oncogenic and metastatic role in HCC as upon *MIAT* knockdown in HCC cell lines, a significant reduction in the levels of Cadherin-1 (e-cadherin, an epithelial marker) and an elevation in the levels of Cadherin-2 (*n*-cadherin, a mesenchymal marker) was observed [105].

7.2.1. Crosstalk between MIAT and miR-214–3p

A study by Huang et al. discovered that HCC cell lines (HepG2, Huh-7, SK-HEP-1, and HLE) and patient tissue samples have higher levels of *MIAT* expression than adjacent normal tissues and normal hepatocyte cell line (L02); this could be considered as an indication that *MIAT* has a role in the pathogenesis of HCC. Mechanistically, it has been found that the H3/H4 epigenetic acetylation of the *MIAT* promoter in tumor tissues is the reason behind the elevated expression of *MIAT* in HCC tumor tissues and cell lines. Nonetheless, it has been experimentally validated that *MIAT* sponges the tumor-suppressor miRNA, miR-214–3p, in HCC cell lines and accordingly ranks *MIAT* as an oncogenic lncRNA in HCC [106]. In addition to this, *MIAT* knockdown *in vivo* resulted in the elevation of miR-214–3p levels, and subsequently, of catenin beta 1 (CTNNB1 or β-catenin) and enhancer of zest homolog 2 (EZH2) which are the downstream targets of miR-214–3p [107], as shown in Fig. 7.

7.2.2. Crosstalk between MIAT and miR-520 d-3p

The role of *MIAT* as a miRNA sponge in the evolution of HCC was underlined in another study [108]. This work showed that miR-520 d-3p, which was previously proven to have an anti-tumorigenic function in HCC, is downregulated by *MIAT*. The authors found that *MIAT* expression affected the downstream target genes of miR-520 d-3p. Specifically, a positive association between *MIAT* and erythropoietin-producing hepatocellular receptor A2 (EPHA2), a miR-520 d-3p downstream target gene was recorded. It has been shown in this study and other studies that EPHA2 regulates MYC proto-oncogene (MYC) and cyclin D1 (CCND1), which are involved in cell cycle regulation and proliferation, and that inducing the expression of miR-520 d-3p in HCC cells results in a reduction in MYC and CCND1 expression by inhibition of EPHA2 [109,110], as shown in Fig. 7.

7.2.3. Crosstalk between MIAT and miR-22–3p

It was also shown that *MIAT* promotes the survival of HCC cells to survive against cellular senescence via regulating the miR-22–3p/*SIRT1* axis (Fig. 7) [111]. Sirtuin 1 (SIRT1) protein is a NAD–dependent histone deacetylase that was reported for its inhibitory effect on cellular senescence via preventing apoptosis, maintaining cellular metabolism, and preventing cells from oxidative stress [112]. This work discovered

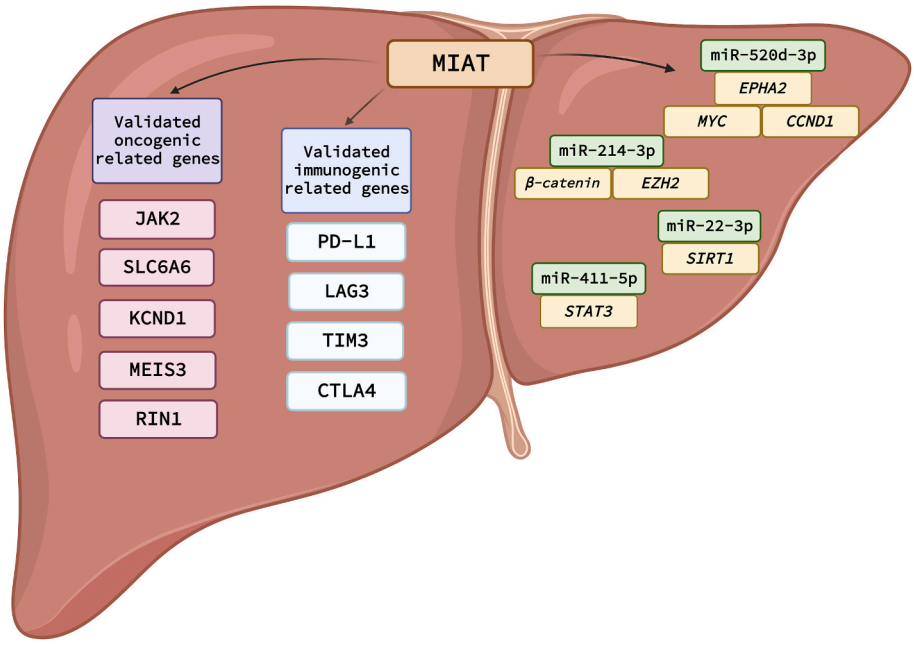

Fig. 7. Graphical representation of signaling cascades and ncRNAs circuits drawn downstream *MIAT* in HCC. A summary for all reported oncogenic related genes, immunogenic related genes and ncRNA-miRNA circuits reported to be modulated by *MIAT* in HCC.

that *MIAT* is a senescence-associated lncRNA in addition to being a differentially expressed lncRNA in HCC by analyzing The Cancer Genome Atlas (TCGA) liver cancer dataset. Experimental validation of whether cellular senescence is activated or not in the presence of *MIAT* was validated in human fibroblast 2BS cells and oncogene-induced 2BS cells. It was shown that *MIAT* was highly present in 2BS young cells whereas its expression decreased during the cellular senescence process of 2BS cells. The decrease of *MIAT* expression levels via its knockdown in 2BS cells led to an increase of senescence–associated beta-galactosidase activity, cell cycle arrest, and cell proliferation inhibition. Similar results were obtained, showing that the *MIAT* expression levels are lower in the HCC senescence models (HEPG2 and SMMC-7721) than in the normal cell lines [111].

7.3. Role of MIAT in HCC chemoresistance and immunotherapy

An important hallmark of cancer in general and HCC in particular is the immune escape [14,16,21,22,113,114]. Immune cells, infiltrating the tumor microenvironment (TME), have an enormous impact in stopping the tumor cells from proliferation, invasion, and dissemination [115–117]. Another considerable barrier in HCC therapeutic protocols is high incidence rates of resistance to the conventional anticancer agents that would consequently lead to more aggressive tumors and a rapid relapse in many cases [50,118]. *MIAT* is involved in the immune cellular response and associated non-cellular components at the TME. In a study performed by Peng et al. , a bioinformatics analysis was carried out using the TIMER database to explore the relationship between *MIAT* and immune cells and mediators in HCC. Analyzing the TIMER database showed a positive correlation between *MIAT* and immune cells: cytotoxic T lymphocytes, T helper cells, macrophages, dendritic cells, neutrophils, and B cells. This positive correlation was also found between *MIAT,* and the expression of immune checkpoint inhibitors programmed cell death 1 (PDCD1 or PD-1), CD274 molecule (PD-L1), cytotoxic T-lymphocyte associated protein 4 (CTLA4), lymphocyte activating 3 (LAG3), and hepatitis A virus cellular receptor 2 (HAVCR2, also known as TIM3). A deeper analysis was performed by using the single-cell sequencing techniques for the $CD45^{+}$ immune cells in HCC. Results showed that *MIAT* contributes to tumor immunosuppression since *MIAT* expression was high in forkhead box P3 (FOXP3) and CD4 positive T cells and PD-1 and granzyme K (GZMK) and CD8 subunit alpha (CD8) positive T cells in tumors and blood, hepatic lymph nodes, and ascites. FOXP3+ $CD4^{+}$ T cells and PDCD1+/GZMK + $CD8^{+}$ T cells correspond to regulatory T cells and exhaustive T cells, respectively [119].

A significant aspect by which *MIAT* exerts its action is its cellular localization. With the assistance of lncLocator, the cellular location of *MIAT* was expected to be in the nucleus [120]. This was a sign that *MIAT* plays a role in gene expression regulation via interacting with transcription factors in the nucleus [120]. These transcription factors include Janus kinase 2 (*JAK2)*, solute carrier family 6 member 6 (*SLC6A6)*, potassium voltage-gated channel subfamily D member 1 (*KCND1)*, Meis homeobox 3 (*MEIS3)*, and Ras and Rab interactor 1 (*RIN1)*. The correlation between *MIAT* and immune cells was further confirmed by exploring the correlation between the previously stated target genes and immune cells.

MIAT expression confers HCC resistance against sorafenib [121]. It was found that the resistance in sorafenib is associated with high expression of *MIAT* in HCC cells and this was also associated with the presence of PD-L1 [121]. Consistent with this, the mRNA and protein of *PD-L1* were decreased upon *MIAT* knockdown in HepG2 and Huh7 cell lines, and the expression of both *MIAT* and *PD-L1* were significantly elevated after treatment of HCC cells with sorafenib. Hence, the resistance of sorafenib in HCC could be attributed to the up-regulation of *PD-L1* by *MIAT* and eventually lead to immune escape [121].

A similar issue of immune escape caused by *MIAT* in HCC was investigated in another study in terms of the potential regulatory network and mechanism of regulation of PD-L1 by *MIAT* in HCC cells. It was discovered that *MIAT* regulates miR-411–5p by functioning as a competitive endogenous RNA that binds to miR-411–5p and inhibits its actions [85]. Upon *MIAT* knockdown in HepG2 and Huh7 cells, a marked reduction in PD-L1 expression levels was witnessed. Signal transducer and activator of transcription 3 (STAT3), a transcription factor that controls PD-L1 by binding to its promoter, was also shown to be one of the putative targets of miR-411–5p. These results were supported by the transfection of a miR-411–5p oligonucleotide into HCC cells, which resulted in repression in PD-L1 and STAT3 on both mRNA and protein levels [121].

7.4. Potential clinical applications of MIAT

MIAT holds promise as a diagnostic biomarker for various cancers, including HCC. The reported upregulation of *MIAT* expression in tissue samples may serve as an early indicator of cancer, facilitating timely diagnosis [106]. Moreover, as the expression levels of *MIAT* have shown potential as prognostic indicators in other types of cancer [122], offering insights into clinical outcomes such as disease progression, metastasis, and overall survival in cancer patients, would be possible in HCC as well. Furthermore, exploring the association between *MIAT* expression and clinical features specific to HCC, such as tumor stage, grade, and vascular invasion, could enhance our understanding of the role of MIAT in HCC development and progression.

In the realm of cancer therapeutics, MIAT may present itself as a promising therapeutic target. MIAT promotes the growth and invasive abilities of HCC tumor cells [106]. Thus, inhibiting the expression of MIAT may be an effective way to treat HCC. This could potentially be achieved with targeted therapies like small interfering RNAs (siRNAs) or antisense oligonucleotides (ASOs) designed to bind to and cause degradation of specific lncRNAs.

Additionally, given the deregulation of *MIAT* in HCC cell lines upon sorafenib treatment, *MIAT* expression levels could be leveraged to predict the response of cancer patients to specific treatments, guiding the development of personalized therapeutic strategies for improved outcomes. Monitoring changes in *MIAT* expression over time could serve as a valuable tool in tracking the progression of cancer. This longitudinal approach may provide insights into the evolving molecular landscape of tumors and help gauge treatment responses or the emergence of resistance [121].

Collectively, *MIAT* has immense potential in the clinical management of HCC, including as a non-invasive biomarker for early detection and prognosis, a therapeutic target, and a predictor of therapeutic response. However, further detailed studies and clinical trials are required to validate these applications of *MIAT* in HCC.

8. Conclusions and future perspectives

While the role of lncRNA *MIAT* is becoming increasingly apparent in HCC, there are some limitations in the current research. Firstly, most of the studies till now have utilized *in vitro* cell models, and human trials are lacking. Hence, the translation of these findings into clinical practice requires caution and remains a significant challenge.

Secondly, there is still a lot to be understood about the complex, multi-layered regulatory mechanisms of lncRNA *MIAT* in HCC. Much of the existing research provides evidence on a molecular level, but the comprehensive picture of physiological and pathological conditions remains incomplete. Another aspect that must be considered is that lncRNA *MIAT* might operate differently depending on the cellular context, which needs to be further investigated.

In terms of future directions, researchers need to focus on elucidating more detailed mechanisms by which *MIAT* regulates hepatocellular carcinoma progression. Also, more clinical studies are necessary to establish the potential of *MIAT* as a diagnostic marker or even a therapeutic target. Furthermore, considering the involvement of *MIAT* with other diseases like myocardial infarction and diabetic retinopathy, studying its systemic influence could provide profound insight and potentially higher clinical relevance.

In conclusion, while there is promising potential for the role of lncRNA *MIAT* in HCC research, it is important to acknowledge the limitations and challenges in the current state and to continue striving for a more detailed and comprehensive understanding.

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Rawan Amr Elmasri: Writing – original draft, Methodology, Investigation, Data curation. **Alaa A. Rashwan:** Writing – original draft, Methodology, Data curation. **Sarah Hany Gaber:** Visualization, Methodology, Investigation. **Monica Mosaad Rostom:** Writing – review & editing, Validation, Investigation, Formal analysis. **Paraskevi Karousi:** Data curation, Writing – original draft, Writing – review & editing. **Montaser Bellah Yasser:** Data curation, Formal analysis, Methodology, Software. **Christos K. Kontos:** Writing – review & editing, Validation, Supervision, Investigation, Formal analysis. **Rana A. Youness:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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