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Long Non-coding RNA NEAT1 in Colorectal Cancer: Molecular Mechanisms, Diagnostic Potential, and Resistance to Therapy

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ABSTRACT

Purpose: Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide. Long non-coding RNA nuclear enriched abundant transcript 1 (NEAT1) has emerged as a key regulator in CRC progression and therapy resistance. This review summarises the molecular mechanisms, diagnostic value, and therapeutic potential of NEAT1 in CRC.
Methods: Relevant literature was systematically reviewed to evaluate NEAT1-mediated molecular pathways, its role as a competing endogenous RNA (ceRNA), clinical associations, and involvement in therapeutic resistance.
Results: NEAT1 promotes CRC tumorigenesis by regulating multiple pathways, including Wnt/β-catenin signalling, epithelial–mesenchymal transition, angiogenesis, and cell cycle progression through miRNA sponging mechanisms. Elevated NEAT1 expression is associated with advanced tumour stage, poor prognosis, and reduced survival. Diagnostic studies report high discriminative performance based on ROC analysis. Additionally, NEAT1 contributes to resistance against chemotherapy and other treatments via autophagy regulation, cancer stem cell maintenance, and drug resistance pathways.
Conclusion: NEAT1 represents a promising biomarker and therapeutic target in CRC. However, further large-scale clinical validation and optimisation of targeted therapies are required for successful clinical translation.

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1.0 Introduction

Colorectal cancer (CRC) had the third-highest incidence rate (9.6% of all cancers globally, with around 20 million new cases) and the second-highest mortality rate (9.3% of all cancers globally, with 9.7 million deaths) among all worldwide cancer sites in 2022, also the third leading cause of cancer cases and deaths in both sexes, male with 10.4% of incidence rate and 9.2% of mortality rate of all cancer globally while female with 9.4% of incidence rate and mortality rate of all cancer globally.[1] It was shown that Asia has the highest incidence and mortality, with the rates of 15.6 ASR and 7.1 ASR, respectively, contributing 50.2% of the global CRC cases in 2022.[2] It was predicted that the incidence and mortality rates in both sexes would increase over the past 25 years in Asia,[3] highlighting the need for improved diagnosis, treatment and early detection. Early screening of cancer is crucial to increase the detection of cancer at an early stage, which is associated with a higher 5-year survival rate. This was proven that the 5-year survival rate was approximately 90% in stage I, while in stage IV, the 5-year survival rate was less than 10%.[4] This could be explained as it reaches stage III or IV, where metastases occur, it would be more difficult to be fully treated and have a higher risk during the treatment.

Non-coding RNAs (ncRNAs) are functional RNA molecules that don't directly involve in protein coding, but they contain regulatory functions such as transcription, translation, translocation, RNA processing and modification.[5] Hence, they are found to participate in multiple biological processes, including regulation and developmental processes that could contribute to diseases, depending on the dysregulation of types of ncRNAs.[6] ncRNA can be categorised based on their functions and sizes, such as tRNA, rRNA, snRNA, miRNA and siRNA, as well as long ncRNAs (lncRNAs).[7]

Long non-coding RNAs (lncRNAs) are single, linear strands longer than 200 nucleotides transcribed by RNA polymerase II that don't code for the function of proteins.[8] Their structure often consists of 7-methyl guanosine (m^7G) capped at their 5' ends and their 3' ends being polyadenylated, which are assumed to be spliced similarly to mRNAs.[9] Although lncRNAs and mRNAs are structured similarly, lncRNAs have lower efficiency in splicing than mRNAs due to the longer distances between the branch point and the 3' splice sites, causing internal splicing signals to be weaker.[10] Hence, they are weakly spliced and their termination of the transcription process doesn't depend on the polyadenylation signals, resulting in the accumulation of lncRNA, which will be degraded by RNA exosomes.[9] They function in mRNA translation, chromatin remodelling, RNA processing, and regulate gene expression at transcription and post-transcription through a variety of mechanisms, such as signal, attraction, platform, guide and enhancer RNAs. [11,12] The expression of lncRNAs will affect the recruitment of transcription factors[13] and remodelling of chromatin[14], causing suppressive effects at their gene promoters, resulting in gene silencing.[15] When gene silencing mechanisms are dysregulated, it could contribute to disease development and progression.

Many studies have shown that lncRNAs are highly expressed in cancerous tissues compared to normal tissues, as they play vital roles in tumour development and metastasis through various molecular mechanisms of cancer cells, depending on the types of lncRNA. For example, Xist could suppress the expression of p21 in osteosarcoma, showing its oncogenic role by sponging miRNAs' effects.[16] LncRNAs play roles in the epithelial to mesenchymal transition (EMT) of cancer cells, which enables cancer cell migration and invasion into neighbouring cells, involving multiple signalling pathways.[17] Apart from that, lncRNAs could alter the actin cytoskeleton to affect cancer progression by binding to actin or actin-associated proteins and regulating related signalling pathways such as the Rho/ROCK pathway.[18] Moreover, lncRNA can recruit RNA modification complexes, such as RNA methyltransferases and editing enzymes, modulating RNA

modification and cancerous gene expression by attracting RNA modifiers to target RNAs, thereby contributing to cancer tumorigenesis.[19]

Several long non-coding RNAs (lncRNAs) have been extensively characterised in colorectal cancer (CRC), highlighting their critical roles in tumour initiation and progression. Oncogenic lncRNAs such as H19, CRNDE, and LSINCT5 have been shown to promote cell proliferation, invasion, and metastasis through mechanisms including microRNA sponging, epigenetic regulation, and modulation of key signalling pathways.[20–22] In contrast, tumour-suppressive lncRNAs such as GAS5 have been reported to inhibit tumour growth by inducing apoptosis, regulating cell cycle progression, and enhancing sensitivity to chemotherapeutic agents.[23] Furthermore, MALAT1 has demonstrated context-dependent roles across multiple cancer types, including colorectal cancer, where it contributes to tumour progression and metastasis through diverse molecular interactions.[24] Collectively, these findings indicate that lncRNAs function within complex and interconnected regulatory networks in CRC.

Among these, nuclear enriched abundant transcript 1 (NEAT1) is one of the most common lncRNAs involved in CRC progression and development, which targets different genes or proteins affecting different signalling pathways that will worsen prognosis and treatment response.[25] This review will explore the role of lncRNA NEAT1 in CRC tumorigenesis through its underlying molecular mechanisms, examine how NEAT1 contributes to therapy resistance in CRC treatment, and discuss its potential as a diagnostic and therapeutic target to enhance prognosis and treatment outcomes.

2.0 LncRNA NEAT1

The lncRNA nuclear enriched abundant transcript 1 (NEAT1) has been stated to play a vital role in cell determination, immune responses and organ development by being involved in the progression of diseases when it is dysregulated.[26] Hence, understanding the structure and biological functions allows the exploration of other potential processes or the involvement of NEAT1 in other disease progressions.

2.1 Structure and Isoforms of NEAT1

NEAT1, also known as LINC00084, is a lncRNA that is located at chromosome 11q13.1, which is transcribed from the multiple endocrine neoplasia locus.[27] It can be transcribed into 2 overlapping monoexonic transcripts, known as the isoforms of NEAT1: NEAT1_1 (NR_028272.1) with the nucleotide length of 3.7kb and NEAT1_2 (NR_131012.1) with the nucleotide length of 22.7kb, as shown in Figure 1.Click or tap here to enter text.[28]

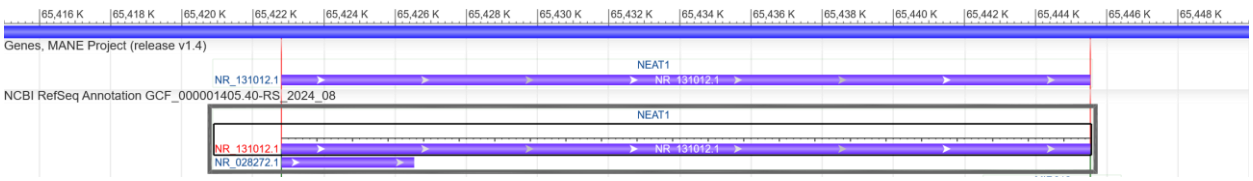

Figure 1 Sequence Range of lncRNA NEAT1 on Chromosome 11q13.1.[29]

Both isoforms start at the same promoter site but end differently, where NEAT1_1 transcription terminates and cleavages when a polyadenylation signal (PAS) released by mammalian cleavage factor I (CFIm) is detected. While NEAT1_2 transcription terminates when heterogenous nuclear ribonucleoprotein K (HNRNPK) binds and suppresses the CFIm complex, allowing the transcription process to continue by ignoring the PAS to

prevent cleavage and form NEAT1_2.[28] The transcription termination of NEAT1_2 occurs when RNase P binds to the tRNA-like structure, produced by the ongoing transcription process will then be cleaved and form triple-helix structures for the stabilisation of NEAT1_2.[30]

2.2 Biological & Cellular Functions of NEAT1

NEAT1 isoforms exhibit different functional roles in cellular processes. NEAT1_1 does not play a structural role in paraspeckle formation as it localises at non-paraspeckle sites.[31] Instead, it primarily functions in paraspeckle-independent functions, such as enhancing glycolysis in cancer progression. A recent study showed the involvement of NEAT1_1 in the response to glucose in breast cancer, supported by the association between NEAT1_1 and glycolytic enzymes, including phosphoglycerate kinase 1 (PGK1), phosphoglycerate mutase 1 (PGAM1), and enolase 1 (ENO1). To add on, reduced rate of glycolysis and significant decreased cell proliferation and invasion were demonstrated in the absence of NEAT1_1 expression.[32] These showed the function of NEAT1_1 as a cancer glycolysis modulator, which enhances the Warburg effect in cancer sites due to the excessive energy supply for cell proliferation and metastasis.

In contrast with NEAT1_1, the NEAT1_2 is involved in the formation of the paraspeckles, where the outer shell of paraspeckles consists of the 5' terminus and the 3' terminus of NEAT1_2, while the inner core consists of the middle region of NEAT1_2.[33] The core-shell structures of the paraspeckles are formed by the binding of RNA-binding proteins, also known as paraspeckle proteins (PSPs).[34] The key PSPs are classified into 2 categories: Category 1A or 1B, where category 1A consists of Non-POU domain-containing octamer-binding protein (NONO), Splicing factor, proline- and glutamine-rich (SFPQ), RNA binding motif protein 14 (RBM14), and heterogeneous nuclear ribonucleoprotein K (hnRNP K). While category 1B includes FUS RNA binding protein (FUS), DAZ-associated protein 1 (DAZAP1), and heterogeneous nuclear ribonucleoprotein H3 (hnRNP H3).[35] SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodelling complex, which could be biochemically distinct mammalian SWI/SNF complexes, such as canonical brahma-associated factors (cBAF), polybromo-BAF (PBAF) and non-canonical BAF (ncBAF), where it was shown that only cBAF-type SWI/SNF interacts with paraspeckles, associating the PSPs and the SWI/SNF complex components with NEAT1 and the DNA-binding ARID1B subunit as the mediator.[36]

The stability of the paraspeckle formed from NEAT1_2 is crucial for its function in controlling gene expression by sequestering proteins, thereby affecting the regulatory function and the mRNA translation.[37,38] For example, paraspeckle size enlargement results in the relocation of SFPQ protein from the chromatin of the targeted site to the paraspeckles, altering the regulation of the SFPQ target genes, such as downregulating adenosine deaminase, RNA-specific, B2 (ADARB2).[39] Apart from that, NEAT1_2 level elevation sequesters transactive response DNA binding protein (TDP-43) protein into paraspeckles, interferes with the function of TDP-43 protein that regulates RNA metabolism, mRNA transport, microRNA maturation and stress granule formation.[40,41]

In addition, the paraspeckles are transcriptional regulators, which sequester nuclear proteins involved in transcription, resulting in nuclear retention that prevents export to the cytoplasm, translating into proteins.[42] The inverted Alu repeats (IRAIus) sequence and 15-nucleotide sequence, located in the 3' untranslated region

(UTR) of some mRNAs, make them the target of paraspeckles, involving some PSPs such as NONO that bind to the IRAIu sequence, while HNRNPK binds to the 15-nucleotide sequence.[42,43]

miRNA regulates the process physiologically and pathologically by inhibiting the targeted mRNA translation or promoting mRNA degradation.[44] It was mentioned that NEAT1_2 can also be involved in targeting RNAs, sponging miRNAs to impair their functions by preventing miRNAs from binding with mRNA in the RNA-induced silencing complex (RISC), leading to the failure in degrading mRNA, causing more translated functional protein from mRNA to be produced, which alters the targeted gene expression levels in the disease development.[45]

The role of NEAT1 as a competing endogenous RNA (ceRNA) in sponging miRNA is the most common mechanism discovered in various cancer diseases, highlighting the significance of NEAT1 in cancer tumorigenesis. This occurs when NEAT1 causes the dysregulated expression of genes, leading to the enhancement of cancer cell proliferation, EMT, migration, invasion, and inhibition of apoptosis and chemotherapy resistance, thereby promoting cancer development and resulting in poor overall survival.[46]

3.0 Role of NEAT1 in Colorectal Cancer Tumorigenesis

The stabilisation of NEAT1 was shown to be contributed by ALKBH5, an m^6A demethylase, which undergo stress induced condensation through the c-terminal intrinsically disordered region, leading to the demethylation of the m^6A in NEAT1.[47,48] An increase in ALKBH5 expression causes a decrease in m^6A level in NEAT1, leading to an upregulation in NEAT1 expression by enhancing the stability of NEAT1.[48] The upregulation and overexpression of NEAT1 dysregulate gene expression by sponging the miRNA, which is a single-stranded ncRNA with a length of 19-25 nucleotides. miRNA functions as a post-transcriptional regulator of gene expression, playing a vital role in disease progression, especially in colorectal cancer development.[49] Table 1 summarises the miRNA or protein affected by NEAT1, causing the upregulation or downregulation of genes or proteins involved, resulting in the biological effect which contributes to the tumorigenesis of CRC. In Figure 2, an illustration of a schematic overview of NEAT1-mediated molecular pathways in colorectal cancer, depicting the interactions with miRNAs, transcriptional factors, and signalling cascades that contribute to tumour progression, therapy resistance and other cellular outcomes.

Table 1 Overview of the Mechanisms Mediated by NEAT1 Involving the miRNAs and Proteins Contributing in the Regulation of CRC Progression

Mechanism	**miRNA/Protein Inhibited by NEAT1**	**Upregulated Genes/Proteins**	**Downregulated Genes/Proteins**	**Model Details**		**Biological Effect**	**References**
				In vitro	***In vivo***		
Transcriptional factor and EMT regulation	miRNA-216b	YY1, TRIAP1	LC3B	LoVo, Caco-2, SW620, HT-29, HCT-116		Induce EMT, causing increased cell mobility	50
	miRNA-448	ZEB1, Vimentin	E-cadherin	SW480, SW620, Caco-2, HCT116	BALB/c nude mice		51

		BHLHE40, vimentin, N-cadherin	E-cadherin	LoVo, HCT-15, Caco-2	BALB/C female nude mice		52
Dysregulation of the Wnt/β-catenin signalling pathway	miRNA-34a	SIRT1, β-catenin	E-cadherin	HCT116, SW480	BALB/c nu de mice	Accumulation of β-catenin causes the increased expression of β-catenin transcriptional targeted genes and facilitating the intracellular signal transduction	53
	miRNA-486-5p	NR4A1, β-catenin, β-catenin transcriptional targeted genes		SW480, HT29			54
	KDM5A	Cul4A, Wnt3a, β-catenin		HCT116	Nude mice		55
		DDX5, β-catenin		HT29, RKO, SW480, SW620, LoVo, HCT116, SW1116, Caco2	Male BALB/c nude mice		56
		BHLHE40, Wnt ligands, β-catenin transcriptional targeted genes		LoVo, HCT-15, Caco-2	BALB/C female nude mice		52
Growth factor and receptor signalling	miRNA-185-5p	IGF2		SW620 HT-29, HCT 116, LoVo, SW480		Enhanced cell proliferation, migration and metastasis	57
	miRNA-196a-5p	GDNF, β1 integrin		HCT116, HT29, SW480, LoVo			58
	miRNA-193-3a	IL17RD		LOVO, HCT116, DLD-1, Caco2 and SW480	BALB/C female nude mice		59
	miRNA-193a-3p	KRAS		SW480, HT29, and Caco2			60
Angiogenesis and ECM remodelling	miRNA-205-5p	VEGFA, MMP2, MMP9		HCT116, HT29, SW620, and SW480		ECM degradation, angiogenesis, metastasis	61
	miRNA-185-5p	IGF2		SW620, HT-29, HCT 116, LoVo,SW480			57
Cell cycle dysregulation	miRNA-34a	SIRT1, β-catenin, c-Myc, cyclin D1		SW620, SW480, HCT116, HT29, CaCo-2, LoVo and Colo205	BALB/c nu de mice	Increased transition from G_1 to S phase causes the uncontrolled cell proliferation	53
	miRNA-495-3p	CDK6		DLD-1, HCT-8, HT-29, HCT-116, SW620	BALB/c nude mice		62

Metabolic reprogramming	miRNA-138	SLC38A1		SW480 and SW620	Male BALB/C nude mice	Promotes glutamine uptake, which enhances the cancer cell survival	63

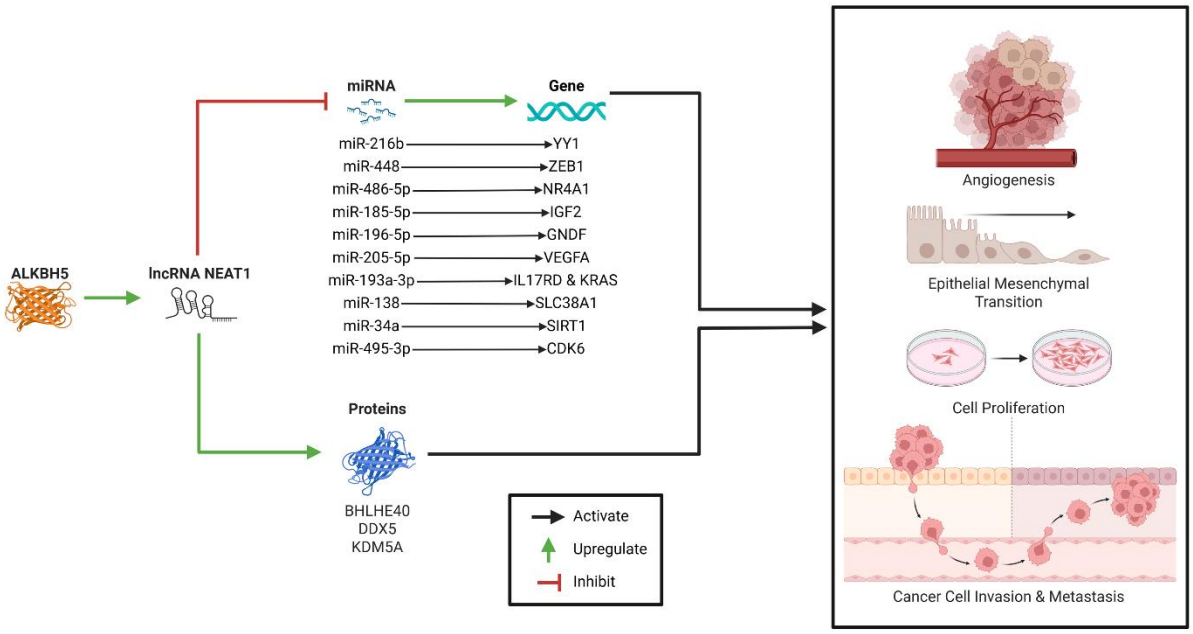

Figure 2 Schematic Overview of NEAT1-Mediated Pathways in CRC. The stabilised and upregulated NEAT1 inhibits various miRNAs (miRNA-216b, miRNA-448, miRNA-486-5p, miRNA-185-5p, miRNA-196-5p, miRNA-205-5p, miRNA-193a-3p, miRNA-138, miRNA-34a and miRNA-495-3p), causing the activation of their respective targeted genes (YY1, ZEB1, NR4A1, IGF2, GDNF, VEGFA, IL17RD, KRAS, SLC38A1, SIRT1 and CDK6) and proteins (BHLHE40, DDX5 and KDM5A). These regulation leads to the upregulation of angiogenesis, EMT activity, cell proliferation, cancer cell invasion and metastasis, contributing to CRC tumorigenesis.

3.1 Regulation of Transcriptional Factor and EMT by NEAT1

The essential mechanism for CRC progression is the regulation of EMT by regulating the expression of transcriptional factors. NEAT1 facilitates this by inhibiting miRNA-216b, causing the upregulation of YY1,[50] stabilised by ubiquitin-specific protease 7 (USP7) through interfering with its K67 linkage ubiquitination.[64] This leads to the exertion of the function of YY1, which activates TRIAP1, a tumour-promoting gene that increases the resistance of cancer cells to apoptosis.[64] Moreover, YY1 expression also suppresses LC3B expression causing a reduction in autophagy levels of cancer cells.[64] This phenomenon represents dysregulated cellular homeostasis, where enhanced cancer cell proliferative activity is not counterbalanced by apoptosis.

Moreover, NEAT1 sponges miRNA-448, which upregulates Zinc finger E-box binding homeobox 1 (ZEB1) expression, which is a transcriptional factor that stimulates tumour cells and promotes multidrug resistance, proliferation, metastasis and poor prognosis by playing a role in the EMT process.[51,65] This further increases the expression of the mesenchymal marker vimentin, while decreasing the expression of structural adhesion proteins, such as E-cadherin.[51,66,67] Moreover, class E basic helix-loop-helix protein 40 (BHLHE40) was shown to be highly expressed in CRC and contributes to the overexpression of NEAT1, which causes the

overexpression of Vimentin and N-cadherin while suppressing the expression of E-cadherin.[52] Vimentin is responsible for the maintenance of cell shape and cytoplasm integrity, while N-cadherin and E-cadherin regulates cell-cell adhesion.[67] The opposite expression of E-cadherin and N-cadherin is called cadherin switch, changing the epithelial characteristics into spindle-shaped mesenchymal cells. Mesenchymal cells usually lack of cell-cell adhesion causing the detachment of cells, which is a characteristic of EMT. [66,68,69]

EMT causes the cancer cells to lose adhesion functions due to the suppression of E-cadherin expression and the ability for basement membrane and ECM degradation. This results in the detachment of tumour and invade the surrounding tissues. After intravasion, intravasation occurs, which is the cancer cells penetrate the ECM and enter the circulation system as circulating tumour cells (CTCs) by increasing vascular permeability. The CTCs will then have a stronger ability to survive through shear forces and anoikis, a programmed cell death when cells undergo detachment compared to normal cells. The CTCs will undergo extravasation and colonise at distant sites, forming metastases.[69] Hence, NEAT1-mediated EMT facilitates the invasive and metastatic properties to cancer dissemination, thereby increases the severity of CRC in patients.

3.2 Dysregulation of the Wnt/β-catenin Signalling Pathway

Overexpression of the Wnt/β-catenin signalling pathway can contribute to CRC development due to the dysregulation of miRNAs and genes related. Figure 3 shows the overview of the mechanism of the Wnt/β-catenin signalling pathway influenced by NEAT1, affecting the expression of miRNAs and proteins, resulting in the dysregulation of β-catenin expression level.

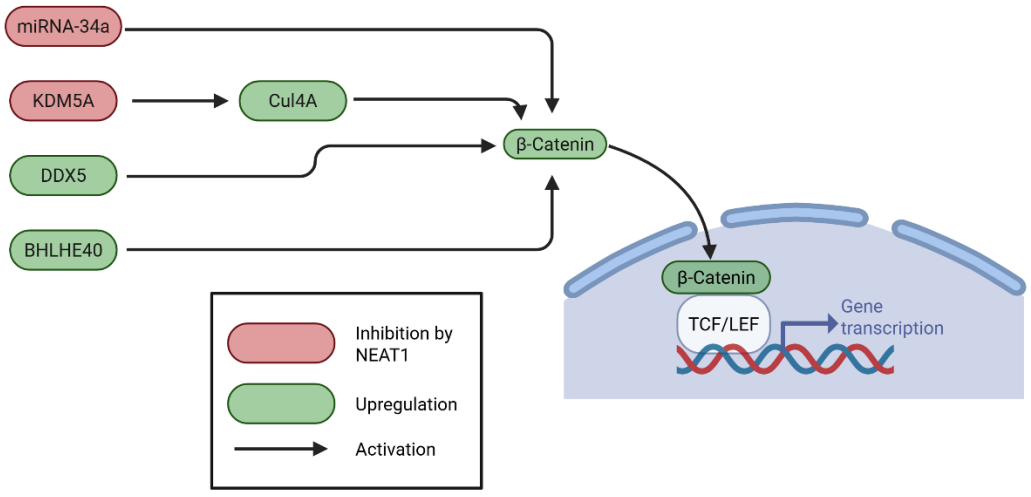

Figure 3 Overview of NEAT1-mediated Regulation of Wnt/β-catenin Signalling Pathway. NEAT1 leads to the overactivation of β-catenin by upregulating DDX5 and BHLHE40 proteins, while inhibiting the expression of miRNA-34a and KDM5A, resulting in the overexpression of the Wnt/β-catenin signalling pathway.

NEAT1 worsens the dysregulation by sponging miRNA-34a, causing an increase in the expression of SIRT1.[53] SIRT1 is a class-III histone deacetylase containing nicotinamide adenine nucleotide (NAD^+)-dependent enzyme, which targets histones and non-histone proteins, playing a role in gene regulation, apoptosis, autophagy and tumorigenesis, including CRC.[70]

The inhibition of miRNA-34a by NEAT1 also increases the levels of β-catenin, as well as a reduction in the E-cadherin expression.[53] Apart from that, NEAT1 sequesters miRNA-486-5p, leading to the overexpression of nuclear receptor subfamily group A member 1 (NR4A1), which causes the dysregulation of the Wnt/β-catenin pathway with an increase in β-catenin and β-catenin transcriptional targeted genes.[54]

Besides the involvement of miRNA, proteins are also contributors to CRC tumorigenesis in dysregulating the Wnt/β-catenin signalling pathway. The presence of NEAT1 inhibits the expression of KDM5A protein by binding to transcriptional factor E2F1, resulting in the upregulation of cullin 4A (Cul4A). Thisactivates the Wnt pathway by an increase in Wnt3a and β-catenin, promoting proliferation & migration of CRC cells.[55] Furthermore, DDX5 protein was shown to be stabilised by NEAT1 to lower the degradation rate of DDX5 protein. This increases the expression of DDX5, leading to the overexpression of β-catenin transcriptional activation.[56] Moreover, BHLHE40 was also shown to be highly expressed in CRC and contributes to the overexpression of NEAT1, increasing the expression of Wnt ligand and β-catenin transcriptional targeted genes.[52]

β-catenin is the transcriptional factor acting as the nuclear effector of the Wnt signalling pathway, stabilised by the Wnt ligands by preventing the degradation of β-catenin, causing the accumulation of β-catenin in the cytoplasm.[71] The accumulated β-catenin will then translocate into the nucleus, resulting in over-inducedexpression of β-catenin transcriptional targeted genes such as MMPs and c-Myc. These targeted genes are responsible for ECM remodelling and cell cycle regulations. Hence, dysregulated β-catenin can cause an increase expression of these targeted genes, leading to an uncontrolled cell proliferation and cancer cell survival.[72–74] β-catenin also binds to the C-terminal of the E-cadherin cytoplasmic tail, forming β-catenin/E-cadherin complexes, which are the essential component of the adherent junctions for cell-cell adhesion and platforms for intracellular signal transduction. The dysregulation in the complexes will disrupt the epithelial structure and the adherent function, induce cell proliferation, migration and invasion, contributing to tumorigenesis.[75,76]

3.3 Growth Factor and Receptor Signalling

Apart from the above, growth factor and receptor signalling contribute substantially to the pathogenesis of CRC. It was explored that NEAT1 inhibits the expression of miRNA-185-5p, causing the upregulation of the insulin-like growth factor 2 (IGF2) expression level, promoting tumorigenesis, migration and invasion, leading to poor prognosis of CRC.[57] IGF2, a 7.5 kDa peptide, is one of the risk factors for the development of CRC when IGF2 accounts for loss of imprinting or aberrant imprinting, causing the upregulation of IGF2, playing a role in metastasis by initiating cancer immunoevasion, migration, invasion and angiogenesis.[77,78]

In addition, NEAT1 acts as the ceRNA for miRNA-196a-5p, inhibiting its function and leading to the overexpression of glial cell line-derived neurotrophic factor (GDNF).[58] GDNF promotes growth and differentiation of enteric neurons, as well as regulates the intestinal environment, playing a role in tumorigenesis. This occurs by binding GDNF receptor-α (GFR-α) and receptor tyrosine kinase, forming the GFR-α/RET receptor complex.[79] GDNF can stimulate the signal from the GFR-α/RET receptor complex to increase the expression of β1 integrin, creating a suitable platform for cancer development by enhancing the adherence of CRC cells to the extracellular matrix (ECM).[80–82]

Moreover, NEAT1 inhibited miRNA-193-3a activity that causes the upregulation of interleukin-17 receptor D (IL17RD), enhancing the malignant progression of CRC.[59] IL17RD, also known as a similar expression to fibroblast growth factor genes (Sef), was shown to increase in expression with the presence of epidermal growth factor (EGF), enhancing the expression of the EGF receptor (EGFR) and leading to the activation of the MAPK and PI3K/Akt signalling pathways.[83,84] EGFRs are receptor tyrosine kinases that allow the binding of EGF, facilitating the recruitment of adaptor proteins to activate Ras-GTP, which further activates RAF. This, in turn, activates MEK, followed by the activation of ERK via phosphorylation, contributing to cancer development through enhanced cell proliferation, angiogenesis, and metastasis.[85,86]

In addition, it was shown that the potential of NEAT1 as ceRNA in inhibiting the expression of miRNA-193a-3p that upregulates kirsten rat sarcoma viral oncogene homolog (KRAS) protein level, leading to the development of CRC.[60] It was also shown that hybridisation's minimum free energy values are closely related, proving that they bind together by the observation of luciferase reporter assays, indicating their interactions between miR-193a-3p and KRAS expression levels.[60] In normal physiology, KRAS will be activated by the binding of guanosine 5'-triphosphate (GTP), releasing signals MAPK and PI3K-AKT to promote cell proliferation and differentiation at a healthy expression level.[87,88] NEAT1-mediated dysregulation leads to aberrant KRAS activation, resulting in uncontrolled cell proliferation and worsen the CRC development in terms of cell proliferation, invasion and metastasis, and poor prognosis of CRC.

3.4 Angiogenesis and ECM Remodelling

Besides cell-autonomous effects, the formation of new blood vessels surrounding the tumour microenvironment, known as angiogenesis, is essential in CRC development. The continuous supply of nutrients and oxygen promotes the development of tumour sites, invasion into surrounding tissues, and metastasis.[89] An overexpressed NEAT1 condition can dysregulate angiogenesis by sequestering miRNAs such as miRNA-205-5p, which leads to the enhancement of the expression of vascular endothelial growth factor A (VEGFA), an angiogenesis regulator.[61] VEGFA protein is a vascular endothelial growth factor (VEGF) family, acting as a secretory factor binding to VEGF receptor-1 and VEGF receptor-2, which are expressed in the endothelial cells of the blood vessels, mainly contributing to angiogenesis.[90] The inhibition of miRNA-205-5p is associated with an increase in the matrix metalloproteinase (MMP), MMP2 and MMP9, which can contribute to CRC progression by ECM remodelling.[61,91,92] To be specific, MMP2 and MMP9 are gelatinase A and gelatinase B, respectively, that digest the main constituents of ECM, type VI collagen and gelatin. This allows the potential of uncontrolled secretion of growth factor to excessively promote angiogenesis and tumour growth by invading the space from degraded basement membranes, supporting metastasis to the surrounding tissues.[93,94] However, their relationship between the MMP-VEGFA pathway involving lncRNA NEAT1 hasn't been fully discovered yet, and it was mentioned that this interaction might involve other components or pathways.[91]

Apart from that, upregulated IGF2 expression by the inhibition of miRNA-185-5p caused by NEAT1 was shown to contribute to the metastasis of CRC, which might be due to angiogenesis.[57] This occurs by enhancing the endothelial cell communications and lengthening the vascular networks through the synthesis of VEGF, which is the pro-angiogenic factor, allowing the formation of new blood vessels around the tumour cells to

provide oxygen for tumour cell survival.[89,95,96] Additionally, IGF2 was shown to influence cancer-associated fibroblasts (CAFs) by promoting CAF proliferation and collagen formation, which changes the tumour immune microenvironment by forming denser extracellular matrix, leading to the difficulty of immune cell infiltration and antitumour immune responses.[97] CAFs will inhibit the functions of CD8+ T cells, contributing to chemotherapy resistance by suppressing the T-cell infiltration into the tumour microenvironment. This reduces the recruitment of T-cells to the tumour sites and affecting the cytotoxic function of T-cells towards cancer cells.[98,99] These increases the survival rate of cancer cells by avoiding the killing effect of T cells and continuous supply of nutrients and oxygen, leading to the imbalance of the growth of cancer cells.

3.5 Cell Cycle Dysregulation

In normal conditions, retinoblastoma protein (RB) functions as the cell cycle checkpoint regulator by binding and suppressing the E2F transcription factor, showing the tumour suppression effect.[100] Hence, the disruption of the normal cell cycle constitutes a key mechanism underlying CRC tumorigenesis. The suppression of miRNA-34a by NEAT1 leads to the upregulation of SIRT1,[53] as mentioned above, showing the association of increased β-catenin due to the accumulation in the cytoplasm, which causes more activation of β-catenin transcriptional targeted genes such as c-Myc and cyclin D1, where c-Myc stimulates the cell cycle and apoptosis, while cyclin D1 controls the cell cycle progression.[101] Apart from that, recent finding showed that NEAT1 sponged the activity of miRNA-495-3p, which allows the upregulation of cyclin D-dependent kinase 6 (CDK6), which causes the development of CRC.[62]

CDK6 binds with D-type cyclins, forming the cyclin D1/CDK complex, which is important in the cell cycle progression from the G_1 phase to the S phase by inactivating RB through phosphorylation. This which will release E2F transcription factors to promote cell proliferation.[102,103] The formation of the cyclin D1/CDK complex can be uncontrollably stimulated by c-Myc expression, causing an uncontrolled cell cycle progression.[104] The cyclin E-CDK2 complex is also required to inactivate all RBs through the synthesis from the binding of E2F and DNA, forming cyclin E that binds to CDK2. This results in the enhancement of the expression of cyclin E, which is essential to regulate the transition from G_1 phase to S phase, DNA replication and proceeding to G_2 phase.[105,106] This shows that an enhanced expression of CDKs will lead to the inhibition of tumour suppressive mechanisms by RBs, resulting in the uncontrolled cell division, further causing the unregulated cell proliferation.

3.6 Metabolic Reprogramming

Alongside the above, metabolic reprogramming has emerged as a hallmark of CRC, enhancing the survival of CRC, which can be affected by NEAT1. NEAT1 was demonstrated to result in the overexpression of SLC38A1 by sponging miRNA-138, which contributes to CRC progression.[63] SLC38A1, also known as SNAT1, expressed on the cell membrane to transports l-glutamine, which is the source of carbon for nucleotide and fatty acid production and the source of nitrogen for purine and pyrimidine biosynthesis, into the cytosol. This facilitates glutaminolysis, a characteristic of cancer cell metabolism to obtain energy via taking up l-glutamine, which will be converted into glutamate then to α-ketoglutarate.[107–109] It has been proven that CRC cells are glutamine-dependent for survival, as glutamine deficiency causes a decrease in cancer growth rate by enhancing apoptosis and resulting in G_0/G_1 cell cycle suppression.[110] Apart from that, it was demonstrated that low serum glutamine levels indicate the high expression of SLC38A1, increasing the intake of glutamine by

highly SLC38A1 expressed cancer cells. This is associated with higher tumour stage, metastasis and lower prognosis.[111] This highlights the crucial role of SLC38A1 as a promoter of glutamine uptake, which enhances the survival of cancer cells by preventing them from undergoing apoptosis, promoting cancer cell proliferation, and facilitating metastasis.

4.0 Diagnostic Potential of LncRNA in Colorectal Cancer

With all the mechanisms of NEAT1 in contributing to CRC tumorigenesis, this shows the potential of NEAT1 to rise as a non-invasive biomarker for CRC detection. This can be supported by the relationship between the expression of NEAT1 and the clinical outcome. It was shown that NEAT1 expression is positively correlated with clinical pathological stage and disease progression. To be specific, elevated NEAT1 expression is usually associated with poor prognosis, lower overall survival and disease-free survival rates.[112,113] A recent paper discovered that NEAT1 expression is higher in the peripheral blood of CRC patients and tumour tissues compared to healthy individuals and normal tissues.[112] Adding on to this, an evaluation of serum NEAT1 obtained from CRC patients compared with healthy controls for the diagnostic potential, with a high area under the receiver operating characteristic (ROC) curve (AUC), indicates the efficient discriminative ability between NEAT1 expression in CRC tissues and normal tissues.[114,115] Hence, these findings highlight the potential of NEAT1 as a specific, sensitive and non-invasive biomarker for CRC diagnosis.

In addition to the general diagnostic relevance described above, several studies have quantitatively assessed NEAT1 using ROC curve analysis, demonstrating robust discriminative performance. Specifically, NEAT1 expression has been reported to achieve high AUC values, indicating strong ability to differentiate CRC patients from healthy individuals.[112,113] Importantly, these studies also reported relatively high sensitivity and specificity values, suggesting that NEAT1 may be effective not only in detection but also in reducing false-negative and false-positive rates in clinical screening settings.[110–113] Such quantitative metrics provide stronger clinical support compared to expression-based observations alone.

Nevertheless, a key limitation lies in the lack of standardisation across studies. Most reports do not consistently define optimal cut-off values for NEAT1 expression, and variations in sample sources like those samples from serum compared to those from tissue, detection platforms, and cohort characteristics contribute to heterogeneity in diagnostic performance.[110,112] Furthermore, many studies are based on relatively small patient populations, which may overestimate diagnostic accuracy and limit reproducibility. Therefore, although NEAT1 demonstrates strong preliminary diagnostic potential, further validation through large-scale, multi-centre clinical studies with standardised protocols is required before it can be reliably implemented in clinical practice.

5.0 Therapy Resistance in Colorectal Cancer Caused by LncRNA NEAT1

Therapeutic resistance remains one of the major causes of poor prognosis and low 5-year survival rate in CRC. Despite the advancement in CRC treatments, the recurrence rate increases as the time (months) after surgery increases, with 14.7% of CRC patients developing local recurrence or distant metastasis, which can be influenced by the staging of CRC.[116] However, the first 2 years after surgery appear to have the highest risk of CRC recurrence. It was also shown that recurrence is negatively correlated with CRC prognosis, with an estimated increase in the 5-year mortality rate from 3.8% for patients with recurrence-free status one year after surgery to 33.6% for patients with recurrence within the first 12 months.[116] These findings suggest the possibility of treatment failure, which may be attributed to the effect of NEAT1 expression on therapy resistance, underscoring the importance of understanding the mechanisms involved in the recurrence of CRC.

5.1 Resistance to 5-Fluorouracil Chemotherapy

5-Fluorouracil (5-FU) is the main chemotherapy agent, which inhibits the thymidylate synthase, an important enzyme for deoxynucleotides (dNTPs) synthesis, leading to a disruption in the DNA synthesis due to the imbalance in the dNTPs. At the same time, 5-FU will be phosphorylated to 2′-deoxyuridine-5′-triphosphate (dUTP) when it enters cancer cells, resulting in the incorporation of uracil into DNA, further causing DNA damage, contributing to CRC recurrence.[117] However, NEAT1 has been demonstrated to mediate 5-FU resistance via several mechanisms.

One of the mechanisms of NEAT1 in causing 5-FU resistance is by promoting autophagy, which is a dual role mechanism in CRC tumorigenesis and protection. In the early stage, autophagy functions as a protective mechanism, suppressing tumorigenesis. However, when CRC reaches a late stage associated with environmental stresses, autophagy will allow tumour growth and promote metastasis of cancer.[118] Relating with NEAT1, it was shown to suppress the expression of miRNA-34a, resulting in the enhancement of autophagy associated with an increase in the Beclin-1, Unc-51 like kinase 1 (ULK1), High Mobility Group Box 1 (HMGB1), autophagy-related protein (ATG), such as ATG9A and ATG4B protein expression, as well as the microtubule-associated protein light chain 3 (LC3), LC3II/LC3I ratio, which are the key components for autophagy regulation.[119] Increased autophagy allows cancerous cells to maintain a dormant status after treatment to resist apoptosis and survive in chemotherapy-induced stress, leading to cancer recurrence and affecting the 5-year survival rate.[118] Autophagy also prevents macrophage infiltration into cancer cells and allows cancer invasion and metastasis by facilitating cell adhesion signalling pathways.[120]

Apart from enhancing autophagy, NEAT1 can also modulate gene expression and mRNA maturation by enhancing the expression of cleavage and polyadenylation specific factor 4 (CPSF4) via the suppression of miRNA-150-5p.[121] It was shown that NEAT1 is correlated with an increase in resistance proteins, P-glycoprotein (P-gp) and glutathione S-transferase π (GST-π) by enhancing the drug efflux contributing to chemoresistance. . This showed the modulation in related signalling pathways, causing inhibition in apoptosis and inducing drug resistance in various cancers, including CRC.[121,122] However, the underlying mechanism of 5-FU chemoresistance caused by NEAT1 remain poorly defined.

Moreover, NEAT1 also promotes chromatin remodelling, which enhances the 5-FU resistance in CRC by increasing the expression of stemness factors in cancer stem cells (CSC). 5-FU mainly targets the cancer cells without targeting CSCs, which allows the CSCs to exhibit their properties and survives to cause cancer recurrence.[123] It was demonstrated that the increase in NEAT1 causes the upregulation of SRY-box transcriptional factor 2 (SOX2), NANOG, c-Myc and Octamer-binding transcription factor 4 (OCT4), which are stem-related genes. These promote the stemness characteristics of CSC by enhancing the acetylation levels of ALDH1 and c-Myc promoter regions. ALDH1 has been recognised as a marker of CSC properties, including self-renewal, multipotency, potential for tumour initiation and poor clinical prognosis.[124] This further increases the resistance of 5-FU in CRC cells, leading to a worse prognosis condition.[125]

5.2 Oxaliplatin Resistance Caused by NEAT1

Besides the resistance to 5-FU caused by NEAT1, it also decreases the chemotherapeutic effectiveness of oxaliplatin, which is commonly used in combination with other cytotoxic drugs for advanced-stage CRC patients.[126] In normal conditions, oxaliplatin allows the formation of DNA adducts, causing the cellular apoptosis to occur in cancer cells by the inhibition of DNA replication and transcription.[127] However, it was shown that several lncRNAs, including NEAT1 contributed to its resistance in CRC treatment.

Sahebnasagh *et al*. demonstrated that the resistance of oxaliplatin in CRC, influenced by NEAT1 expression, was characterised by an increase in IC_{50}, indicating that a higher dosage of oxaliplatin is required for treatment. In addition, a delay in the G_1 phase was demonstrated, suggesting that the reduction in cell growth rate will allow DNA damage repair in cancer cells, as well as inhibiting the binding of drug metabolites to the DNA.[126] This cellular adaptation, confirms the development of oxaliplatin resistance by tolerating and repairing oxaliplatin-induced DNA damage. In addition, an increased NEAT1 expression was detected in isolated exosomes released by CRC cells and was significantly higher in oxaliplatin-resistant CRC cell line compared to the normal CRC cell line, which suggested that these might protect a larger cancerous site from the cytotoxicity of chemotherapeutic drugs by facilitating the intracellular transfer of chemoresistant characteristics through paracrine interactions.[126] While exosomal NEAT1 has been discovered to cause oxaliplatin resistance in CRC, the specific molecular interactions between them in CRC remain undiscovered.

5.3 NEAT1 Causing Resistance to Photodynamic Therapy Treatment

Apart from chemotherapeutic drugs, NEAT1 expression in CRC was shown to contribute to the resistance to photodynamic therapy treatment (PDT). PDT is a minimal invasive treatment using photosensitiser consumed by patients. Light at a specific wavelength depending on the absorption property of the sensitisers and oxygenwill react with photosensitiser to generate cytotoxic singlet oxygen and other reactive oxygen species (ROS) to generate oxidative damage to cancer cells. This activates the immune responses to release antigens and recruit immune cells, resulting in the enhancement of cancer cell destruction and death.[128]

However, this treatment method could be resisted by CRC with the expression of NEAT1, as stated by Liu *et al*. It was stated that the increase in NEAT1 expression by c-Myc and the absence of functional p53 will inhibit miRNA-124 expression. This increases the expression of inhibitor of apoptosis-stimulating protein of p53 (iASPP) protein, causing an increase in PDT resistance.[129] PDT is able to inhibit the c-Myc expression, which further causes the decrease in NEAT1 expression. As NEAT1 is being silenced, the expression of miRNA-124 will not be affected and will suppress iASPP, resulting in the increase in p53 activity, which contributes to the apoptosis of cancer cells.[129] This highlights the importance of p53 and NEAT1 in regulating the miRNA-124/iASPP axis in response to PDT treatment of CRC.

6.0 Emerging Therapy Approaches in Colorectal Cancer

Taken together, the various mechanisms by which NEAT1 contributes to CRC tumorigenesis and therapy resistance highlight the vital role of lncRNA as the molecular regulator and a major barrier in achieving effective CRC treatment and management. This highlights the importance of emerging therapeutic approaches

that target lncRNA expression, offering promising interventions to overcome resistance and obtain better treatment outcomes.

6.1 AI-Driven lncRNA Target Prediction Tool

Artificial intelligence (AI), including machine learning and deep learning models, has been applied to predict lncRNA in terms of characteristics, properties and functions, enabling the rapid discovery of lncRNA-related information, such as its regulation of gene expression, and contributions to targeted drugs and diseases. This enhances the understanding of lncRNA-mediated pathways and molecular mechanisms in cancer progression and therapy resistance.

LncADeep, a novel tool which allows both lncRNA identification and functional discovery with the use of deep learning models. For identification purposes, it integrates the sequence intrinsic features and homology features into a deep belief network. This involves the deep learning algorithm, which allows the recognition of both full- and partial-length lncRNA transcripts, even for cross-species lncRNA. It also uses both sequence and structure details to predict the lncRNA-protein interactions with the use of deep neural networks of deep learning algorithms to mainly identify the functional annotation.[130]

After understanding the function of the lncRNA, the mechanism of the lncRNA through its interaction with the gene should be discovered to understand how it contributes to disease development. Hence, lncRNA-Top, a predictive tool involving deep learning approaches designed to accurately predict the lncRNA-gene relationship.[131] This tool investigates the lncRNA sequence and the 3' UTR sequence in the gene with multi-dimensional analysis, as well as the use of both machine-learning and guided deep learning models, allowing it to obtain higher AUC/AUPR correlated with the accuracy of the prediction.[131]

To predict the unrevealed relationship between lncRNA and disease, VADLP is designed. It is a prediction model with the use of deep learning components, such as autoencoders, to construct the multi-layer heterogeneous graph. This graph includes the information on pairwise topology, which identifies the indirect or structural interactions between the related lncRNA and disease, node attributes, which discover the correlation between pairs of lncRNA and disease as well as feature distributions, which allows the prediction of the underlying relationship.[132] This model was validated via an ablation study and comparing this model with other prediction tools, as well as its usage of this model in known lncRNA-disease relationships,[132] showing that the 3 components are important in obtaining more accurate predictive results than the other methods.

The interactions between lncRNA and drugs contribute to therapy resistance as lncRNA regulates drug-sensitive-related genes. This shows the need for HGNNLDA, an AI-based model using the dual-channel hypergraph neural network, which involves the lncRNA hypergraph and drug hypergraph to deduce the lncRNA-drug interactions in terms of sensitivity. This model uses the most suitable and efficient parameters, such as embedding size, number of layers of the hypergraph neural network and high-order connectivity with high AUC and AUPR to provide accurate and effective results. The difference between this model and other models is the usage of a hypergraph, in which the association between lncRNA and drug sensitivity is displayed in a hyperedge, allowing a better handling of the higher-order connectivity.[133]

Apart from these, the DWLMI method is used to predict the association between different biological aspects, lncRNAs, miRNAs, diseases, proteins and drugs. Unlike the other models, this model includes all aspects, showing a broader and comprehensive relationship. This model obtains data from various databases for the construction of a global heterogeneous graph with the use of Deepwalk, k-mer, Mesh descriptor and drug molecular fingerprint to provide a molecular interaction between each biological aspect.[134]

These AI-driven prediction models allow rapid and accurate discovery of complex lncRNA relationships involved in disease progression and drug relations. Revealing these possible interactions provides insight into the development of emerging therapy approaches targeting lncRNA-mediated regulatory communication.

6.2 RNA-based Therapeutics in CRC

RNA-based therapeutics have emerged as promising treatment strategies in CRC, which offer precise regulatory function to overcome therapy resistance and inhibit tumorigenesis. One of the discovered methods to overcome chemoresistance is the novel molecular therapeutic approach, aptamer-guided survivin RNA interference (RNAi).[135] Survivin is a member of the Inhibitors of Apoptosis proteins, functioning as the antiapoptotic protein via both caspase-involved pathway and non-caspase-dependent pathways, which is shown to be highly expressed in CRC stem cells.[136] The use of a synthetic aptamer-siRNA chimera, made with an epithelial cell adhesion molecule (EpCAM)-specific aptamer and a survivin silencer, enhances the sensitivity of chemotherapeutic drugs in CSCs, contributing to the reduction in self-renewal and tumour development by inducing apoptosis. This conjugate also expresses a specific target system due to the usage of an aptamer, which targets the EpCAM to release survivin siRNA.[137] EpCAM is highly expressed in CRC and possesses stem cell-like characteristics, which affects the aggressiveness of CRC and the poor prognosis when overexpressed.[138] The release of survivin siRNA via receptor-mediated endocytosis, depending on the presence of EpCAM, allows the precision delivery to the targeted site, enhancing the treatment efficiency.[137]

Apart from that, nanoparticles have shown potential as a cancer treatment with the conjugation of chemotherapeutic drugs. A recent study revealed the potential of carboxymethyl dextran chitosan nanoparticles encapsulated with snail siRNA and doxorubicin (ChNPs-drug/siRNA). This conjugate increases the stability of siRNA and allows controlled release into targeted cancerous sites based on the pH caused by the tumour microenvironment. This prevents any adverse effects or reduced efficacy due to the unspecific drug release sites during treatment. This conjugate reduces the expression of Snail, which is important in inducing EMT as a member of the zinc finger transcription factor Snail family, while increasing E-cadherin protein. Moreover, this dual-agent nanoparticle exerts apoptotic function, inhibits cancer cell proliferation and metastasis, as well as downregulates EMT.[139,140]

Apart from that, the usage of plant miRNA, which is stable in structure and complementary to target mRNA, shows its potential in gene regulation. Several review studies summarised their anti-cancerous properties in various types of cancer cells, such as breast cancer cells[141] and nasopharyngeal cancer cells[142]. In a recent study, it was found that plant-derived miRNA, specifically gma-miR-4995, binds to and regulates NEAT1 expression by affecting its stability, resulting in a 70-80% reduction in cell proliferation. The underlying mechanism in cell proliferation regulation is through the dysregulation of G_1, S and G_2 phases of the cell cycle progression without inducing apoptosis, which indicates it is a p53-independent mode of action.[143]

Therefore, the RNA-based therapeutic strategies are still emerging approaches, highlighting their speciality and beneficial characteristics in CRC treatment, such as target-specific, dual-agent combined therapy and less toxic innovations. Despite the promising therapeutic potential described above, several critical challenges limit the clinical translation of NEAT1-targeted RNA-based therapies. A major barrier is the efficient in vivo delivery of RNA molecules, as they are highly susceptible to rapid degradation by endogenous nucleases and exhibit poor cellular uptake without specialised delivery systems.[129,133] Although nanoparticle-based carriers and aptamer-mediated targeting strategies have shown improved stability and specificity, their in vivo behaviour, including biodistribution and long-term toxicity, remains insufficiently characterised.[129,133,134] This raises concerns regarding their safety and effectiveness in clinical settings.

In addition, RNA-based therapeutics are associated with potential off-target gene regulation and unintended immune activation, which may compromise therapeutic specificity and lead to adverse effects.[129] Moreover, most NEAT1-targeted strategies remain at the preclinical stage, with limited validation in animal models and a lack of clinical trials evaluating their efficacy in CRC patients. This highlights a significant gap between experimental findings and clinical application. Therefore, while RNA-based approaches offer a promising strategy for targeting NEAT1, substantial optimisation in delivery systems, safety profiling, and clinical validation is required to enable successful translation into therapeutic use.

6.3 CRISPRi as the Functional Discovery Tool Contributing to Epigenetic Silencing Approaches

Epigenetic silencing approaches have become an emerging research area in CRC treatment, offering the regulation of aberrant gene expression with the usage of clustered regularly interspaced short palindromic repeats interference (CRISPRi) to identify gene function.

CRISPRi is a modified CRISPR-Cas9 system designed to repress gene expression without degrading DNA, involving the catalytically inactive CRISPR-associated protein 9 (dCas9) and single guide RNA (sgRNA). This inhibits gene transcription by binding with the complementary targeted DNA sequence. The dCas9 protein binds to any complementary DNA and only inhibits transcription by blocking RNA polymerase without cleaving DNA due to the modification of nuclease domains involved in the DNA cleavage. However, the dCas9 protein exerts a non-target system, which requires a designed sgRNA to guide dCas9 to the targeted DNA sequence.[144,145] This complex is usually used with Krüppel Associated Box (KRAB) repressor, with the recruitment of KAP1, it increases the repression effect on the targeted sites by causing heterochromatin formation.[146] It is also a better option for lncRNA investigation, as lncRNA consists of secondary structure responsible for its function, which cannot be completely knocked down by small deletions within the sequence that is usually done with standard CRISPR/Cas9 complex.[147] Hence, CRISPRi addresses this problem by silencing the lncRNA transcription at the promoter region, allowing the precise functional characterisation and facilitating the identification of lncRNA contributions to disease mechanisms.

Several studies have demonstrated the usage of CRISPRi for lncRNA functional screening and validation. For example, Tsung K *et al.* identified the lncRNA that affects the invasive property in glioma cells by using a CRISPRi-based invasion screening method. Subsequent repression using antisense oligonucleotides confirmed the biological effects of the identified lncRNA, establishing the correlation between the suppression

effect and disease progression.[148] Similarly, John *et al*. demonstrated the use of CRISPRi in identifying unexplored lncRNA Glioma Radiation Sensitisers (lncGRS), showing its potential as enhancers of the radiation therapy when silenced by either antisense oligonucleotides or CRISPRi.[149] These studies highlight the application of CRISPRi as a functional discovery tool and the epigenetic silencing approaches in exploring novel potential therapeutic targets.

7.0 Limitations and Future Perspectives

Despite the extensive evidence supporting the oncogenic role of NEAT1 in colorectal cancer, several limitations in the current literature should be acknowledged. A substantial proportion of studies are based on in vitro experiments or limited patient cohorts, which may not fully capture the complexity of tumour biology in clinical settings. Furthermore, many proposed molecular mechanisms rely on single-pathway analyses without comprehensive validation across multiple models, raising concerns regarding the robustness and reproducibility of these findings.

In addition, the limitation of current studies is the focus on oncogenic functions of NEAT1 with limited investigations into its potential tumour-suppressive roles. Previous study have showed that p53 can be induced by the expression NEAT1, contributing to the tumour-suppressive functions.[150] However, the relevance of p53-NEAT1 interaction in CRC remains poorly understood. This suggest the possibility of existence of a broader regulatory network and the dual-function of NEAT1 in CRC. Future investigations can aim to elucidate p53 and isoforms of NEAT1 interaction to better define the dual functional role of NEAT1 in tumour progression.

Besides, there is a lack of understanding between NEAT1 research and CRC molecular subtyping. Most studies have demonstrated the pathway-based findings without stratifying the findings according to the consensus molecular subtypes or the key genomic features, such as KRAS/BRAF mutations and microsatellite instability. This limits the ability to define whether NEAT1 exhibits subtype-specific functions. Further studies should evaluate the NEAT1 expression and function across CRC subtypes to identify the context-dependent role of NEAT1.

Additionally, inconsistencies in reported NEAT1 functions across studies suggest potential context-dependent roles influenced by tumour microenvironment, disease stage, or genetic background. Majority of studies reporting positive associations also raises the possibility of publication bias, where negative or inconclusive findings are underreported. Moreover, several mechanistic interactions described, such as ceRNA networks, lack thorough in vivo validation, limiting their translational relevance. Therefore, future research should prioritise well-controlled, large-scale studies integrating clinical data and functional validation to establish a more definitive role of NEAT1 in CRC.

8.0 Conclusion

LncRNA NEAT1 plays a vital role in CRC progression by regulating several oncogenic pathways, such as the dysregulation of transcriptional pathways, Wnt/β-catenin signalling pathway and cell cycle, as well as enhanced growth factor signalling, angiogenesis and metabolic reprogramming. This involves the role of ceRNA in dysregulating the miRNAs and downstream targeted proteins, contributing to tumorigenesis,

metastasis and therapeutic resistance. Although its overexpression leads to poor prognosis and treatment outcomes, it also shows potential as a diagnostic biomarker and therapeutic target, allowing for the advancement of diagnostic and therapeutic approaches. Future research into the unrevealed mechanisms or emerging diagnostic and therapeutic strategies that enhance treatment precision and maximise the clinical efficacy for CRC patients.

Abbreviation Lists

Abbreviation	Definition
5-FU	5-fluorouracil
ADARB2	adenosine deaminase, RNA-specific, B2
AI	artificial intelligence
ATG	autophagy-related protein
AUC	area under the ROC curve
BHLHE40	class E basic helix-loop-helix protein 40
CAF	cancer-associated fibroblast
cBAF	canonical brahma-associated factors
CDK6	cyclin D-dependent kinase 6
ceRNA	competing endogenous RNA
CFIm	mammalian cleavage factor I
ChNPs-drug/siRNA	Chitosan nanoparticles encapsulated with snail siRNA and drug
CPSF4	cleavage and polyadenylation specific factor 4
CRC	colorectal cancer
CRISPRi	clustered regularly interspaced short palindromic repeats interference
CSC	cancer stem cell
CTCs	Circulating tumour cells
Cul4A	Cullin 4A
DAZAP1	DAZ-associated protein 1
dCAS9	denatured CRISPR-associated protein 9
dNTPs	deoxynucleotides
dUTP	2′-deoxyuridine-5′-triphosphate
ECM	extracellular matrix
EGF	epidermal growth factor
EGFR	EGF receptor
EMT	epithelial-mesenchymal transition
ENO1	enolase 1
EpCAM	epithelial cell adhesion molecule
FUS	FUS RNA binding protein
GDNF	glial cell line-derived neurotrophic factor
GFR-α	GDNF-α receptor
GST-π	glutathione S-transferase π
GTP	guanosine 5’-triphosphate
HMGB1	High Mobility Group Box 1
hnRNP H3	heterogeneous nuclear ribonucleoprotein H3
hnRNP K	heterogeneous nuclear ribonucleoprotein K
iASPP	inhibitor of apoptosis-stimulating protein of p53
IGF2	insulin-like growth factor 2
IL17RD	interleukin-17 receptor D

IL-8	interleukin-8
IRAIus	inverted Alu repeats
KRAB	Krüppel Associated Box
KRAS	kirsten rat sarcoma viral oncogene homolog
LC3	microtubule-associated protein light chain 3
lncGRS	lncRNA Glioma Radiation Sensitisers
lncRNAs	long non-coding RNA
m7G	7-methyl guanosine
MMP	matrix metalloproteinase
NAD+	nicotinamide adenine nucleotide
ncBAF	non-canonical brahma-associated factors
ncRNAs	non-coding RNAs
NEAT1	lncRNA nuclear enriched abundant transcript 1
NONO	Non-POU domain-containing octamer-binding protein
NR4A1	nuclear receptor subfamily group A member 1
OCT4	Octamer-binding transcription factor 4
PAS	polyadenylation signal
PBAF	polybromo-brahma-associated factors
PDT	photodynamic therapy treatment
PGAM1	phosphoglycerate mutase 1
PGK1	phosphoglycerate kinase 1
P-gp	P-glycoprotein
PSPs	paraspeckle proteins
RB	retinoblastoma protein
RBM14	RNA binding motif protein 14
RISC	RNA-induced silencing complex
RNAi	RNA interference
ROC	receiver operating characteristic
ROS	reactive oxygen species
Sef	similar expression to fibroblast growth factor genes
SFPQ	Splicing factor, proline- and glutamine-rich
sgRNA	single guide RNA
SOX2	SRY-box transcriptional factor 2
SWI/SNF	SWItch/Sucrose NonFermentable
TDP-43	transactive response DNA binding protein
ULK1	Unc-51 like kinase 1
USP7	ubiquitin-specific protease 7
UTR	untranslated region
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
ZEB1	Zinc finger E-box binding homeobox 1

Authors contributions

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