Mário Penna Journal - molecular and clinical cancer research, Belo Horizonte, v. 2, n.1, p. 68-99, jan./jun. 2024. DOI: 10.61229/mpj.v2i1.32

DESCODIFICANDO O CÓDIGO DO CÂNCER: Revelando o Potencial dos RNAS Longos não Codificantes em Oncologia

Integrative Review Article

DECODING THE CANCER CODE: Unveiling The Potential Of Long Non-Coding RNAS In Oncology

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RESUMO

A carcinogênese prevê 30 milhões de novos casos até 2040, tornando-se a segunda principal causa de morte global. No Brasil, as doenças neoplásicas resultaram em mais de 229.000 mortes em 2020, com previsão de 704.000 novos casos para cada ano do triênio 2023-2025. Fatores como tabagismo, estresse e predisposição genética influenciam a oncogênese. Intervenções em oncologia enfrentam desafios como resistência terapêutica e heterogeneidade tumoral. Cerca de 75% do genoma humano é composto por RNAs não codificadores (ncRNAs), com foco em longos ncRNAs. Anteriormente considerados 'lixo evolutivo', os lncRNAs regulam genes e afetam o câncer. LncRNAs nucleares impactam na arquitetura da cromatina, transcrição e processamento de RNA. Eles funcionam por meio de vias complexas, modulando oncogênicos e afetando resistência ao tratamento. Vários lncRNAs, incluindo MALAT1, ANRIL, HOTAIR, GAS5, MEG3 e H19, modulam vias oncológicas e influenciam processos celulares e resistência ao tratamento. Embora promissores como biomarcadores, a complexidade estrutural dos lncRNAs

dificulta sua aplicação clínica.

Palavras-chave: Câncer, lncRNAs, Biomarcadores.

ABSTRACT

Carcinogenesis predicts 30 million new cases by 2040, making it the second leading cause of death globally. In Brazil, neoplastic diseases resulted in more than 229,000 deaths in 2020, with 704,000 new cases expected between 2023 and 2025. Factors such as smoking, stress and genetic predisposition influence oncogenesis. Oncology interventions face challenges such as therapeutic resistance and tumor heterogeneity. Around 75% of the human genome is made up of non-coding RNAs (ncRNAs), with a focus on long ncRNAs. Previously considered 'evolutionary junk', lncRNAs regulate genes and affect cancer. Nuclear lncRNAs impact chromatin architecture, transcription and RNA processing. They function via complex pathways, modulating oncogenes and affecting resistance to treatment. Several lncRNAs, including MALAT1, ANRIL, HOTAIR, GAS5, MEG3 and H19, modulate oncogenic pathways and influence cellular processes and treatment resistance. Although promising as biomarkers, the structural complexity of lncRNAs hinders their clinical application.

Keyword: *Cancer, lncRNAs, Biomarkers.*

Data de submissão: 20/04/2024.
Data de aprovação: 12/06/2024.

1. INTRODUCTION

Cancer persists as a predominant cause of mortality globally, representing a critical public health challenge. Epidemiological data indicate approximately 20 million new cancer diagnoses and 10 million cancer-related deaths worldwide annually[1]. Future projections suggest a substantial increase of about 60% in cancer incidence over the next two decades, potentially resulting in approximately 30 million new cases by 2040[2,3]. In the Brazilian context, forecasts anticipate approximately 704,000 new cancer cases between 2023 and 2025[4]. National health records from Brazil's Ministry of Health revealed that of the 1,556,824 recorded deaths in 2020, cancer was responsible for 229,300 cases[5]. The etiology of cancer is multifaceted, encompassing risk factors such as tobacco use, alcohol consumption, addictive substance use, sleep disorders, chronic stress, infections, sedentary lifestyle, and exposure to environmental carcinogens and ionizing radiation[6,7]. Furthermore, genetic predispositions and socioeconomic determinants are recognized as contributory factors in cancer pathogenesis[8].

Primary oncological interventions predominantly comprise surgical tumor resection, often supplemented with adjuvant radiotherapy and chemotherapy. These modalities face significant challenges, notably the emergence of resistance to pharmacological agents and issues related to the efficacy of drug delivery systems in oncology[9,11]. Beyond these conventional approaches, a spectrum of alternative therapies exists, albeit with less frequent application. These include hematopoietic stem cell transplantation (commonly referred to as bone marrow transplantation), immunotherapeutic regimes, hormonal manipulation in hormone-sensitive cancers, targeted molecular therapies that disrupt specific cancer-driving pathways, cryoablation for localized destruction of tumor cells, and radiofrequency ablation for minimally invasive tumor removal. Additionally, clinical trials continually explore novel therapeutic avenues and regimens. The critical nature of cancer as a global public health challenge underscores the necessity of comprehensive research in this field. An in-depth understanding of cancer biology, pathophysiology, and epidemiology is imperative for developing and refining effective strategies in cancer prevention, early detection, diagnosis, and treatment, ultimately aiming to enhance global health outcomes.

Cancer, inherently characterized by unregulated cellular proliferation, presents a multifaceted complexity deeply entrenched in human biology. At its core, oncogenesis is driven by genetic alterations, where DNA mutations disrupt molecular interactions and signaling pathways, precipitating the transformation of normal cells into malignant ones and ultimately leading to tumor genesis[12]. The heterogeneity of cancer is evident at multiple biological levels — molecular, cellular, and histological — significantly complicating its therapeutic management. These genetic aberrations, frequently implicated in cancer, interfere with fundamental cellular processes, including cell cycle regulation, apoptosis, and DNA repair mechanisms. Further complicating the oncological landscape is the diversity of immune responses within the tumor microenvironment. The intricate interplay between various immune cells and the tumor cells themselves is crucial in shaping both the progression of the disease and the response to treatment modalities[13].

In view of this problem, new approaches are needed. In the last decade, a growing number of studies have investigated the role of long non-coding RNAs (lncRNAs) in the context of cancer. LncRNAs show changes in expression in both normal and cancer cells and are involved in many biological processes related to tumorigenesis and drug resistance[14]. They are therefore considered promising candidates as biomarkers for cancer diagnosis and prognosis. This paper provides an overview of the potential of lncRNAs as biomarkers. It also elucidates their mechanisms of action in biological processes and their implications for oncology.

2. METHODOLOGY

2.1 Theoretical-Methodological Framework

Oncology's interest in scientific evidence is motivated by the need to understand the mechanisms underlying cancer and to develop effective interventions[95]. Through rigorous, evidence-based research, oncologists can identify risk factors, prognostic biomarkers, and novel therapeutic options[96]. This approach enables the formulation of personalized treatment strategies that increase survival and improve patients' quality of life[97,98]. Evidence-based practice also ensures that clinical decisions are based on the best available data, thereby promoting more effective and safer health care[99].

Integrative review is a methodology that allows the integration of empirical and theoretical studies to provide a comprehensive understanding of a particular health phenomenon. It is a particularly useful technique in the health field because it combines data from different sources to provide a more detailed and holistic view of the subject under study. Souza, Silva and Carvalho[105] state that integrative review allows for the critical appraisal and synthesis of multiple studies, providing a complete understanding of the current state of knowledge and identifying gaps in the literature.

2.2 Methods

This is an integrative review on the role of lncRNAs in oncology, their applications in diagnosis and treatment, and the perspectives and challenges involved. According to Souza, Silva and Carvalho[105], the preparation of an integrative review follows six steps: formulation of the guiding question; literature search or sampling; data collection; critical analysis of the included studies; discussion of the results; and presentation of the integrative review.

In accordance with these principles, the search strategies were developed based on the research question: **"What is the role of long non-coding RNAs in oncology and how can they be used as biomarkers for cancer?"**. Thus, efforts were focused on the cellular and molecular biology of lncRNAs, including their biogenesis, classification and function, as well as their role in the development of neoplasms and their contribution to diagnosis and treatment.

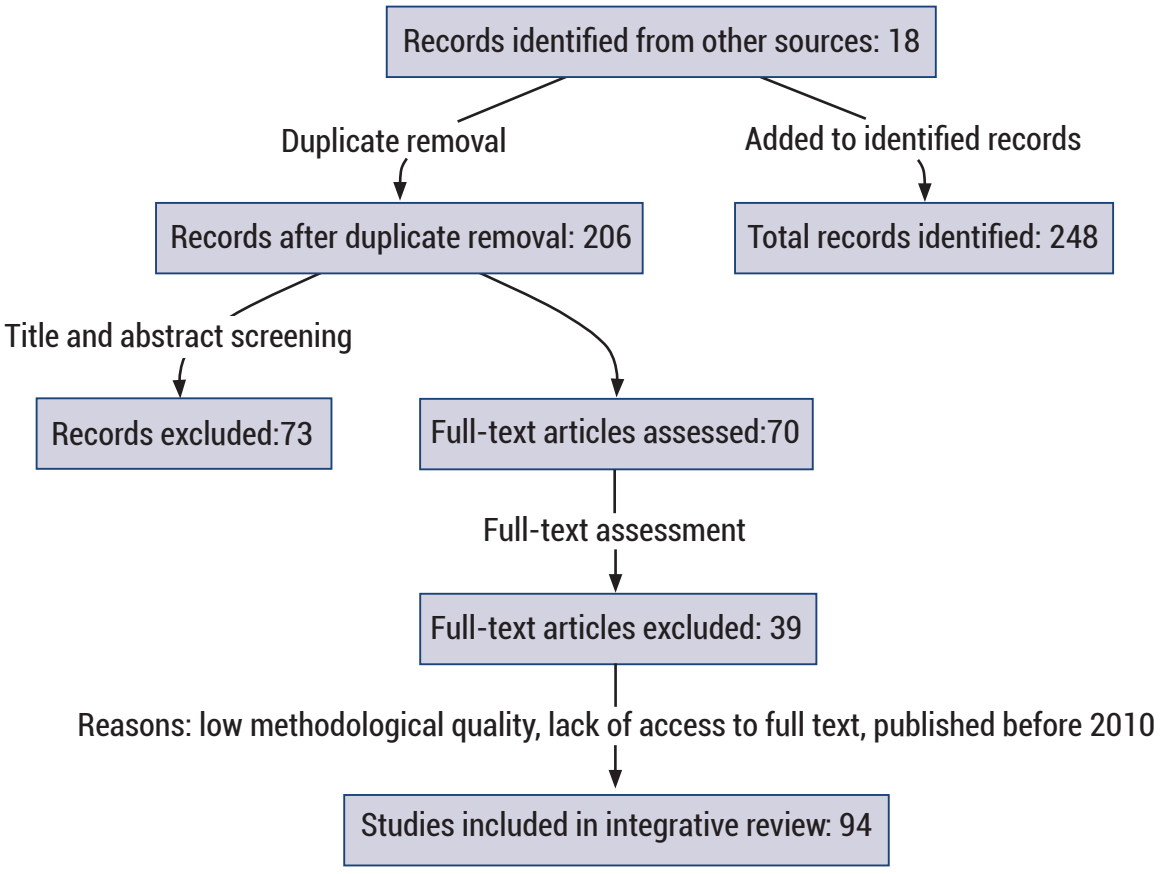
The studies in this review were published between 2010 and 2023, a time period chosen to capture the most recent and relevant changes in lncRNA research in oncology. Inclusion criteria were: publications between 2010 and 2023; original

studies and literature reviews focusing on the role of lncRNAs in oncology; and national and international scope. Experimental, cohort, case-control studies, systematic reviews and meta-analyses that addressed the topic of long non-coding RNAs and their application in oncology were included. The studies reviewed were published in English, as this is the universal language of scientific articles.

The electronic databases selected for this review were PubMed, ClinicalTrials.gov, Google Scholar, Medical Literature Analysis and Retrieval System Online (Medline), PubMed Central (PMC), and Index Medicus, as well as institutional sources such as the International Agency for Research on Cancer (IARC), the World Health Organization (WHO), the Pan American Health Organization (PAHO) and Datasus. The descriptors used in the searches were: 'long non-coding RNAs', 'lncRNAs', 'cancer', 'oncology' and 'biomarkers'.

The search strategies included combinations of the above descriptors using Boolean operators (AND, OR) to refine the results and ensure inclusion of the most relevant studies. Exclusion criteria included duplicate studies, studies published before 2010, and studies that did not fit the purpose of the guiding question. (Figure 1).

Figure 1 - Flowchart of the selection of articles for the theoretical review.



3. LITERATURE REVIEW

3.1 Tumor Heterogeneity: Unraveling Complexity with Technological Innovations

Tumor heterogeneity represents a significant barrier to the efficacy of oncological therapies, encapsulating both genotypic and phenotypic variations. The intratumoral heterogeneity refers to the diversity observed within a single neoplastic mass, encompassing variations in genetic, epigenetic, and phenotypic profiles. This diversity can manifest as distinct cellular populations within the same tumor, each exhibiting unique molecular characteristics and behaviors. In contrast, intertumoral heterogeneity describes the variations observed among tumors of the same histopathological classification across different patients. These differences can significantly influence the tumor's response to therapeutic interventions and disease progression patterns. Additionally, spatial heterogeneity is noted when comparing primary and metastatic lesions or multiple tumors within the same patient, often reflecting the evolutionary dynamics of cancer cells in response to environmental pressures and therapeutic challenges[15,17]. The complex genetic and epigenetic regulations underlying tumorigenesis contribute to this heterogeneity, underscoring the need for personalized and adaptive therapeutic strategies in cancer management.

The synergistic integration of bioinformatics with advanced molecular methodologies is pivotal for an in-depth understanding of oncogenic processes, thereby facilitating early diagnosis and tailoring treatment strategies[18]. The advent of high-throughput sequencing technologies, particularly in whole-genome and transcriptome analyses, has been transformative. It has been elucidated that a fraction, less than 2%, of the human genome encodes proteins. In stark contrast, over 75% of the genome is actively transcribed into various forms of non-coding RNAs, a revelation that underscores the complexity of genomic regulation[19,20]. Consequently, RNA sequencing (RNA-seq) has emerged as a predominant approach for the comprehensive analysis of genetic and epigenetic alterations driving cancer progression[21]. This technique enables the precise profiling of gene expression within a specific tumor microenvironment, providing a detailed 'snapshot' of the active genomic landscape. Such insights are crucial for expanding our understanding of the molecular pathways altered during carcinogenesis, thereby enhancing the precision of targeted therapeutic interventions.

The majority of transcribed sequences in the human genome are classified as long non-coding RNAs, characterized by their length exceeding 200 nucleotides[19].

According to the latest data from the GENCODE Consortium (version 41), the human genome contains 19,095 genes responsible for encoding a diverse repertoire of 54,291 lncRNA transcripts[22]. These transcripts are primarily non-coding, possessing minimal or no protein-coding potential. Historically, non-coding RNAs (ncRNAs) were relegated to the category of 'evolutionary junk' or dismissed as mere 'transcriptional noise.' This perception dramatically shifted following comprehensive sequencing efforts of cDNA libraries, which unveiled the extensive diversity and complexity of ncRNAs in the human genome[23,24]. LncRNAs have since been recognized as critical regulatory elements in gene expression, with a significant impact on the pathophysiology of various diseases, including cancer. Their involvement ranges from modulating chromatin architecture to influencing transcriptional and post-transcriptional gene regulation, thus playing a pivotal role in cancer development and progression[25].

3.2 Biogenesis and Classification of lncRNAs

The biogenesis of lncRNAs is a distinct and complex process, intricately regulated by various cellular contexts, developmental stages, and external stimuli[26]. LncRNAs originate from diverse genomic sources, including enhancer elements, dedicated promoters, promoters shared with protein-coding or other non-coding genes, and intergenic regions[27]. Despite this diversity, most annotated lncRNAs exhibit molecular features reminiscent of messenger RNAs (mRNAs), such as the presence of a 5′-methyl-guanosine cap and a 3′-polyadenylated tail, with their transcription primarily mediated by RNA polymerase II (Pol II). However, lncRNAs differ markedly from mRNAs in their splicing efficiency. They often undergo less efficient alternative splicing processes compared to mRNAs, a characteristic that frequently results in their nuclear retention and distinct functional roles within the cellular milieu[28,29].

The classification of lncRNAs is intricately defined by their genomic positioning relative to protein-coding genes. LncRNAs transcribed from regions overlapping a protein-coding gene, utilizing the same promoter and transcriptional direction, are classified as 'sense lncRNAs'. In contrast, 'antisense lncRNAs' or 'natural antisense transcripts (NATs)' originate from the complementary DNA strand of a protein-coding gene[30,31]. 'Intronic lncRNAs' are derived exclusively from the introns of coding genes. 'Bidirectional' or 'divergent lncRNAs' are characterized by their transcription from the same promoter as a coding gene but on the opposite strand, leading to transcripts oriented away from each other. Lastly, 'intergenic lncRNAs' (lincRNAs) are those transcribed from specific gene loci situated between two genes on the same DNA strand, without overlapping with both genes[32,33] (Figure 2).

The subcellular localization of lncRNAs is a critical determinant of their functional roles. Predominantly localized within the nucleus, lncRNAs are integral to various nuclear processes. They are involved in chromatin organization, transcriptional regulation, RNA processing, and the structuring of nuclear domains[34]. Owing to their nuclear residency, lncRNAs can exert regulatory effects in both cis and trans. In cis regulation, lncRNAs modulate the expression of adjacent genes, whereas in trans-regulation, they influence the transcription of mRNAs at distal genomic loci[35,36]. LncRNAs with fewer exons can be transported to the cytoplasm, a process facilitated by the nuclear RNA export factor 1 (NXF1). This export is mediated through efficient interactions with RNA-binding proteins (RBPs), implicating lncRNAs in a variety of crucial biological functions[27]. Conversely, in scenarios where transcriptional efficiency is compromised, lncRNAs are retained in the nucleus, where they are subjected to degradation by the nuclear exosome complex[26,37].

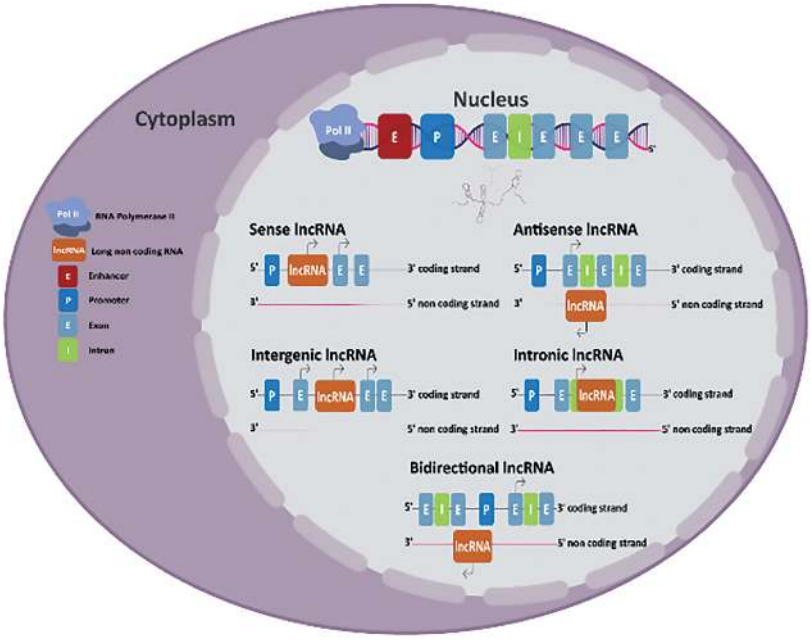


Figure 2. LncRNA biogenesis based on their site of origin. The genetic origin of lncRNAs allows for their classification into five distinct groups. Sense: the lncRNAs are transcribed in the same direction as the protein-coding gene, overlapping the introns/exons of different genes in the sense RNA chain. Antisense: the lncRNAs are transcribed in the opposite strand to a known overlapping gene, originating from the promoter of a protein-coding gene, but in the opposite direction. Intergenic: when the lncRNAs are transcribed from regions between genes, not overlapping with other genes, having their regulatory elements, and located genomically between two protein-coding genes. Intronic: the lncRNAs are overlapping one or more exons, or incorporated into introns, without touching exons, being fully transcribed from the

introns of protein-coding genes. Bidirectional: (or divergent), the lncRNAs are derived from promoters with bidirectional activity, transcribed from the promoter of a protein-coding gene, but in the opposite direction.

Source: Prepared by the authors (2024).

3.3 Functional Dynamics: Understanding the Mechanisms of Action of Long Non-Coding RNAs

The molecular actions of lncRNAs, pivotal for their regulatory roles, encompass a spectrum of mechanisms derived from a combination of distinct functional archetypes. As signaling molecules, lncRNAs can be responsive to specific cellular or environmental stimuli, thereby participating in signal transduction pathways[38,39]. Functioning as decoys, they sequester transcription factors or other protein complexes, effectively modulating their availability and activity[40]. In their role as guides, lncRNAs direct specific transcription factors or protein complexes to targeted genomic loci, influencing gene expression patterns[41]. As scaffolds, they facilitate the assembly of multi-protein complexes, orchestrating complex molecular interactions[42]. Furthermore, lncRNAs can act as enhancers, strengthening the connectivity between enhancer elements and promoter regions, often through chromosomal looping mechanisms, thus modulating transcriptional activity[43]. Another significant mechanism involves their function as competing endogenous RNAs (ceRNAs) or 'molecular sponges.' In this capacity, lncRNAs bind to microRNAs (miRNAs), diminishing their availability to target messenger RNAs (mRNAs), thereby indirectly regulating gene expression[44,45] (Figure 3).

LncRNAs exert regulatory control over gene expression through multiple levels, encompassing transcriptional, post-transcriptional, and epigenetic mechanisms. Their subcellular localization plays a critical role in determining their specific functional impacts. Within the nucleus, lncRNAs are key players in epigenetic regulation. This includes inducing allosteric modifications, recruiting chromatin-modifying enzymes, and interacting with repetitive genomic elements to modulate chromatin structure and gene expression[46,47]. They are also involved in transcriptional autoregulation, functioning as cofactors for transcription factors or exerting inhibitory effects on gene transcription[48,49]. In the cytoplasm, lncRNAs contribute significantly to post-transcriptional gene regulation. They participate in the maintenance and regulation of pre-mRNA splicing, stabilize and facilitate the translation of mRNAs, affect protein stability and activity, and act as competing endogenous RNAs (ceRNAs). As ceRNAs,

they sequester microRNAs (miRNAs), thereby modulating the miRNA-mediated regulation of target mRNA transcripts[50,33].

Long non-coding RNAs exhibit a broad spectrum of interactions with diverse biomolecules, including microRNAs (miRNAs), messenger RNAs (mRNAs), and DNA, each leading to distinct regulatory outcomes. In their interaction with miRNAs, lncRNAs often function as molecular sponges or competing endogenous RNAs (ceRNAs). By sequestering miRNAs, lncRNAs inhibit their activity, thereby upregulating the expression of genes normally repressed by these miRNAs[51,52]. In the context of mRNA interaction, lncRNAs can affect the processing and stability of specific target mRNAs. This is achieved by interfacing with the methylation machinery, influencing translation efficiency, and modulating splicing events, which in turn alters the diversity of mRNA isoforms produced[53,54].

Furthermore, lncRNAs regulate gene expression via direct interactions with DNA. They can modify chromatin architecture, influencing the accessibility of genomic regions to transcriptional machinery, and participate in the establishment or removal of epigenetic marks, such as methylation or demethylation[55,56]. The functional mechanisms of lncRNAs are highly context-dependent, relying on the specific sequence interactions between the lncRNA and its associated biomolecules[57]. In the oncogenic landscape, cancer cells exploit these interactions for various pathological processes. These include promoting cellular proliferation, facilitating the epithelial-mesenchymal transition (EMT), enabling invasion into surrounding tissues, and developing resistance to therapeutic interventions[58].

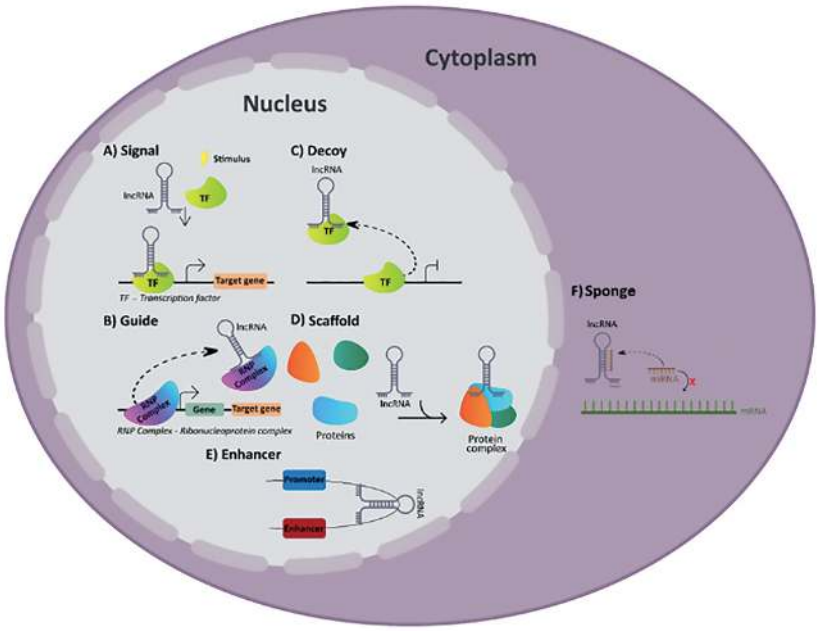


Figure 3. Classification of lncRNAs according to their mechanisms of action. The lncRNAs have different archetypes that allow them to perform different regulatory roles. **(A) Signal:** Under different stimuli, the lncRNAs are transcribed and act as signal transduction molecules, interacting with chromatin-modifying enzymes to modulate transcription in response to the stimulus. **(B) Guide:** the lncRNAs recruit chromatin-modifying enzymes to target genes, influencing their expression at specific locations in the genome. They also organize transcription factors and contribute to chromatin regulation. **(C) Decoy:** the lncRNAs, when transcribed, bind directly to proteins, acting as "baits" for specific regulatory factors. This interaction blocks signaling pathways and leads to transcriptional repression, preventing these factors from binding to DNA. **(D) Scaffold:** the lncRNAs serve as central platforms, allowing the binding of various transcription factors. Acting as scaffolds, they facilitate the formation of RNA-protein complexes, activating or repressing the transcription of target genes. **(E) Enhancer:** the lncRNAs, like RNA enhancers (eRNAs), influence chromatin interactions, acting as enhancers and modulating the activation of target genes. In addition, they promote chromosomal looping to intensify the association between enhancer and promoter regions. **(F) Sponge:** the lncRNAs indirectly regulate gene expression by acting as molecular "sponges" for miRNAs, competing with them and reducing the number of miRNAs available to bind to mRNAs, thus influencing gene expression.

Source: Prepared by the authors (2024).

3.4 Implications of Long Non-Coding RNAs in Oncogenesis: Roles in Cancer Development and Progression

The process of tumorigenesis is intricately complex, involving the acquisition of specific capabilities by cells that facilitate sustained growth signaling. These capabilities include promoting cellular invasion, stimulating angiogenesis, and evading apoptosi[59,60] (Figure 4). Recent developments in tumor biology have shed light on four additional hallmarks of cancer: the emergence of phenotypic plasticity, epigenetic reprogramming independent of mutations, the influence of polymorphic microbiomes, and the role of senescence in tumor cells[61]. Within this multifaceted context, genomic alterations in non-coding regions have been identified as a source for the genesis of long non-coding RNAs. These lncRNAs play a pivotal role in the establishment and progression of tumors. Their significance is underpinned by their tissue-specific expression patterns and their involvement in key regulatory processes, including cellular homeostasis and immune response modulation[62,63].

The lncRNAs exhibit dualistic roles in oncogenesis, functioning either as tumor suppressors or oncogenes. This functional dichotomy is largely influenced by their transcriptional regulation through interactions with key regulatory factors such as tumor protein TP53, MYC oncogene, and the estrogen receptor[64]. A significant number of lncRNAs modulate the activity of the polycomb repressive complex 2 (PRC2), directing it to specific genomic loci to enact transcriptional silencing of genes distal to their site of synthesis[27,65]. Beyond their transcriptional roles, lncRNAs also exert substantial influence in post-transcriptional regulation. They are involved in modifying various aspects of mRNA biology, including splicing, stability, nuclear export, and translational efficiency[66].

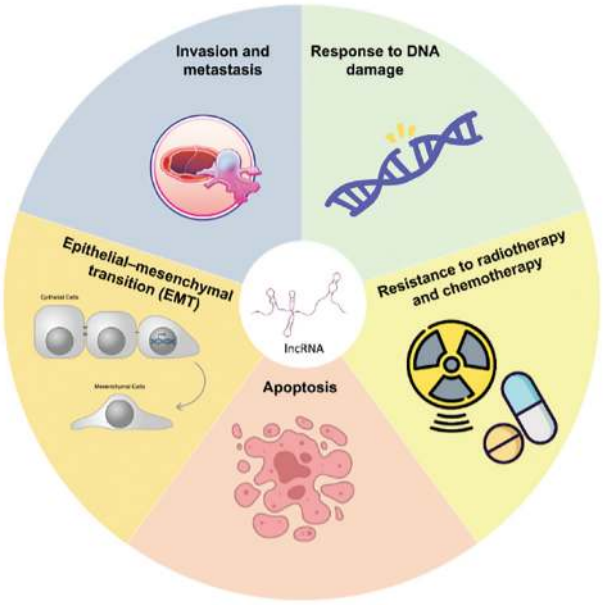


Figure 4. Involvement of lncRNAs in significant processes of cancer. The implications of lncRNAs in the tumor context include active participation in metastasis, angiogenesis, epithelial-mesenchymal transition (EMT), drug resistance, and response to treatments such as chemotherapy and radiotherapy. Additionally, lncRNAs play a prominent role in regulating critical events such as cell invasion and apoptosis, with intricate and interconnected roles significantly influencing cancer progression and aggressiveness.

Source: Prepared by the authors (2024).

3.5 Long Non-Coding RNAs in Oncology: Key Players in Cancer Pathogenesis

Numerous lncRNAs have been implicated in cancer pathogenesis, each exhibiting unique roles in various malignancies. Among them, Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) stands out for its ubiquitous presence across

diverse neoplastic conditions, including gynecological cancers. Initially identified in lung adenocarcinoma, MALAT1 is critically involved in the deregulation of cellular signaling pathways, significantly impacting cancer development, progression, and therapeutic response[67,68]. Antisense non-coding RNA in the INK4 locus (ANRIL) is another lncRNA associated with oncogenic processes. In cancer cells, ANRIL has been linked to enhanced proliferation, metastasis, epithelial-mesenchymal transition (EMT), and inhibition of apoptotic pathways[69].

HOX antisense intergenic RNA (HOTAIR) is recognized for its involvement in multiple facets of tumor malignancy. It plays a pivotal role in promoting tumor cell mobility, invasion, proliferation, and lymphatic metastasis. Furthermore, HOTAIR is instrumental in initiating EMT and in the maintenance of cancer stem cells (CSCs), contributing to the aggressive behavior of cancer cells[70].

Growth arrest-specific 5 (GAS5) lncRNA exhibits a strong association with histopathological features and patient survival metrics, such as the International Federation of Gynecology and Obstetrics (FIGO) stage, vascular invasion, and lymph node metastasis. Functionally, GAS5 acts predominantly as a tumor suppressor, inhibiting cell proliferation and invasion, while concurrently promoting apoptotic pathways[71,72]. Its reduced expression is linked to adverse prognostic outcomes, contributing to the onset and aggressiveness of cancer. Conversely, over-expression of Maternally expressed gene 3 (MEG3) has been shown to exert tumor-suppressive effects. MEG3 inhibits cellular proliferation, induces apoptosis, and may influence chemotherapeutic resistance. This lncRNA is normally expressed across a range of tissues and plays a vital role in the development of cancer[73,74].

H19 imprinted maternally expressed transcript (H19) is another lncRNA frequently expressed in various cancer types, where it functions as an oncogene. H19 promotes cellular migration, invasion, metastasis, epithelial-mesenchymal transition (EMT), and autophagy. It is also implicated in various clinicopathological characteristics and clinical parameters, including tumor size and overall survival. Furthermore, H19 is a critical component of regulatory networks that foster aggressive tumor phenotypes, underscoring its importance in oncogenic processes[75,76].

3.6 LncRNAs as Biomarkers: Diagnostic and Prognostic Applications in Oncology

The unique characteristics of long non-coding RNAs, such as their high tissue specificity, aberrant expression patterns in cancer, and the feasibility of non-invasive detection, position them as potentially superior biomarkers for specific cancer

diagnosis and prognosis compared to DNA-based markers[77]. Studies indicate that approximately 60% of lncRNAs exhibiting abnormal expression are cancer-type-specific, thereby offering a high degree of precision oncology. These lncRNAs can function as standalone biomarkers or synergistically with other lncRNAs or proteins to enhance diagnostic and prognostic accuracy[78,79].

An illustrative example is the lncRNA H19, which has been observed to have elevated levels in breast cancer patients. H19 demonstrates enhanced sensitivity and specificity in diagnosing breast cancer compared to traditional biomarkers[80]. Similarly, the expression levels of HOTAIR and GAS5 have been found to correlate with survival outcomes in cervical cancer, thereby serving as valuable prognostic indicators for patient management[81].

3.6.1 Exploring the Role of lncRNAs as Clinical Biomarkers

LncRNAs have garnered significant attention in recent years due to their diverse roles in gene regulation and their potential as clinical biomarkers for cancer. Unlike protein-coding RNAs, lncRNAs do not encode proteins but are involved in regulating various cellular processes, including chromatin remodeling, transcriptional and post-transcriptional regulation, and the modulation of protein activity. Here are some of their applications as biomarkers:

1. Diagnostic Biomarkers: LncRNAs can be highly specific to particular types of cancer, making them excellent candidates for early diagnosis. Their expression patterns often differ significantly between cancerous and normal tissues, enabling the identification of malignancies at an early stage[82]. For example, lncRNAs like HOTAIR and PCA3 have been associated with breast and prostate cancers, respectively, providing a non-invasive means to detect these diseases through blood or urine tests[83].

2. Prognostic biomarkers: The expression levels of some lncRNAs are often related to survival rates and disease progression. LncRNAs such as MALAT1 have been associated with poor prognosis in several cancers, including lung and liver[84]. Monitoring these lncRNAs can help predict the trajectory of the disease and adapt treatment plans accordingly.

3. Therapeutic biomarkers: lncRNAs can be useful in personalized treatments, providing probability of response to specific therapies. For example, lncRNAs involved in drug resistance mechanisms can inform physicians about potential resistance to

chemotherapy, allowing for adjustments in therapeutic strategies[85]. LncRNA GAS5, for example, has been implicated in glucocorticoid resistance in lymphoblastic leukemia, suggesting its role in guiding therapeutic choices[86].

3.7 Targeting lncRNAs in Oncology: Innovative Approaches in Cancer Therapies

The development of cancer therapies targeting lncRNAs represents a significant advancement in the field, aiming to modulate their expression and thereby control key processes in tumor progression[87]. For instance, therapeutic modulation of the H19 lncRNA, which exhibits oncogenic properties in various cancers, has demonstrated promising potential[76]. Innovative strategies have been explored, including the use of plasmids engineered to express diphtheria toxin. While this method may seem unrelated to lncRNAs at first glance, it is an example of leveraging lncRNA regulatory sequences for targeted cancer therapy. Specifically, the plasmid is designed to express the diphtheria toxin under the control of regulatory sequences derived from the H19 and IGF2-P4 lncRNAs, which are known to be overexpressed in bladder cancer. This approach has shown efficacy in reducing tumor size in bladder cancer xenograft models[88,89].

A promising avenue in the development of lncRNA-targeted cancer therapies involves the use of antisense oligonucleotides or small interfering RNAs. These molecules are designed to specifically target and suppress the expression of oncogenic lncRNAs, thereby reversing their transcriptional repression effects on critical genes[80,90]. Additionally, modulating lncRNA expression can also be achieved using genomic editing techniques. For example, CRISPR/Cas9 technology can be employed to create steric hindrances at lncRNA promoters, effectively altering their transcriptional activity[91].

Recent advancements in oncological research have increasingly spotlighted lncRNAs for their dynamic functional roles and therapeutic potential. One such promising lncRNA is ELNAT1, which has garnered attention in the context of bladder cancer. Identified within urinary exosomes, ELNAT1 exhibits markedly elevated expression levels in bladder cancer patients. Its association with the promotion of lymphatic metastasis positions it as a potential target for personalized therapeutic interventions. The discovery of ELNAT1 in exosomes not only offers a non-invasive diagnostic tool but also serves as an independent preoperative predictor of lymph node metastasis, thereby enhancing the diagnostic and therapeutic landscape for bladder cancer[92].

In the realm of papillary thyroid cancer, the quest for effective circulating biomarkers has led to the exploration of lncRNAs as potential therapeutic targets. Advanced techniques like data mining and next-generation sequencing have been instrumental in revealing the distinctive potential of lncRNAs. These studies have shown that lncRNAs can be utilized to differentiate between papillary thyroid cancers and benign thyroid tumors. This distinction is crucial for developing more precise and non-invasive treatment approaches, paving the way for improved patient outcomes in thyroid oncology[93].

The exploration of lncRNAs in the context of acute myeloid leukemia (AML) has unveiled promising avenues for targeted therapeutic interventions, particularly with the lncRNA XIST. Research has revealed a notable association between the absence of XIST and the development of myeloproliferative neoplasms, underscoring the tumor-suppressive role of XIST in vivo. This finding indicates the potential of XIST as a therapeutic target, offering new possibilities for personalized treatment strategies in AML[94].

In addition, the study of cancer-associated thromboembolism has brought to light the significance of circulating biomarkers, including lncRNAs, in a comprehensive therapeutic approach. The intricate interplay between lncRNAs, the immune system, and thromboembolic events presents unique challenges and opportunities for the development of novel therapeutic strategies. The identification and characterization of these lncRNA biomarkers could lead to significant advancements in cancer treatment, particularly in addressing issues related to chemotherapy resistance and optimizing therapeutic combinations. This approach holds the promise of revolutionizing cancer treatment by providing deeper insights into the molecular mechanisms underlying cancer progression and treatment response[95].

3.8 LncRNAs in Cancer: Addressing Challenges and Future Perspectives

While significant strides have been made in elucidating the roles of long non-coding RNAs in cancer and developing related therapeutic strategies, their intricate structural complexity poses notable challenges in translating these advances into clinical practice[96]. A promising approach to modulate the epigenetic landscape of cancer cells involves the use of small molecules designed to disrupt lncRNA-associated chromatin-modifying complexes. These molecules aim to interfere with the regulatory functions of lncRNAs at the epigenetic level, offering a novel therapeutic pathway[97].

However, a critical hurdle in the clinical application of these therapies lies in the interspecies variability, particularly the sequence differences between human and animal models. This aspect highlights the cautious interpretation and application of findings from animal studies to human clinical settings. The extrapolation of results from preclinical models to human patients must be approached with rigorous validation to ensure efficacy and safety in the context of human biology[98].

3.9 What is being done

Despite the inherent challenges, research of lncRNAs as therapeutic and diagnostic biomarkers is continuously advancing in cancer. Our research group is at the forefront of this endeavor, specifically focusing on identifying and characterizing lncRNAs associated with the response to chemoradiotherapy in cervical cancer. Our objective is to construct a comprehensive regulatory profile of these lncRNAs. This involves elucidating their interactions with key biomolecules and assessing their potential as predictive biomarkers for treatment response. The study employs a methodology based on sequencing data derived from cervical tissue biopsies collected from cancer patients before the initiation of chemoradiotherapy. Our preliminary findings are promising, revealing a significant association of specific lncRNAs with both positive and negative responses to chemoradiotherapy. These lncRNAs are also implicated in fundamental oncogenic processes and exhibit critical interactions with essential biomolecules. Through this research, our team intends to significantly contribute to this knowledge field, fostering the development of effective and personalized treatment strategies for a wide range of cancer types.

4. RESULTS AND DISCUSSION

Cancer arises from genomic instability and multiple processes, including genetic and epigenetic alterations. Genetic mutations mapped to non-coding segments of the genome, such as lncRNAs, are implicated in cancer progression. Thus, lncRNAs are key players in oncogenesis, including their relevance in various types of cancer and their potential as diagnostic and therapeutic markers[106,107].

lncRNAs play an important role in oncology, with several critical functions related to cancer initiation and progression. Many lncRNAs have been identified as oncogenes or tumor suppressors. For example, lncRNAs such as HOTAIR[70], MALAT1[68], and XIST[94] have been implicated in various cancers, including breast, prostate, and lung

cancer. These lncRNAs affect cell proliferation, apoptosis, invasion and metastasis of cancer cells[108].

Aberrant expression of lncRNAs has been correlated with early diagnosis and prognosis of various types of cancer. Studies suggest that altered levels of specific lncRNAs in blood or tissues may serve as biomarkers for early detection of cancer and prediction of clinical outcomes[109].

Modulation of lncRNAs by RNA-based therapies, such as siRNAs and antisense oligonucleotides, has shown potential in preclinical models. Inhibition of oncogenic lncRNAs or restoration of tumor suppressor lncRNAs may provide novel therapeutic strategies[110].

This integrative review highlights the growing importance of lncRNAs in oncology, both in understanding the molecular mechanisms underlying cancer and in developing new diagnostic and therapeutic approaches. lncRNAs represent a promising frontier in precision medicine. Their ability to specifically regulate gene expression makes them attractive targets for personalized therapies[111]. In addition, the identification of lncRNAs as biomarkers opens avenues for less invasive and earlier diagnostic methods, allowing for more effective interventions[107].

Despite the potential, the translation of lncRNA discoveries into clinical applications faces several challenges. The specificity of lncRNAs for different cell and tissue types, their stability in biofluids, and the delivery efficiency of RNA-based therapies are all issues that require further investigation[112]. In addition, the complexity of the mechanisms of action of lncRNAs requires a deeper understanding to avoid off-target effects and ensure patient safety[113].

lncRNAs are emerging as key components of cancer biology, offering new opportunities for diagnosis and treatment. However, to translate these advances into concrete clinical benefits, additional research is needed to overcome existing challenges and validate findings in rigorous clinical trials. Continued integration of data from multiple sources through integrative reviews, such as this one, will continue to be key to mapping the evolving landscape of the role of lncRNAs in oncology.

5. FINAL CONSIDERATIONS

This integrative review highlights the growing importance of lncRNAs in oncology, both in understanding the molecular mechanisms underlying cancer and in developing new diagnostic and therapeutic approaches. lncRNAs are emerging as key components of cancer biology, offering new opportunities for personalized diagnosis and treatment.

Despite the promising potential of lncRNAs, the translation of these discoveries into concrete clinical applications faces several challenges. The specificity of lncRNAs for different cell and tissue types, their stability in biofluids, and the efficient delivery of RNA-based therapies are issues that still require in-depth investigation. In addition, the complexity of the mechanisms of action of lncRNAs requires a deeper understanding to avoid off-target effects and ensure patient safety.

Ongoing research and the integration of data from multiple sources through integrative reviews such as this one are essential to map the evolving landscape of the role of lncRNAs in oncology. Collaborative, multidisciplinary efforts can overcome the challenges that exist in this landscape.

ACKNOWLEDGEMENTS

We would like to express our gratitude to the Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) (*Minas Gerais State Research Support Foundation*) for providing financial support in the form of a scholarship, and to the Programa Nacional de Apoio à Atenção Oncológica (Pronon) (*National Program to Support Oncological Care*) for their financial support.

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Table 1. Information about the articles used to write the theoretical.

ID Article	Title	Database	Year/ Country	Objective	Method
A1	*Tumor heterogeneity in the clinic: is it a real problem?*	PubMed PMC	2013/ USA	Explore tumor heterogeneity in clinical practice and its implications.	Literature review and clinical analysis.
A2	*Mutations: Driver Versus Passenger*	Google Scholar	2019/ Ireland	Distinguish between driver and passenger mutations in cancer.	Theoretical review based on existing literature.
A3	*Cancer heterogeneity: Implications for Targeted Therapeutics*	Google Scholar	2013/ UK	Discuss the heterogeneity of cancer and its implications for targeted therapies.	Review of scientific and clinical studies.
A4	*Review of cancer from perspective of molecular*	Google Scholar	2017/ Iran	Reviewing cancer from a molecular perspective.	Review of scientific literature on the molecular aspects of cancer.
A5	*The emerging role of lncRNAs in cancer*	MEDLINE PubMed Index medicus	2015/ Spain	Exploring the emerging role of lncRNAs in cancer.	Review and analysis of recent research on lncRNAs.
A6	*Tumour heterogeneity and resistance to cancer therapies*	MEDLINE PubMed	2017/ USA	Investigating tumor heterogeneity and resistance to cancer therapies.	Literature review focusing on therapeutic resistance.
A7	*GENCODE: reference annotation for the human and mouse genomes in 2023*	MEDLINE PubMed Index medicus PMC	2022/ UK	Provide reference annotations for human and mouse genomes.	Bioinformatic analysis and genome annotation.
A8	*Involvement of lncRNAs in cancer cells migration, invasion and metastasis: cytoskeleton and ECM crosstalk*	MEDLINE PubMed Index medicus PMC	2023/ France	To examine the participation of lncRNAs in the migration, invasion and metastasis of cancer cells.	Review of experimental and clinical studies on lncRNAs.
A9	*Long Non-Coding RNA Function in CD4+ T Cells: What We Know and What Next?*	PubMed PMC	2019/ UK	Evaluate the function of lncRNAs in CD4+ T cells and discuss future perspectives.	Literature review and proposal of future research directions.

ID Article	Title	Database	Year/ Country	Objective	Method
A10	*LncRNAs and cancer (Review)*	Google Scholar	2016/ China	Investigating the relationship between lncRNAs and cancer.	Review of studies on the role of lncRNAs in cancer.
A11	*Long non-coding RNA: Classification, biogenesis and functions in blood cells*	MEDLINE PubMed Index medicus	2019/ India	Review the classification, biogenesis and functions of lncRNAs in blood cells.	Literature review.
A12	*Gene regulation by long non-coding RNAs and its biological functions*	MEDLINE PubMed Index medicus	2021/ Spain	Discuss gene regulation by lncRNAs and their biological functions.	Literature review.
A13	*Long noncoding RNAs: biogenesis, regulation, function, and their emerging significance in toxicology.*	MEDLINE PubMed	2023/ USA	Explore the biogenesis, regulation and function of lncRNAs and their emerging importance in toxicology.	Literature review.
A14	*The Biological Roles of lncRNAs and Future Prospects in Clinical Application*	PubMed PMC	2021/ China	Investigating the biological roles of lncRNAs and their future prospects in clinical applications.	Literature review.
A15	*Classification and experimental identification of plant long non-coding RNAs*	MEDLINE PubMed Index medicus	2019/ Pakistan	Classifying and experimentally identifying lncRNAs in plants.	Experimental research and review.
A16	*Mysterious long noncoding RNAs and their relationships to human disease*	PubMed PMC	2022/ China	To explore the relationship between lncRNAs and human diseases.	Literature review.
A17	*On the classification of long non-coding RNAs*	MEDLINE PubMed Index medicus PMC	2013/ China	Discuss the classification of lncRNAs.	Literature review.
A18	*Long non-coding RNAs (lncRNAs) in spermatogenesis and male infertility.*	MEDLINE PubMed Index medicus PMC	2020/ India	To investigate the role of lncRNAs in spermatogenesis and male infertility.	Literature review.
A19	*Nuclear Long Noncoding RNAs: Key Regulators of Gene Expression.*	MEDLINE PubMed Index medicus	2018/ USA	Examining nuclear lncRNAs as key regulators of gene expression.	Literature review.
A20	*Long noncoding RNAs and human disease*	Google Scholar	2011/ USA	Exploring the link between lncRNAs and human diseases.	Literature review.
A21	*Mechanisms of long noncoding RNA function in development and disease*	MEDLINE PubMed Index medicus PMC	2016/ Germany	To review the mechanisms of function of lncRNAs in development and disease.	Literature review.
A22	*Emerging role of long non-coding RNAs in endothelial dysfunction and their molecular mechanisms*	MEDLINE PubMed Index medicus	2022/ India	To explore the emerging role of lncRNAs in endothelial dysfunction and their molecular mechanisms	Literature review.
A23	*The multidimensional mechanisms of long noncoding RNA function*	MEDLINE PubMed Index medicus PMC	2017/ Spain	Discuss the multidimensional mechanisms of lncRNA function.	Literature review.
A24	*Long Non-Coding RNAs: The Regulatory Mechanisms, Research Strategies, and Future Directions in Cancers*	PubMed PMC	2020/ China	To explore the regulatory mechanisms of lncRNAs, research strategies and future directions in cancers.	Literature review.
A25	*Unique features of long non-coding RNA biogenesis and function*	MEDLINE PubMed Index medicus	2015/ USA	Discuss the unique characteristics of the biogenesis and function of lncRNAs.	Literature review.
A26	*Molecular Mechanisms of Long Noncoding RNAs*	Google Scholar	2011/ USA	Review the molecular mechanisms of lncRNAs.	Literature review.
A27	*Exploring the mechanisms behind long noncoding RNAs and cancer*	PubMed PMC	2018/ USA	Exploring the mechanisms behind lncRNAs and cancer.	Literature review.
A28	*Long non-coding RNAs in the failing heart and vasculature*	PubMed PMC	2018/ Netherlands	Investigating lncRNAs in the failing heart and vasculature.	Literature review.

ID Article	Title	Database	Year/ Country	Objective	Method
A29	*α-Asarone suppresses the proliferation and migration of ASMCs through targeting the lncRNA-PVT1/miR-203a/ E2F3 signal pathway in RSV-infected rats*	MEDLINE PubMed Index medicus PMC	2017/ China	To investigate the effect of α-Asarone on the proliferation and migration of ASMCs through the lncRNA-PVT1/ miR-203a/E2F3 signaling pathway in RSV-infected mice	Experimental research.
A30	*Long noncoding RNA LINC00941 promotes pancreatic cancer progression by competitively binding miR-335-5p to regulate ROCK1-mediated LIMK1/Cofilin-1 signaling*	MEDLINE PubMed PMC	2021/ China	To investigate the role of LINC00941 in the progression of pancreatic cancer.	Experimental research.
A31	*Regulation of lncRNA expression*	MEDLINE PubMed Index medicus PMC	2014/ China	Review the regulation of lncRNA expression.	Literature review.
A32	*LncRNA Structural Characteristics in Epigenetic Regulation*	MEDLINE PubMed PMC	2017/ China	Exploring the structural characteristics of lncRNAs in epigenetic regulation.	Literature review.
A33	*Mechanisms and Functions of Long Non-Coding RNAs at Multiple Regulatory Levels*	MEDLINE PubMed PMC	2019/ China	Discuss the mechanisms and functions of lncRNAs at multiple regulatory levels.	Literature review
A34	*Transcriptional and Post-transcriptional Gene Regulation by Long Non-coding RNA*	MEDLINE PubMed Index medicus PMC	2017/ UK	Review transcriptional and post-transcriptional gene regulation by lncRNAs.	Literature review.
A35	*The long noncoding RNA Malat1: Its physiological and pathophysiological functions*	MEDLINE PubMed Index medicus PMC	2017/ USA	To investigate the physiological and pathophysiological functions of the lncRNA Malat1.	Literature review.
A36	*Human Long Noncoding RNA Interactome: Detection, Characterization and Function*	MEDLINE PubMed PMC	2020/ Poland	Characterize the human lncRNAs interactome and its functions.	Literature review.
A37	*Mechanisms of lncRNA/ microRNA interactions in angiogenesis*	MEDLINE PubMed Index medicus	2020/ China	Exploring the mechanisms of interaction between lncRNAs and microRNAs in angiogenesis.	Literature review.
A38	*The Role of lncRNAs in Gene Expression Regulation through mRNA Stabilization*	PubMed PMC	2021/ Spain	Investigating the role of lncRNAs in regulating gene expression through mRNA stabilization.	Literature review.
A39	*Long non-coding RNAs and transposable elements: A functional relationship*	MEDLINE PubMed	2021/ Canada	Exploring the functional relationship between lncRNAs and transposable elements.	Literature review.
A40	*Mutual interaction of lncRNAs and epigenetics: focusing on cancer*	Google Scholar	2023/ Iran	Investigating the mutual interaction between lncRNAs and epigenetics with a focus on cancer.	Literature review.
A41	*LncRNAs as Chromatin Regulators in Cancer: From Molecular Function to Clinical Potential*	PubMed PMC	2019/ Greece	Reviewing lncRNAs as chromatin regulators in cancer and their clinical potential.	Literature review.
A42	*Long noncoding RNA: an emerging paradigm of cancer research*	MEDLINE PubMed Index medicus	2013/ China	Reviewing the emerging role of lncRNAs in cancer research.	Literature review.
A43	*Long Non-Coding RNAs: Biogenesis, Mechanism of Action and Role in Different Biological and Pathological Processes*	Google Scholar	2022/ India	Review the biogenesis, mechanism of action and role of lncRNAs in different biological and pathological processes.	Literature review.

ID Article	Title	Database	Year/ Country	Objective	Method
A44	*Molecular principles of metastasis: a hallmark of cancer revisited*	MEDLINE PubMed PMC	2020/ USA	Review the molecular principles of metastasis as a characteristic of cancer.	Literature review.
A45	*The Tumor Microenvironment in Tumorigenesis and Therapy Resistance Revisited*	PubMed PMC	2023/ South Africa	Reviewing the tumor microenvironment in tumorigenesis and resistance to therapy.	Literature review.
A46	*Hallmarks of Cancer: New Dimensions*	MEDLINE PubMed	2022/ Switzerland	Reviewing the new dimensions of cancer milestones	Literature review.
A47	*Long Noncoding RNA and Cancer: A New Paradigm*	MEDLINE PubMed Index medicus	2017/ USA	Reviewing the role of lncRNAs in cancer	Literature review.
A48	*Tumour mutations in long noncoding RNAs enhance cell fitness*	MEDLINE PubMed PMC	2023/ Switzerland	Investigating how mutations in lncRNAs increase cellular fitness in tumors.	Experimental research.
A49	*The Role of lncRNA in the Development of Tumors, including Breast Cancer*	MEDLINE PubMed PMC	2021/ Poland	Review the role of lncRNAs in the development of tumors, including breast cancer.	Literature review.
A50	*Selective Concurrence of the Long Non-Coding RNA MALAT1 and the Polycomb Repressive Complex 2 to Promoter Regions of Active Genes in MCF7 Breast Cancer Cells*	MEDLINE PubMed Index medicus PMC	2023/ Chile	Investigating the selective competition of the lncRNA MALAT1 and the Polycomb 2 Repressor Complex in the promoter regions of active genes in MCF7 breast cancer cells.	Experimental research.
A51	*Posttranscriptional Gene Regulation by Long Noncoding RNA*	MEDLINE PubMed Index medicus	2013/ USA	Reviewing post-transcriptional gene regulation by lncRNAs.	Literature review.
A52	*MALAT1: a potential biomarker in cancer*	PubMed PMC	2018/ China	Exploring the lncRNA MALAT1 as a potential biomarker in cancer.	Literature review.
A53	*MALAT1: A long non coding RNA highly associated with human cancers (Review)*	PubMed PMC	2018/ China	Reviewing the MALAT1 lncRNA highly associated with human cancers.	Literature review.
A54	*ANRIL: A lncRNA at the CDKN2A/B Locus With Roles in Cancer and Metabolic Disease*	MEDLINE PubMed PMC	2018/ USA	Exploring the role of lncRNA ANRIL in cancer and metabolic diseases.	Literature review.
A55	*HOTAIR: an oncogenic long non-coding RNA in different cancers*	MEDLINE PubMed PMC	2015/ Iran	Reviewing the HOTAIR lncRNA as an oncogene in different types of cancer.	Literature review.
A56	*Tumor Suppressive Effects of GAS5 in Cancer Cells*	PubMed PMC	2022/ Malaysia	Investigating the tumor-suppressing effects of lncRNA GAS5 in cancer cells.	Literature review.
A57	*Long non coding RNA GAS5 in human cancer (Review)*	PubMed PMC	2020/ China	Reviewing the GAS5 lncRNA in human cancer.	Literature review.
A58	*Potential applications of MEG3 in cancer diagnosis and prognosis*	MEDLINE PubMed PMC	2017/ China	Exploring the potential applications of MEG3 lncRNA in cancer diagnosis and prognosis.	Literature review.
A59	*Long Non-Coding RNA MEG3 in Metal Carcinogenesis*	PubMed PMC	2023/ USA	Investigating the role of lncRNA MEG3 in metal-induced carcinogenesis	Literature review.
A60	*H19 lncRNA: Roles in tumorigenesis*	MEDLINE PubMed Index medicus	2020/ Iran	Reviewing the roles of lncRNA H19 in tumorigenesis.	Literature review.

ID Article	Title	Database	Year/ Country	Objective	Method
A61	*LncRNA H19: A novel oncogene in multiple cancers*	MEDLINE PubMed PMC	2021/ China	Exploring lncRNA H19 as a new oncogene in multiple types of cancer.	Literature review.
A62	*Long non-coding RNAs in colorectal cancer: implications for pathogenesis and clinical application*	PubMed PMC	2014/ China	Reviewing lncRNAs in colorectal cancer and their implications in pathogenesis and clinical application.	Literature review.
A63	*Long Non-coding RNAs in Cancer: Implications for Diagnosis, Prognosis, and Therapy*	PubMed PMC	2020/ China	Reviewing lncRNAs in cancer and their implications for diagnosis, prognosis and therapy.	Literature review.
A64	*Comprehensive analysis of lncRNAs as biomarkers for diagnosis, prognosis, and treatment response in clear cell renal cell carcinoma.*	PubMed PMC	2021/ China	Analyzing lncRNAs as biomarkers for diagnosis, prognosis and response to treatment in clear cell renal cell carcinoma.	Experimental research
A65	*The role of long non coding RNA H19 in breast cancer (Review)*	PubMed PMC	2019/ China	Reviewing the role of lncRNA H19 in breast cancer.	Literature review.
A66	*LncRNA as a diagnostic and prognostic biomarker in bladder cancer: a systematic review and meta-analysis*	PubMed PMC	2018/ China	Systematic review and meta-analysis of lncRNA as a diagnostic and prognostic biomarker in bladder cancer.	Systematic review and meta-analysis.
A67	*Therapeutic Targeting of Long Non-Coding RNAs in Cancer*	MEDLINE PubMed Index medicus	2018/ USA	Reviewing the therapeutic targeting of lncRNAs in cancer.	Literature review.
A68	*Improving the therapeutic efficiency of noncoding RNAs in cancers using targeted drug delivery systems*	MEDLINE PubMed Index medicus	2020/ Saudi Arabia	Improving the therapeutic efficiency of non-coding RNAs in cancer using targeted drug delivery systems.	Literature review.
A69	*Development of targeted therapy for bladder cancer mediated by a double promoter plasmid expressing diphtheria toxin under the control of H19 and IGF2-P4 regulatory sequences*	MEDLINE PubMed PMC	2010/ Israel	Developing targeted therapy for bladder cancer mediated by a dual-promoter plasmid expressing diphtheria toxin under the control of the H19 and IGF2-P4 regulatory sequences.	Experimental research.
A70	*ncRNAs in Therapeutics: Challenges and Limitations in Nucleic Acid-Based Drug Delivery*	MEDLINE PubMed PMC	2021/ Spain	Review the challenges and limitations in nucleic acid-based drug delivery using ncRNAs.	Literature review.
A71	*MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside*	MEDLINE PubMed	2020/ UK	Reviewing miRNAs and lncRNAs as new tools for cancer therapy: first steps from the laboratory to the clinic.	Literature review.
A72	*Strategies to target long non-coding RNAs in cancer treatment: progress and challenges*	Google Scholar	2020/ Iran	Reviewing strategies to target lncRNAs in cancer treatment: progress and challenges.	Literature review.
A73	*Noncoding RNA therapeutics — challenges and potential solutions*	MEDLINE PubMed Index Medicus	2021/ USA	Reviewing non-coding RNA therapies - challenges and potential solutions.	Literature review.
A74	*Targeting non-coding RNAs to overcome cancer therapy resistance*	MEDLINE PubMed PMC	2022/ China	Reviewing the targeting of non-coding RNAs to overcome resistance to cancer therapy.	Literature review.
A75	*Cervical Cancer Stem-Like Cell Transcriptome Profiles Predict Response to Chemoradiotherapy*	PubMed PMC	2021/ Brazil	Analyzing the transcriptome profiles of similar stem cells in cervical cancer to predict response to chemoradiotherapy.	Experimental research.

Table 2. Information on the clinical trials used to develop the theoretical framework.

Test Name	ID	Methodology	Year	Location	Description
A Prospective, Multicenter Cohort Study of Urinary Exosome lncRNAs for Preoperative Diagnosis of Lymphatic Metastasis in Patients With Bladder Cancer	NCT05270174	Prospective, multicenter cohort study. Collection of urinary exosomes for lncRNAs analysis.	2023	Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, China.	Preoperative evaluation of lymphatic metastases in patients with bladder cancer through the analysis of lncRNAs in urinary exosomes.
Circulating Biomarkers to Identify Thyroid Cancer	NCT04594720	Observational study to identify circulating biomarkers, including lncRNAs, for thyroid cancer diagnosis.	2020	Chang Gung Memorial Hospital, Taiwan.	Identification of circulating biomarkers for thyroid cancer diagnosis, focusing on lncRNAs.
Immunophenotyping and XIST Gene in AML (XIST)	NCT04288739	Observational study to analyze the immunophenotypic profile and expression of the XIST gene in acute myeloid leukemia (AML).	2020	Assiut University, Egypt.	Investigation of the expression of the XIST gene and its role in acute myeloid leukemia (AML) and its relationship with the immunophenotypic profile.
Exploring Cancer-Associated Thromboembolism Prognosis Biomarkers and Polymorphisms (CAT_PB)	NCT06065592	Observational study to identify prognostic biomarkers and polymorphisms associated with thromboembolism in cancer patients.	2023	Lebanese University, Lebanon.	Identification of biomarkers and polymorphisms associated with the prognosis of thromboembolism in cancer patients, including lncRNAs.

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FINANCIAMENTO

Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) (*Minas Gerais State Research Support Foundation*).

Programa Nacional de Apoio à Atenção Oncológica (Pronon) (*National Program to Support Oncological Care*).

APROVAÇÃO DE COMITÊ DE ÉTICA EM PESQUISA

Não se aplica.

CONFLITO DE INTERESSES

Não se aplica.