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REVIEW ARTICLE

The Dual Role of Non-Coding RNAs in Regulating HSC and MSC Fate: Modulating Survival, Death, and Intercellular Communication

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ABSTRACT

Background: **Non-coding RNAs (ncRNAs) play crucial roles in regulating hematopoietic and mesenchymal stem cells skewing towards regenerative or modulating commitment. There is gap in understanding how ncRNAs regulate diverse pathways that offer new opportunities for therapeutic targeting in regenerative medicine and disease management.**
Methods: **The current review examines the dual regulatory mechanisms of ncRNAs in stem cell biology, analyzing their roles as positive (upscale) and negative (downscale) cellular modulators through comprehensive review of ncRNA signaling pathways.**
Results: **As positive regulators, ncRNAs promote cell survival, regulate the cell cycle, enhance differentiation, self-renewal, delay senescence, and modulate autophagy to maintain stem cell function. As negative regulators, ncRNAs induce various forms of cell death, including apoptosis, necroptosis, pyroptosis, and ferroptosis, often through interactions with long ncRNAs. Additionally, ncRNAs modulate inflammatory responses by influencing proinflammatory cytokines and reducing cell adhesion, further impacting stem cell survival. ncRNAs also influence intercellular communication and signaling pathways, enhancing or suppressing cellular crosstalk essential for stem cell differentiation.**
Conclusions: **Therefore, ncRNAs demonstrate complex dual regulatory functions in stem cell biology, serving both as protective and detrimental influencers/modulators depending on cellular context. Future research should focus on elucidating ncRNA signaling networks and developing ncRNA-based interventions for stem cell dysfunction and associated pathologies.**
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KEYWORDS

non-coding RNAs, hematopoietic stem cells, mesenchymal stem cells, cell death, autophagy, senescence, inflammatory response, intercellular communication, regenerative medicine, apoptosis, necroptosis

INTRODUCTION

Stem cells of different origins have been successfully used in regenerative medicine, all though often there are failures post successful transplantation. There have been huge research insights in past decade on understanding the molecular and genetic mechanisms that regulate stem cell survival, regeneration, modulation and renewal in the microenvironment [1]. Advanced genomic techniques have revealed that 98% - 99% of the human genome does not code for structural of functional proteins. Nonetheless, much of it is transcriptionally active, producing a diverse range of non-coding RNAs (ncRNAs) with intricate regulatory and structural roles. However, specific functions have been identified for only a small proportion of known ncRNAs [1-5].

ncRNAs are a diverse group of RNA genes that lack functional open reading frames (ORF) and are not translated into proteins. Due to these biological traits, they were long regarded as “junk RNA” [6].

ncRNAs can be classified by size and function into two main types: structural and regulatory [7]. Structural ncRNAs include ribosomal (rRNA), transfer (tRNA), small nuclear (snRNA), and small nucleolar (snoRNA) RNAs. Regulatory ncRNAs are further divided based on their length: short ncRNAs, such as microRNAs (miRNAs; 22 - 23 nt), PIWI-interacting RNA (piRNAs; 26 - 31 nt), medium ncRNAs (50 - 200 nt), and long ncRNAs (lncRNAs; > 200 nt), which possess distinct, independent functions [7-9]. Growing evidence indicates that lncRNAs play a key role in regulating transcription, which has prompted significant efforts to uncover the molecular mechanisms underlying their function [10] which might be harnessed for successful intervention and management.

The discovery that approximately 85% of the human genome is transcribed has fueled a new area of research focused on identifying the functions of non-protein-coding transcripts, known as ncRNAs [11]. Currently, there are few good studies revealing the role and importance of lncRNAs and miRNAs as essential regulators of various cellular functions, such as immunity [12], inflammatory signals [13], cell proliferation, differentiation, apoptosis [14], reproduction, aging, and disease [15,16]. Recent studies have uncovered the involvement of lncRNAs in various health conditions, including hepatocellular carcinoma (HCC) [17-20], colorectal cancer (CRC) [21], Alzheimer’s disease [22], breast cancer [23], type 2 diabetes [24], and leukemia [25]. It is well established that lncRNAs can negatively regulate biomolecules and more significantly, interfere with and inhibit a large number of miRNAs, thereby counteracting their suppressive effects on gene expression [26].

Stem cells can self-renew and differentiate into various cell types. These capabilities are controlled by the dynamic interplay between external signals, epigenetic influences, and molecules that regulate gene expression [27]. Mesenchymal stem cells (MSCs) originate from the mesoderm and are heterogeneous. Multipotent adult stem cells derive from various tissues, including adipose, placenta, cartilage, and bone marrow, and further differentiate into target organs [28]. Due to their self-renewal, immunomodulatory properties, tissue regeneration capacity, and multilineage differentiation potential, MSCs are widely used in various therapeutic applications and highly sought for biomedical research [29, 30]. These cells are influenced by a variety of molecules and their microenvironment. MSCs release various biomolecules and extracellular vesicles (EVs) to support hematopoiesis and regulate immune responses while some of these tend to be ncRNAs [30,31]. Numerous lncRNAs and miRNAs regulate MSC function or, conversely, are influenced by MSCs [32]. Similarly, with their ability to self-renew, hematopoietic stem cells (HSCs) are highly proficient at regenerating blood and immune cells throughout an individual’s life. Microarray analyses of protein-coding genes expressed by HSCs have revealed their essential roles in these functions [33]. miRNAs such as miR-126 and miR-155 are known to regulate HSC functions, while miR-125b modulation of HSCs has been associated with myeloproliferative disorders and alterations in hematopoiesis [34-36].

The exact number of functional ncRNAs remains uncertain, with evidence for the roles of most ncRNAs still limited, suggesting that many may simply be transcriptional by-products. However, there is a long way to go in deciphering the exact actions of these ncRNAs. In addition, some ncRNAs may be functionally redundant participating in both cell survival and death. Increasing numbers of ncRNAs have been identified and documented; they are known to play significant roles in cellular processes. Here, we review the roles of ncRNAs that are well documented as positive and negative regulators of various cellular processes in HSCs and MSCs biology.

MATERIALS AND METHODS

Survey methodology

Our search criteria focused on the role of ncRNAs in regulating HSCs and MSCs, examining their dual function as positive and negative modulators of cellular processes. We conducted a comprehensive search using the keywords “non-coding RNA”, “hematopoietic stem cell”, “mesenchymal stem cell”, “cell survival”, “autophagy”, “lncRNA interaction in necroptosis”, and “lncRNA interaction in ferroptosis”. Searches were performed across multiple databases, including Google Scholar, PubMed, Web of Science, and ScienceDirect, to identify relevant studies published between 1978 and 2024. All searches were finalized in October 2024.

We included both review and research articles that are published post peer review within this timeframe that aligned with our scope. The initial search yielded many results: 6,750 articles from Google Scholar, 1,915 from PubMed, 367 from Web of Science, and 6,661 from ScienceDirect. After applying our screening criteria, 117 articles were selected for inclusion in this review. Only English-language publications were considered.

In addition to database searches, we manually screened references for further relevant studies. The authors independently assessed the eligibility of each title and abstract according to the defined inclusion and exclusion criteria. A double-check process was employed to en-

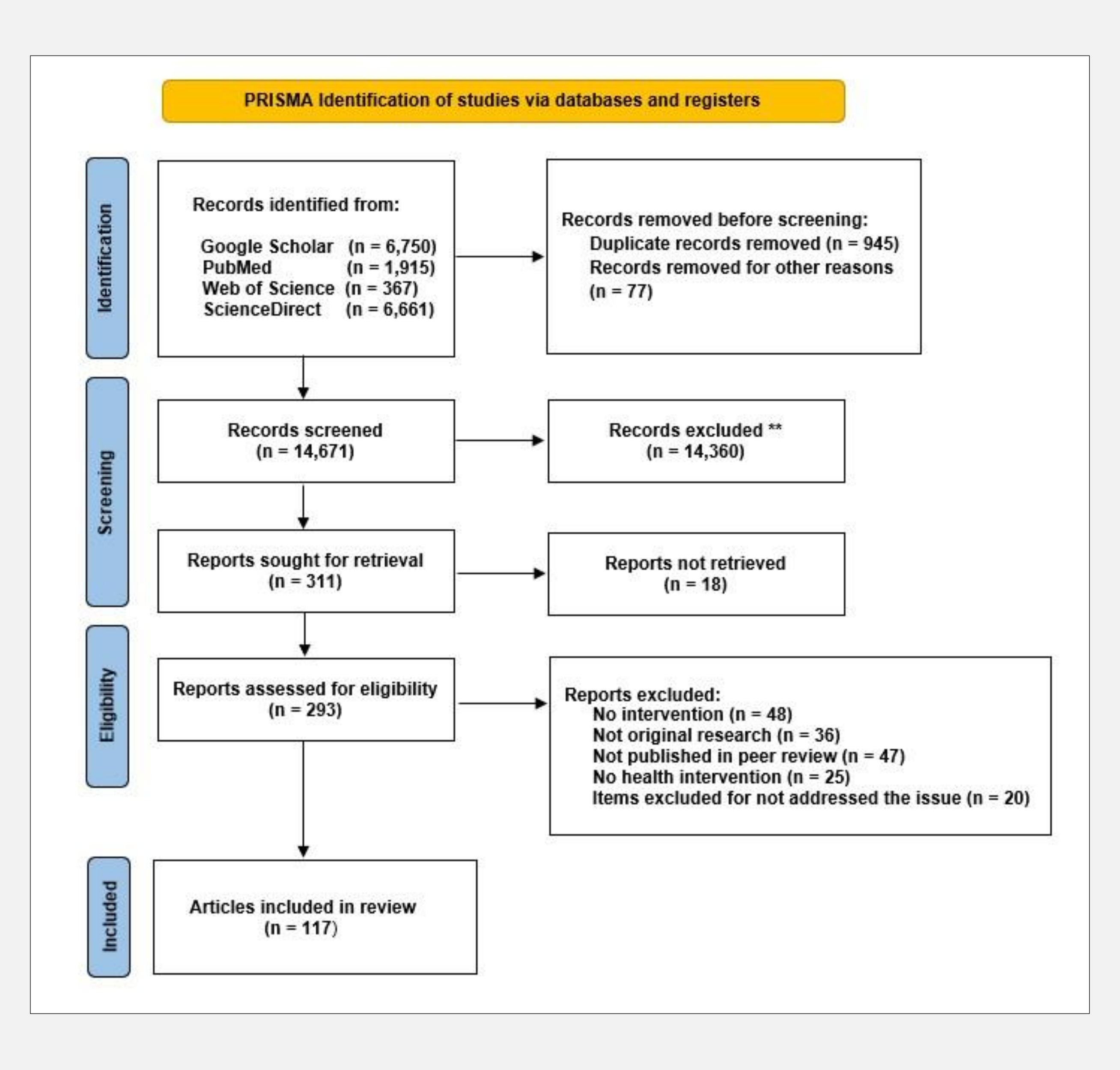

Figure 1. The PRISMA flow diagram of the study.

**** Articles that were excluded after the inclusion criteria.**

sure consistency, and any discrepancies were resolved collaboratively. This thorough approach helped ensure that the final selection of articles aligned closely with the objectives of our study.

Study selection

The search strategy initially identified 15,693 articles across the examined databases. After removing duplicates, 14,671 titles and abstracts were screened, leading to the selection of 311 articles for further review. Of these, 176 articles were excluded for the following reasons: no intervention (n = 48), not original research (n = 36), not published in peer-reviewed journals (n = 47), absence of health intervention (n = 25), and not addressing a relevant issue (n = 20). Ultimately, 117 articles that met the review criteria were included in the analysis (Figure 1).

RESULTS AND DISCUSSION

ncRNAs as positive regulators

Cell survival

HSCs and MSCs are regarded as the primary choice for cell-based therapies due to their remarkable ability to differentiate into various cell types. MSCs have become ideal for both cell-based therapy and research due to the low rejection rate. However, their limited survival and reduced transdifferentiating capacity in the microenvironment present challenges to their effectiveness in therapeutic applications [37-39]. Enhancing cell survival or identifying the key molecular mechanisms underlying differentiation or self-renewal is essential for advancing cell-based therapies. The lncRNA H19 imprinted maternally expressed transcript (H19) was found to increase MSC cell survival by targeting the miRNA miR-199a-5p, which suppresses vascular endothelial growth factor A (VEGFA). H19 reduces miR-199a-5p expression, thereby upregulating VEGFA. Conversely, knocking down H19 upregulated miR-199a-5p and downregulated VEGFA [40].

Myocardial infarction (MI) was artificially induced in mice and treated with MSCs. MSCs activated by peroxisome proliferator-activated receptor gamma (Pparg) resulted in expression of gap junction protein alpha 1 (Gja1/Cx43) in the infarct heart by inhibiting the transforming growth factor beta 1 (TGFB1) signaling pathway promoting MSC survival [39]. Additionally, miR-221/222 directly interacted with the 3` untranslated region (UTR) of the Cx43 messenger RNA (mRNA), downregulating its translation in a mouse model induced with unpredictable chronic mild stress [41].

The survival of HSCs is particularly important in various therapeutic approaches. Previous studies have shown that CX43 helps to prevent senescence in HSCs after myeloablation by transporting reactive oxygen species (ROS) to bone marrow stromal cells and that overexpressing Cx43 promotes MSC survival [42,43] due to the interaction of various ncRNAs involved in stem cell survival and regeneration.

Cell cycle

The cell cycle is a tightly regulated sequence of events that ensures the accurate duplication of genetic material and the development of two identical daughter cells. ncRNAs are increasingly recognized as key regulators within this complex control system. Extensive research has shown that ncRNAs strongly interfere with cell cycle regulation, particularly in cancer cells. Numerous proteins are involved in regulating the cell cycle, DNA repair, and checkpoint responses, which are often aberrant in cancer. These changes contribute to the uncontrolled cell growth that defines cancerous cells [44,45]. Moreover, these proteins play a vital role in gene expression through various known and potentially unknown mechanisms of interaction with genetic materials [46].

The cell cycle comprises four phases: i) growth (G1), ii) DNA replication (S), iii) preparation for division (G2), and iv) division (M). Cell replication is initiated by growth factors or various stimuli, guiding progression from the growth phase to cell division [47]. miRNAs primarily regulate gene expression by binding to the 3’ or 5’ untranslated regions (UTRs) of mRNAs in the cytoplasm, inducing mRNA denaturation to halt the translation process. Moreover, miRNAs can inhibit the translation initiation event, thereby hindering translation [48]. Numerous miRNAs have been investigated for their roles in cell cycle regulation, particularly in controlling the mRNAs of cyclin-dependent kinases and cyclins, which are essential for the transition from the G1 to S phase. Specifically, cyclin-dependent kinase 4 (CDK4) and 6 (CDK6) mRNAs are degraded when the miRNAs miR-149, miR-6785-5p, miR-4728-5p, and miR-6883-5p bind to their 3’ UTR [49].

Moreover, several lncRNAs directly regulate the E2F mRNA to promote cell cycle progression from the G1 to S phase in cancer cells. The genetic locus at 1p36.31 region contains the ICMT divergent transcript (ICMT-DT/LINC00337), a coactivator of E2F transcription factor 1 (E2F1) whose binding leads to elevated E2F1 expression in pancreatic ductal adenocarcinoma cells. This upregulation promotes cell proliferation and growth, as E2F1 was found to mediate cancer cell proliferation, along with higher levels of LINC00337 [50].

In a different context, the lncRNA E2F3 intronic transcript 1 (E2F3-IT1/RBAT1) regulates E2F transcription factor 3 (E2F3), enhancing its oncogenic functions [51]. Additionally, the nuclear proliferation-related protein TPX2 microtubule nucleation factor (TPX2), which plays a role in spindle assembly and mitosis, is transcribed by lncRNA LINC00337 via E2F transcription factor 4 (E2F4). In esophageal squamous cell carcinoma cells, TPX2 induction by E2F4 generates resistance to apoptosis induced by the chemotherapy drug cisplatin [52]. These findings are critical for understanding the role of lncRNAs in regulating E2F family members during the cell cycle.

Differentiation

Stem cells are primarily undifferentiated cells with regenerative functions that are carefully regulated through self-renewal and differentiation. The stem cell niche, or tissue microenvironment, regulates stem cell functions to be skewed to be regulatory/modulatory/regenerative or immune by providing molecular signals that impact their preservation, proliferation, and differentiation, a concept first proposed by Schofield [53]. HSCs, like all other stem or progenitor cells, are characterized by two key properties, self-renewal and multipotent differentiation, enabling them to generate cells from all blood lineages [54-56]. Similarly, MSCs can differentiate into various mesodermal cells, such as endotheliocytes, smooth muscle cells, fibroblasts, cardiomyocytes, macrophages, myoblasts, and pericytes, and non-mesodermal cells, such as Langerhans islets cells, hepatocytes, oligodendrocytes, astrocytes, neuron-like cells, and Schwann cells [57].

MSCs’ potential to differentiate into various cells is

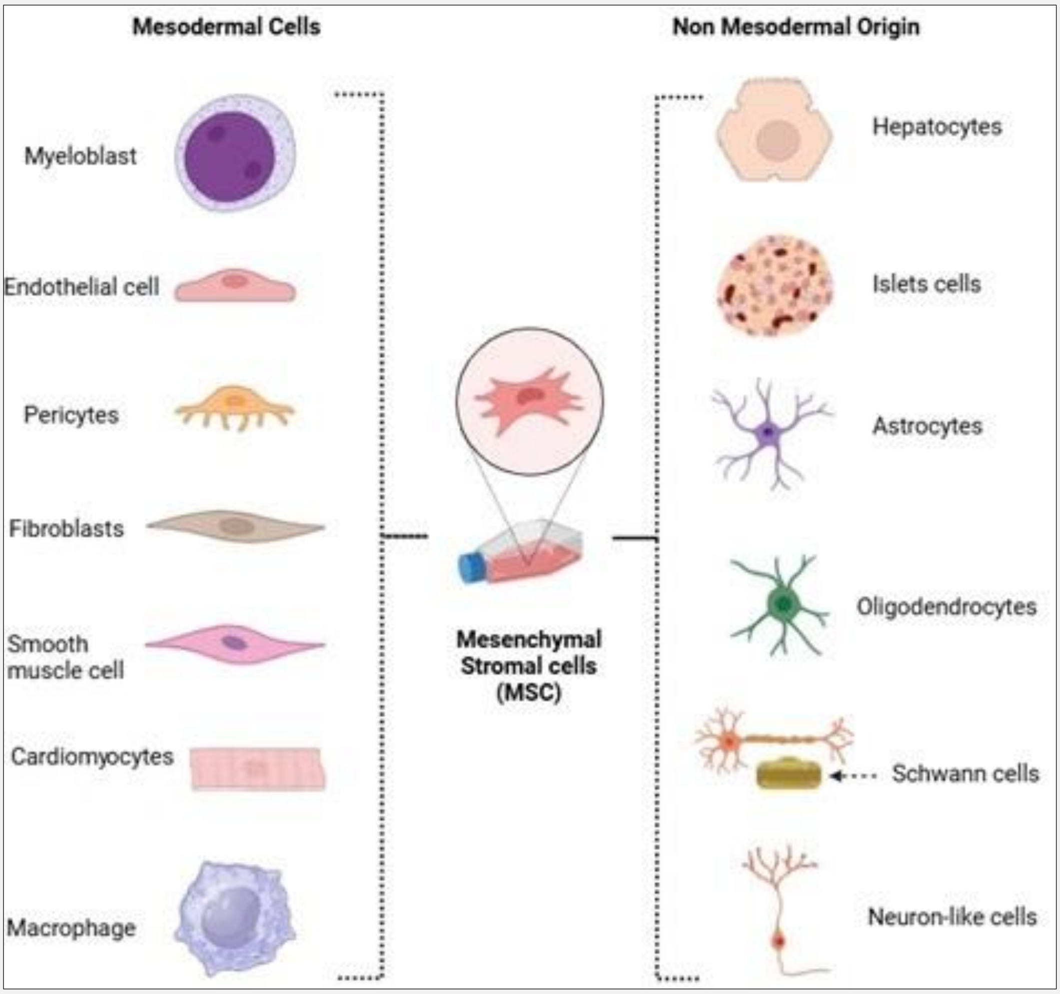

Figure 2. The differentiation potential of MSCs.

graphically presented in Figure 2. Their ability to differentiate and proliferate makes them a valuable tool for tissue engineering and advanced biomedical and clinical research. Like HSCs, MSCs occupy the highest level in the hierarchy of mesenchymal cells. They progress through distinct stages of differentiation systematically, giving rise to functional, phenotypically mature tissues such as smooth muscle, bone, cartilage, and tendons [58]. Several miRNAs, including miR-17-5p [59], hsa-miR-15a-5p [60], hsa-miR-27a-3p [60], hsa-miR-106b-5p [60], and miR-17 [59], have been shown to influence adipogenesis in adipose-derived MSCs. These miRNAs modulate specific signaling pathways, such as the Wnt/β-catenin (CTNNB1) pathway, in a pro-adipogenic manner [61].

Similarly, a study on human adipose-derived MSCs (hADMSCs) examined their adipogenic differentiation potential when the miRNA miR-26b-5p that interacted with the mRNA of T cell factor 4 (TCF-4, currently called transcription factor 7 like 2 [TCF7L2]). The study found that miR-26b-5p suppressed the expression of both TCF-4 and CTNNB1 in hADMSCs. MiR-26b-5p was shown to directly target the TCF-4 gene, and synthetic insertion of miR-26b-5p reduced protein levels of both TCF-4 and CTNNB1. Overexpressing miR-26b-5p promoted adipogenesis in hADMSCs, whereas elevated levels of TCF-4 and CTNNB1 inhibited adipogenesis [62].

Furthermore, a novel lncRNA AC092834.1 was found to be significantly upregulated during the preadipocyte stage. Gain- and loss-of-function experiments demonstrated that AC092834.1 elevates adipogenic differentiation by directly increasing the expression of Dickkopf WNT signaling pathway inhibitor 1 (DKK1). DKK1

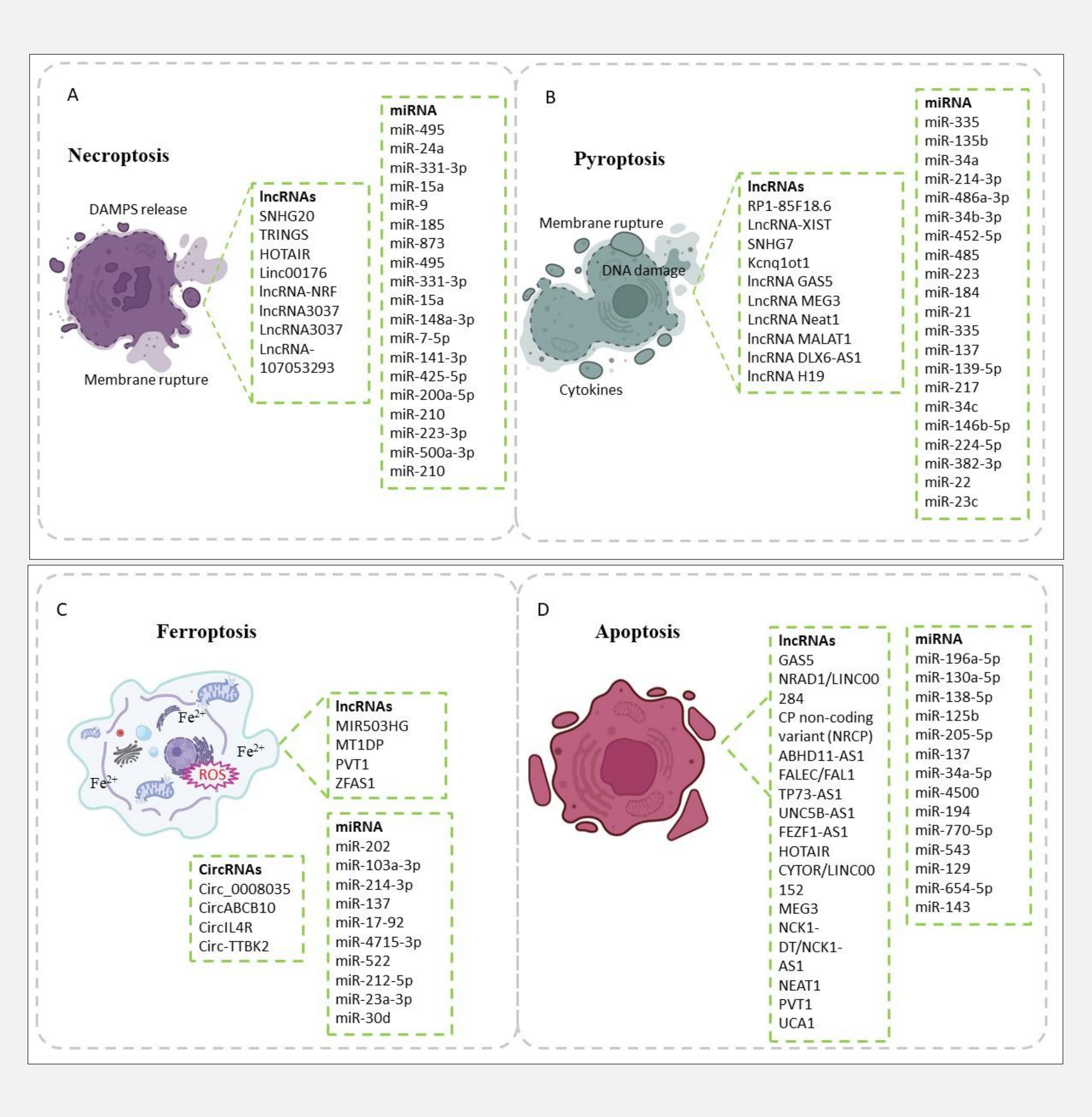

Figure 3. Various ncRNAs involved in different forms of PCD.

A: Necroptosis [89 - 92], B: pyroptosis [89,93 - 95], C: ferroptosis [95 - 99], and D: apoptosis [100 - 106]. These forms of PCD are positively and negatively regulated by lncRNAs, circular RNAs (circRNAs), and miRNAs.

competitively binds to LDL receptor-related protein 5 (LRP5), inhibiting the Wnt/β-catenin signaling pathway and thereby reducing its suppression of adipogenesis. This finding provides new mechanistic insights into the critical role of lncRNA AC092834.1 in regulating adipogenic differentiation [63].

Senescence

In vivo, MSCs contribute to sustaining and regulating the homeostasis of associated organs. Consequently, enhanced or transplanted MSCs have emerged as a promising treatment for various pathological conditions. Their therapeutic potential is primarily due to their role as a lifelong reservoir for multiple cell types and their ability to respond to inflammation and other pathological signals. This potential makes MSC-based regenerative strategies highly effective in therapy [64]. However, MSCs from aged donors *in vivo* or those cultivated *in vitro* at late passages exhibit a distinct decline in immunomodulatory efficiency, regenerative potential, and homing ability. The mechanism behind such diminished activity has not been largely investigated [65]. One accepted explanation is MSCs undergoing senescence can contribute to age-related diseases and may also result in reduced or even adverse therapeutic outcomes. In addition to the risk of treatment failure, aged MSCs may worsen the pathological process and further deteriorate the condition [66]. Various mechanisms have been identified that influence cellular senescence. DNA damage or telomere shortening can trigger a DNA damage response, leading to senescence. Additionally, senescent cells secrete large amounts of proteins, such as chemokines, proinflammatory cytokines, and matrix metalloproteinases, which can induce senescence in neighboring cells [67]. However, all these cellular processes and protein expressions are transcriptionally controlled and may be attributed to ncRNAs [68].

The expression of lncRNAs changes during senescence with some lncRNAs having the potential to induce or inhibit cellular senescence. lncRNA growth arrest-specific 5 (GAS5) has been shown to act as a sponge (absorbent) for miR-223, reducing its availability. Silencing GAS5 controls the proliferation of endothelial progenitor cells (EPCs) and promotes their senescence by interfering with miR-223’s inhibition of nicotinamide phosphoribosyl transferase (NAMPT) expression. Consequently, GAS5 regulates EPC proliferation and senescence by modulating the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway [67].

Senescent adipose-derived stem cells (ASCs) exhibit limited therapeutic potential for wound healing. The lncRNA senescence-associated non-coding RNA (SAN) was found to be upregulated in aged ASCs and plays a role in regulating cellular senescence. Knocking down SAN in ASCs enhanced their functionality and inhibited senescence. SAN acts as a sponge for miR-143-3p, modulating the expression of adducin 3 (ADD3). Transplanting SAN-depleted aged ASCs significantly improved re-epithelialization, collagen deposition, and neovascularization, resulting in faster skin wound closure compared to transplanting aged ASCs. SAN mediates ASC senescence via the miR-143-3p/ADD3 pathway, offering a potential target for rejuvenating senescent ASCs and enhancing wound repair [69,70].

Similarly, a recent study demonstrated that lncRNA bone marrow-associated non-coding RNA (Bmncr) acts as a scaffold to facilitate the formation of transcriptional complexes, regulating the fate of bone marrow MSCs during aging [71]. The lncRNA urothelial cancer associated 1 (UCA1) is a direct target of a repressor complex and induces senescence in human and murine cells [72].

Autophagy

Macroautophagy, also known as autophagy is an evolutionarily conserved process present in all eukaryotic cells. It plays a key role in the intracellular degradation of aged or aggregation-prone proteins, organelles, such as mitochondria, with the help of lysosome-mediated cellular degradation [73]. While autophagy can contribute to cell death in some cases, it also helps to maintain homeostasis and shield cells from nutrient stress via cytoprotective mechanisms [74]. The disruption of autophagy results in various diseases, such as growth disorders, cancers, and neurodegenerative diseases [75]. Moreover, it is involved in stress response mechanisms, as it is upregulated during stress conditions such as nutrient depletion, hypoxia, mitochondrial stress, and exposure to pathogens and toxins. Under certain stress conditions, autophagy mediates protein, cellular organelle, and RNA degradation by supporting cell homeostasis [76]. Autophagy is initiated when external stimuli are detected through the interaction between two key entities: adenine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1) [77].

miRNAs play an unparalleled role in cellular processes, particularly in regulating signaling pathways that initiate autophagic degradation. Conversely, autophagy also influences the regulation of miRNAs and contributes to cellular homeostasis [76,78]. Nearly 3,000 miRNAs have been identified to date, with hundreds of them are directly involved in the autophagy process. MiR-145 was found to contribute to acute MI (AMI), with its downregulation associated with elevated cardiac cell apoptosis, phosphorylated (p)-RAC-γ serine/threonine-protein kinase (AKT3), and p-mechanistic target of rapamycin (mTOR) protein expression and suppressed autophagy in an in vitro AMI model. In contrast, overexpressing miR-145 decreased cardiac cell apoptosis, increased p-AKT3 and p-mTOR protein expression, and mediated autophagy. Additionally, the upregulation of miR-145 was suppressed by blocking AKT3, resulting in decreased apoptosis in AMI. These findings indicate that miR-145 prevents AMI-induced apoptosis through the AKT3/mTOR signaling pathway [79].

While drugs like sorafenib have advanced the treatment of HCC, drug resistance has significantly limited its success. Both drug resistance and chemoresistance play significant roles in reducing sorafenib’s effectiveness. Increasing HCC sensitivity by inhibiting autophagy has been shown to enhance sorafenib’s effect on HCC, mediated through the miRNA miR-375 which is one of the major breakthroughs in understanding the role of ncRNAs. MiR-375 directly targets autophagy-related protein 14 (ATG14) and regulates the sensitivity of HCC cells to sorafenib. Notably, miR-375 and ATG14 are well-established as crucial factors involved in sorafenib resistance in HCC cells [80].

Similarly, the miRNA miR-125a was upregulated in mice with induced thyroiditis, leading to reduced autophagy and cell proliferation while increasing apoptosis and the release of proinflammatory factors interleukin (IL)-1β and IL-6. This effect occurs through the downregulation of the PI3K/AKT/mTOR signaling pathway. Additionally, inhibiting PI3K enhances the effect of miR-125a, further contributing to autophagy inhibition [81].

ncRNAs as negative regulators

Cell death and the cell cycle

Various cellular and molecular events are involved in the process of cell death or programmed cell death (PCD) which are broadly classified as apoptosis, necroptosis, ferroptosis [81], pyroptosis [82], and autophagy [82]. The cellular process responsible for PCD is essential in restoring homeostasis after acute or chronic injury by limiting the spread of inflammatory signals and preventing tissue function loss [83]. Various ncRNAs mediate or abrogate critical PCD processes, with some listed in Figure 3. Apoptosis is initiated by caspases through various mechanisms and leads to cell death [84, 85]. It was previously believed that caspase clusters were closely linked to apoptosis. However, recent studies have shown that suppressing the caspase mechanism does not regulate cell death mediated by death receptors; instead, necrosis plays a vital role in cell death [86]. Upon stimulation, tumor necrosis factor (TNF) combines with TNF receptor superfamily member 1A (TNFRSF1A/TNFR1) and recruits multiple proteins to form complex 1. When caspase 8 (CASP8) is inhibited, receptor-interacting serine/threonine kinase 1 (RIPK1) complex 1 triggers receptor-interacting serine/threonine kinase 3 (RIPK3) through the RIP homotypic interaction motif domain and mediates the necrosome via phosphorylation [87,88].

lncRNA interactions in necroptosis

Numerous lncRNAs have been reported to regulate necroptosis by acting as competitive endogenous RNAs, inducing the expression of target genes through their effects on miRNAs, either increasing or decreasing their levels. The lncRNA small nucleolar RNA host gene 20 (SNHG20) regulates tumor metastasis by modulating erb-b2 receptor tyrosine kinase 2 (ERBB2/HER2) via miR-495 in breast cancer cells. SNHG20 also plays a vital role in the proliferation, invasion, and migration of infection. Moreover, miR-24a negatively regulates HER2 in breast cancer [92].

The miRNA miR-331-3p is downregulated in non-small cell lung cancer (NSCLC), which promotes tumor cell proliferation, epithelial-mesenchymal transition-driven tumor progression, and invasion by targeting the MLLT10 histone lysine methyltransferase DOT1L cofactor (MLLT10) gene. MiR-331-3p acts as a tumor suppressor in NSCLC development. Current findings suggest that miR-331-3p and its target gene MLLT10 may be a potential clinical diagnostic target for NSCLC [107].

Hydrogen sulfide is an air pollutant known to adversely affect lung health. A toxicity study on chicken tracheal tissue revealed apoptosis, necroptosis, and the differential expression of 16 lncRNAs and 18 miRNAs. Notably, lncRNA3037 was downregulated, while miR-15a was upregulated. MiR-15a is a direct target of lncRNA3037, and they negatively regulate each other upon binding. Furthermore, miR-15a negatively regulates the TNF alpha-induced protein 3 (TNFAIP3/A20) and BCL2 apoptosis regulator (BCL2) genes. Overexpression of miR-15a triggers apoptosis and necroptosis, whereas inhibiting miR-15a reverses these processes [102].

lncRNA interactions in ferroptosis

Ferroptosis is a form of PCD characterized by cell shrinkage, mitochondrial contraction, increased membrane density, and a ruptured outer membrane. It involves the iron-dependent accumulation of ROS in the membrane, resulting from the failure of the membrane lipid repair process governed by glutathione peroxidase. Unlike apoptosis, ferroptosis is a non-apoptotic pathway driven by ROS accumulation through iron [96,98]. Several studies have reported roles for ncRNAs in ferroptosis. A recent study explored the protective effects of MSCs on acute liver injury (ALI) induced by carbon tetrachloride (CCl_4). Ferroptosis was identified as a contributing factor to CCl_4-induced ALI.

The significant downregulation of solute carrier family 7-member 11 (SLC7A11) protein levels in the ALI mouse model facilitated ferroptosis in hepatocytes. Treatment with MSC-derived exosomes (MSC-Exo) increased Slc7a11 expression in the mouse liver and upregulated CD44 antigen (Cd44) and OTU domain, ubiquitin aldehyde binding 1 (Otub1). Notably, the stability of SLC7A11 was linked to OTUB1-mediated deubiquitination. Finally, MSC-Exo mitigates hepatocyte ferroptosis and promotes liver repair in ALI mouse models by preserving SLC7A11 function [108].

The lncRNA long intergenic non-protein coding RNA 578 (LINC00578) significantly suppressed ferroptosis-related processes, such as cell proliferation, ROS production, and mitochondrial membrane potential depolarization, which is directly related to SLC7A11. Furthermore, the ferroptosis-suppressing effect of LINC00578 could be reversed by knocking down SLC7A11. With a property similar to an oncogene, LINC00578 promotes pancreatic cancer cell progression and inhibits ferroptosis as a direct target of ubiquitin-conjugating enzyme E2 K (UBE2K), thereby preventing the ubiquitination of SLC7A11 [97]. Thus, the negative regulation of lncRNAs draws attention to various ferroptosis-inducing and -suppressing processes.

lncRNA interactions in pyroptosis

Identifying new types of immune cell death and their involvement in immunity and promoting tumor development has driven advances in anti-tumor treatment approaches. Pyroptosis typically occurs in macrophages following pathogen infection. Pyroptosis is triggered either through the canonical caspase 1 (CASP1) inflammasome pathway or via targeted activation by caspases 4 (CASP4), 5 (CASP5), and 11 (CASP11), which bind to lipopolysaccharide [94].

Inflammasomes are multiprotein complexes activated in response to microbial infections, pathogen-associated molecular patterns (PAMPs), and damage-associated molecular patterns (DAMPs). Inflammasome initiation is followed by gasdermin D (GSDMD) cleavage and IL-1β and IL-18 release [109]. Moreover, they are implicated in non-microbial diseases, with substantial evidence suggesting that inflammasomes and their associated cytokines play critical roles in oncogenesis, including tumor proliferation, metastasis, and invasion. Inflammasomes are recognized to play an important role in immune response pathways that lead to pyroptosis. Pyroptosis is initiated via four pathways identified to date: i) inflammasome-reliant or -non-reliant pathways, ii) canonical and non-canonical pathways that rely on inflammasomes, iii) independent pyroptosis pathways involving caspase 3 (CASP3), and iv) the granzyme protease-mediated pathway [83,93,94]. Several studies have explored the mechanisms of pyroptosis in defending against both invasive and non-invasive infections. The lncRNA RP1-85F18.6 was found to be upregulated in CRC tissues and cell lines. Knockdown of RP1-85F18.6 suppressed tumor growth by reducing cell proliferation and invasion, disrupting the cell cycle, and promoting apoptosis and pyroptosis in CRC cells. In contrast, overexpressing RP1-85F18.6 had the opposite effect, promoting CRC cell proliferation, invasion, and cell cycle disruption while inhibiting various cell death processes and pyroptosis, likely by regulating the expression of an amino-terminally truncated isoform of the tumor protein p63 (TP63) gene, ΔNp63 [110].

NSCLC development is regulated by the lncRNA X inactive specific transcript (XIST), which is overexpressed in NSCLC tissues. The knockdown of XIST enhanced apoptosis and inhibited NSCLC cell growth, further increasing ROS production. The overexpression of XIST promoted the expression of superoxide dismutase 2 (SOD2) by sponging miR-335. Additionally, silencing XIST suppressed NSCLC proliferation through pyroptosis by modulating the miR-335/ROS and SOD2 pathways [111,112]. Similarly, the knockdown of XIST increased ROS levels and activated the NOD-like receptor protein 3 (NLRP3) in A549 cells, activating CASP1, which is known to initiate pyroptosis [113].

Various reports have shown that miRNAs and lncRNAs negatively regulate various pathways to defend against microbial and non-microbial infections. However, a deeper understanding of lncRNA involvement is essential for developing effective therapeutic approaches.

lncRNA interactions in apoptosis

Understanding apoptosis in disease context is crucial as it provides insights into disease mechanisms and associated pathology and offers potential strategies for treatment. For instance, the balance between cell division and cell death is disrupted in cancer. Cells that should undergo apoptosis fail to receive the necessary PCD signals, leading to uncontrolled growth and tumor formation. This dysregulation of apoptosis is a key factor in cancer progression and highlights potential therapeutic targets to restore normal cell death pathways. For example, the downregulation of tumor protein p53 (TP53), a key tumor suppressor gene, inhibits apoptosis, enabling abnormal cells to evade PCD.

This disruption promotes unchecked cell proliferation, contributing to tumor growth and progression [114, 115].

Caspases play a pivotal role in apoptosis, functioning as both initiators and executioners of PCD. Their activation triggers the cascade required to systematically dismantle cellular components. Caspases can be activated through three primary pathways: i) the intrinsic (mitochondrial) pathway, ii) the extrinsic (death receptor) pathway, and iii) the endoplasmic reticulum pathway [100]. Some recent reports have shown that ncRNAs are negative regulators of apoptosis and minimize or stop PCD in diseased conditions. MSCs modulate apoptosis in target cells through various molecules like ncRNAs and pathways. MSC-based therapies, including the exosomes and extracts that have not been characterized, have been shown to significantly reduce apoptosis in disease-affected tissues by activating multiple signaling cascades. Additionally, MSCs release EVs and soluble factors, such as cytokines and growth factors, which further enhance anti-apoptotic signaling in damaged tissues [105,116]. MSCs play a vital role in preventing apoptosis in various diseases, such as cardiovascular, kidney, and neurodegenerative diseases [106].

The roles of miRNAs in apoptosis processes have been studied in various cells, including stem cells and cancer cells. Cell survival is heavily influenced by the PI3K/AKT signaling pathway, which plays a critical role in preventing unnecessary apoptosis. Upon activation, this pathway stimulates various anti-apoptotic genes and proteins, which inhibit key apoptotic processes [117]. The PI3K/AKT signaling pathway involved in cell growth and proliferation was suppressed by the phosphatase and tensin homolog (PTEN) gene via dephosphorylation as a negative regulator and induced apoptosis. However, miRNAs derived from MSCs, such as miR-29b-3p, miR-223, miR-144, and miR-486-5p, activate the PI3K/AKT signaling pathway and inhibit apoptosis by blocking PTEN [118,119]. Another report stated that an anti-apoptotic mechanism was triggered through MSC-Exo-derived miR-132-3p, and the lncRNA KLF-AS1 initiates the PI3K/AKT signaling pathway and prevents apoptosis [104].

The lncRNA in the aldehyde dehydrogenase 1A pathway (NRAD1/LINC00284) is predominantly expressed in ovarian cancer. Overexpressing NRAD1 in H08910 and OVCAR3 cells undergoing apoptosis stopped the apoptotic process [120].

Similarly, various lncRNAs and miRNAs have apoptosis-suppressive roles to protect infected cells. MSC-Exos have shown great potential in treating MI. MSC derivatives such as ncRNAs and exosomes showed significant therapeutic effects by preventing cardiomyocyte apoptosis. MSC-Exos inhibited apoptosis as a cardioprotective treatment under hypoxic conditions by targeting the PTEN/AKT pathway by directly delivering the miRNA miR-144 [121].

ncRNAs enhance or inhibit cell-to-cell communication and signaling

Cell signaling is essential in regulating various cellular processes in response to intracellular and extracellular stimuli. Numerous signaling pathways play key roles in triggering cascades of biological reactions and gene expression. Each pathway typically involves multiple signaling molecules that, while not directly involved in transcription, can influence gene expression by directly or indirectly regulating the activity of transcription factors. One such well-established example, transcription factor p53, is a well-established cancer suppressor that is often mutated or deleted in cancer cells. Levels of p53 are primarily regulated during translation and further controlled via post-translational modifications and protein stability. lncRNAs play a critical role in the p53 network, impacting effectors involved in downstream cellular processes [122].

The lncRNA known as damage-induced long non-coding RNA (DINOL/DINO) is basically induced by DNA damage and mediated via p53. P53 mediates the expression of various genes, apoptosis, and cellular arrest via DINO. Therefore, DINO is primarily activated to initiate DNA damage signaling and inhibit cell cycle progression. DINO directly binds to p53 to initiate downstream molecular events that also involve DINO. To prevent prolonged activation of p53 signals after cellular damage, the MDM2 proto-oncogene (MDM2), a negative regulator of p53, suppresses excess signaling to maintain cellular stability by deactivating p53 following acute DNA damage. In addition to MDM2, the lncRNA long intergenic non-protein coding RNA regulator of reprogramming (LINC-ROR), which is induced by p53, also contributes by inhibiting p53 expression [123,124].

The Notch signaling pathway has a highly conserved cellular mechanism that plays a key role in stemness, cell proliferation, apoptosis, and cellular differentiation. Numerous lncRNAs are involved in signaling in stem cell and tumor development. Taurine-upregulated gene 1 (TUG1) expression was induced by notch receptor 1 (NOTCH1), a glioma stem cell self-renewal inducer. Therefore, NOTCH1 plays a vital role in signaling self-renewal [125].

Furthermore, NOTCH1-associated lncRNA in T-cell acute lymphoblastic leukemia 1 (NALT1) was highly expressed in T-cell acute lymphoblastic leukemia samples, and suppressing NALT1 or NOTCH1 via RNA interference led to tumor growth in a xenograft model [126].

CONCLUSION

ncRNAs serve as pivotal regulators in the complex interplay of cellular processes, influencing both HSCs/MSCs and other cell types, too. Their dual role as positive and negative regulators or modulators highlights their functional versatility in maintaining cellular homeostasis and determining cell fate. While ncRNAs promote cell survival, regulate the cell cycle, drive differentiation, and modulate autophagy and senescence, they can act as negative regulators, facilitating processes such as necroptosis, ferroptosis, pyroptosis, apoptosis, and suppressing proinflammatory responses and cell adhesion. Additionally, ncRNAs impact intercellular communication and signaling, enhancing or reducing it as key players mediating transcriptional regulation, further shaping the cellular microenvironment. These insights into the multifaceted roles of ncRNAs offer new perspectives on their therapeutic potential in regulating stem cell behavior and controlling pathological processes. Understanding these mechanisms will pave the way for developing ncRNA-based interventions to modulate stem cell function and improve treatments for various acute and chronic diseases.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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