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NON-CODING RNA NETWORKS REGULATING NLRP3 INFLAMMASOME ACTIVATION IN NEURODEGENERATIVE AND CARDIOVASCULAR DISEASES

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ABSTRACT

The NLRP3 inflammasome is a critical multiprotein complex that drives inflammatory responses in both neurodegenerative and cardiovascular diseases through caspase-1 activation and subsequent maturation of interleukin-1β and interleukin-18. Emerging evidence demonstrates that non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, function as master regulators of NLRP3 inflammasome signaling by modulating expression of inflammasome components, upstream activators, and downstream effectors. In neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and stroke, dysregulated non-coding RNA networks contribute to microglial activation, neuroinflammation, and neuronal pyroptosis through NLRP3-dependent mechanisms. Similarly, in cardiovascular diseases including atherosclerosis, myocardial infarction, and heart failure, non-coding RNAs regulate macrophage polarization, endothelial dysfunction, and cardiomyocyte death via NLRP3 inflammasome pathways. MicroRNAs such as miR-223, miR-146a, and miR-155 directly target NLRP3 pathway components, while long non-coding RNAs including NEAT1, MALAT1, and HOTAIR function as competing endogenous RNAs that sequester microRNAs and amplify inflammatory signaling. Circular RNAs such as circHIPK3 further modulate NLRP3 activation through miRNA sponging mechanisms. This review synthesizes current understanding of non-coding RNA-mediated regulation of NLRP3 inflammasome activation across neurodegenerative and cardiovascular disease contexts, highlighting shared molecular mechanisms, translational biomarker potential, and therapeutic targeting opportunities. We discuss knowledge gaps, methodological limitations, and future directions for harnessing non-coding RNA networks to modulate NLRP3-driven inflammation in precision medicine approaches.
Keywords: NLRP3 inflammasome; non-coding RNA; microRNA; long non-coding RNA; neurodegeneration; cardiovascular disease

INTRODUCTION

The NLRP3 (nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing protein 3) inflammasome represents a central innate immune signaling platform that orchestrates inflammatory responses to diverse cellular stressors, pathogen-associated molecular patterns, and damage-associated molecular patterns (Swanson et al., 2019). Upon activation, NLRP3 recruits the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and procaspase-1 to form a large oligomeric complex that catalyzes caspase-1 activation, leading to proteolytic maturation of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18), as well as execution of pyroptosis, a lytic form of programmed cell death (Kelley et al., 2019; Shi et al., 2015). Dysregulated NLRP3 inflammasome activation has been implicated in the pathogenesis of numerous chronic inflammatory conditions, including neurodegenerative diseases such as Alzheimer disease, Parkinson disease, and stroke, as well as cardiovascular diseases including atherosclerosis, myocardial infarction, and heart failure (Heneka et al., 2018; Grebe et al., 2018).

Non-coding RNAs, which constitute the majority of the human transcriptome, have emerged as critical regulators of gene expression and cellular phenotypes without encoding proteins (Esteller, 2011). MicroRNAs (miRNAs) are small (~22 nucleotide) non-coding RNAs that post-transcriptionally suppress target messenger RNAs through sequence-specific binding to 3' untranslated regions (Bartel, 2018). Long non-coding RNAs (lncRNAs) are transcripts exceeding 200 nucleotides that regulate gene expression through diverse mechanisms including chromatin remodeling, transcriptional regulation, and competing endogenous RNA (ceRNA) networks (Kopp and Mendell, 2018). Circular RNAs (circRNAs) are covalently closed RNA molecules generated through back-splicing that function primarily as miRNA sponges and protein scaffolds (Kristensen et al., 2019). Accumulating evidence demonstrates that non-coding RNAs exert profound regulatory control over NLRP3 inflammasome signaling in both neurodegenerative and cardiovascular disease contexts (Wang et al., 2021; Hu et al., 2023).

In neurodegenerative diseases, microglial activation and neuroinflammation driven by NLRP3 inflammasome signaling contribute to progressive neuronal loss and cognitive decline (Heneka et al., 2018; Liang et al., 2022).

MicroRNAs such as miR-223, miR-146a, and miR-155 are dysregulated in Alzheimer disease, Parkinson disease, and stroke, modulating neuroinflammatory responses through direct targeting of NLRP3 pathway components (Saresella et al., 2020; Gui et al., 2023). Long non-coding RNAs including NEAT1 and HOTAIR promote neuronal pyroptosis by functioning as miRNA sponges that de-repress NLRP3 expression (Singh et al., 2024; Zhang et al., 2022). Similarly, in cardiovascular diseases, macrophage activation, endothelial dysfunction, and cardiomyocyte death are mediated by NLRP3 inflammasome-dependent mechanisms (Grebe et al., 2018; Tanase et al., 2023). MicroRNAs such as miR-223 and miR-155 regulate atherosclerotic plaque stability and myocardial ischemia-reperfusion injury through modulation of NLRP3 signaling (Wang et al., 2020; Lu et al., 2025). Long non-coding RNAs including MALAT1, HOTAIR, and MEG3 control cardiomyocyte pyroptosis and cardiac fibrosis via ceRNA-mediated regulation of miRNA-NLRP3 axes (Che et al., 2020; Rao et al., 2025).

The convergence of non-coding RNA dysregulation and NLRP3 inflammasome hyperactivation across neurodegenerative and cardiovascular diseases suggests shared molecular mechanisms and potential therapeutic targets (Song et al., 2022; Silva et al., 2025). Understanding the molecular architecture of non-coding RNA networks that govern NLRP3 inflammasome activation is essential for developing precision medicine approaches targeting chronic inflammatory diseases. This review synthesizes current knowledge of non-coding RNA-mediated regulation of NLRP3 inflammasome signaling, emphasizing molecular mechanisms, disease-specific contexts, translational biomarker potential, and therapeutic targeting opportunities.

MOLECULAR ARCHITECTURE AND ACTIVATION OF THE NLRP3 INFLAMMASOME

The NLRP3 inflammasome is a multiprotein complex comprising the sensor protein NLRP3, the adaptor protein ASC, and the effector protease caspase-1 (Swanson et al., 2019). NLRP3 contains three functional domains: an N-terminal pyrin domain that mediates protein-protein interactions, a central NACHT domain with ATPase activity required for oligomerization, and C-terminal leucine-rich repeats that sense activating stimuli (Bauernfeind et al., 2009). ASC functions as a bipartite adaptor containing a pyrin domain that binds NLRP3 and a caspase recruitment domain (CARD) that recruits procaspase-1 (Lu et al., 2014). Upon activation, ASC oligomerizes into large filamentous structures termed ASC specks that serve as platforms for caspase-1 activation (Franklin et al., 2014).

NLRP3 inflammasome activation requires two distinct signals (Kelley et al., 2019). The priming signal, typically mediated by Toll-like receptor or cytokine receptor engagement, activates nuclear factor-κB (NF-κB) to induce transcriptional upregulation of NLRP3 and pro-IL-1β (Bauernfeind et al., 2009). The activation signal is triggered by diverse stimuli including extracellular ATP, pore-forming toxins, crystalline materials, and mitochondrial dysfunction, leading to NLRP3 oligomerization and inflammasome assembly (Swanson et al., 2019). Key cellular events that trigger NLRP3 activation include potassium efflux, calcium flux, mitochondrial reactive oxygen species (ROS) production, and release of oxidized mitochondrial DNA (Zhong et al., 2018). Thioredoxin-interacting protein (TXNIP), which dissociates from thioredoxin under oxidative stress, directly binds NLRP3 to promote inflammasome activation (Zhou et al., 2010).

Activated caspase-1 cleaves pro-IL-1β and pro-IL-18 into their mature bioactive forms, which are secreted to propagate inflammatory signaling (Dinarello, 2018). Caspase-1 also cleaves gasdermin D (GSDMD), generating an N-terminal fragment that oligomerizes to form membrane pores, resulting in pyroptotic cell death characterized by plasma membrane rupture, cellular swelling, and release of intracellular contents including IL-1β and IL-18 (Shi et al., 2015; Kayagaki et al., 2015). Pyroptosis amplifies inflammatory responses by releasing damage-associated molecular patterns and alarmins that activate neighboring immune cells (Bergsbaken et al., 2009).

The molecular architecture of NLRP3 inflammasome activation provides multiple regulatory nodes susceptible to modulation by non-coding RNAs (Figure 1). MicroRNAs can directly target NLRP3, ASC, caspase-1, IL-1β, and IL-18 transcripts to suppress inflammasome signaling (Wang et al., 2021). Long non-coding RNAs and circular RNAs function as competing endogenous RNAs that sequester microRNAs, thereby de-repressing inflammasome component expression (Hu et al., 2023). Additionally, non-coding RNAs regulate upstream activators of NLRP3 including NF-κB, TXNIP, and mitochondrial dysfunction pathways, providing indirect control over inflammasome activation (Song et al., 2022).

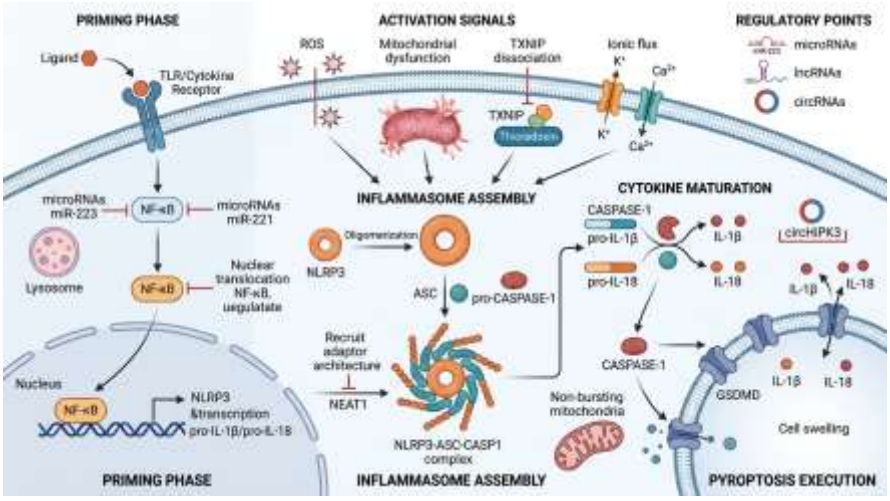

Figure 1. Overview of NLRP3 inflammasome activation and points of non-coding RNA regulation. The NLRP3 inflammasome pathway consists of two distinct phases: priming and activation. During priming, pathogen-associated molecular patterns or damage-associated molecular patterns engage pattern recognition receptors such as Toll-like receptors, activating nuclear factor-κB (NF-κB) signaling to induce transcriptional upregulation of NLRP3 and pro-interleukin-1β (pro-IL-1β). The activation phase is triggered by diverse cellular stressors including potassium efflux, calcium flux, mitochondrial reactive oxygen species (ROS) production, and thioredoxin-interacting protein (TXNIP) release. These signals promote NLRP3 oligomerization and recruitment of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD) and procaspase-1 to form the active inflammasome complex. Activated caspase-1 proteolytically processes pro-IL-1β and pro-IL-18 into mature bioactive cytokines and cleaves gasdermin D (GSDMD) to execute pyroptotic cell death. Non-coding RNAs, including microRNAs (miR-223, miR-221), long non-coding RNAs (lncRNAs), and circular RNAs (circHIPK3), regulate multiple nodes in this pathway, including transcriptional priming, oxidative stress responses, inflammasome assembly, and downstream cytokine maturation. These regulatory interactions provide therapeutic opportunities for modulating NLRP3-driven inflammation in neurodegenerative and cardiovascular diseases.

NON-CODING RNA CLASSES INVOLVED IN NLRP3 REGULATION

MicroRNAs

MicroRNAs are small non-coding RNAs that post-transcriptionally regulate gene expression by binding to complementary sequences in target messenger RNA 3' untranslated regions, leading to translational repression or mRNA degradation (Bartel, 2018). A growing body of evidence demonstrates that specific microRNAs function as critical regulators of NLRP3 inflammasome signaling by directly targeting inflammasome components, upstream activators, and downstream effectors (Wang et al., 2021; Silva et al., 2025).

MicroRNA-223 (miR-223) is one of the most extensively characterized negative regulators of NLRP3 inflammasome activation (Bauernfeind et al., 2012). MiR-223 directly targets the 3' untranslated region of NLRP3 mRNA, suppressing NLRP3 protein expression and subsequent inflammasome activation in macrophages and microglia (Saresella et al., 2020). In Alzheimer disease patients, miR-223 expression is reduced in peripheral blood mononuclear cells, correlating with elevated NLRP3 expression and enhanced IL-1β production (Saresella et al., 2020). Similarly, miR-223 downregulation has been observed in atherosclerotic plaques, myocardial infarction models, and heart failure patients, contributing to NLRP3-mediated inflammation (Wang et al., 2020; Rao et al., 2025). Restoration of miR-223 expression through therapeutic delivery attenuates NLRP3 inflammasome activation, reduces pyroptosis, and improves disease outcomes in preclinical models of cerebral ischemia-reperfusion injury and oxidized low-density lipoprotein-induced endothelial dysfunction (Sha et al., 2019; Xu et al., 2020).

MicroRNA-146a (miR-146a) functions as an endogenous negative feedback regulator of innate immune signaling by targeting TRAF6 and IRAK1, key adaptor proteins in NF-κB activation pathways (Taganov et al., 2006). By suppressing NF-κB signaling, miR-146a reduces transcriptional priming of NLRP3 and pro-IL-1β, thereby attenuating inflammasome activation (Hou et al., 2021). MiR-146a expression is dysregulated in multiple neurodegenerative and cardiovascular diseases, with reduced levels associated with enhanced inflammatory responses (Silva et al., 2025). Therapeutic upregulation of miR-146a has demonstrated efficacy in reducing NLRP3-mediated inflammation in experimental models of lipopolysaccharide-induced endothelial injury and neuroinflammation (Hou et al., 2021).

MicroRNA-155 (miR-155) exhibits context-dependent pro-inflammatory or anti-inflammatory effects on NLRP3 inflammasome signaling (Peng et al., 2022). In atherosclerotic plaques, miR-155 promotes NLRP3 inflammasome activation by targeting the MEK/ERK/NF-κB pathway, enhancing inflammatory cytokine production and plaque instability (Peng et al., 2022). In contrast, in cerebral ischemia-reperfusion injury, miR-155-5p upregulation

accelerates neuronal pyroptosis through the DUSP14/TXNIP/NLRP3 pathway (Shi et al., 2022). Conversely, inhibition of miR-155-5p in cardiomyocytes subjected to hypoxia-reoxygenation reduces pyroptosis by targeting SIRT1-mediated NLRP3 inflammasome activation (Lu et al., 2025). These findings highlight the complex, context-dependent roles of miR-155 in NLRP3 regulation across different disease states and cell types.

Additional microRNAs implicated in NLRP3 inflammasome regulation include miR-7, miR-22, miR-30e, miR-21, miR-33, miR-181, and miR-20a (Figure 2). MiR-22 directly targets NLRP3 mRNA and is sequestered by lncRNA MALAT1 in diabetic cardiomyopathy and lncRNA HOTAIR in hyperuricemia-induced endothelial pyroptosis, leading to NLRP3 de-repression (Che et al., 2020; Chi et al., 2021). MiR-30e targets NLRP3 and is downregulated in cardiovascular inflammatory conditions (Silva et al., 2025). MiR-21 exhibits pleiotropic effects on inflammation, targeting multiple components of NLRP3 signaling pathways (Silva et al., 2025). The diversity of microRNAs regulating NLRP3 inflammasome activation underscores the complexity of non-coding RNA-mediated control of inflammatory responses.

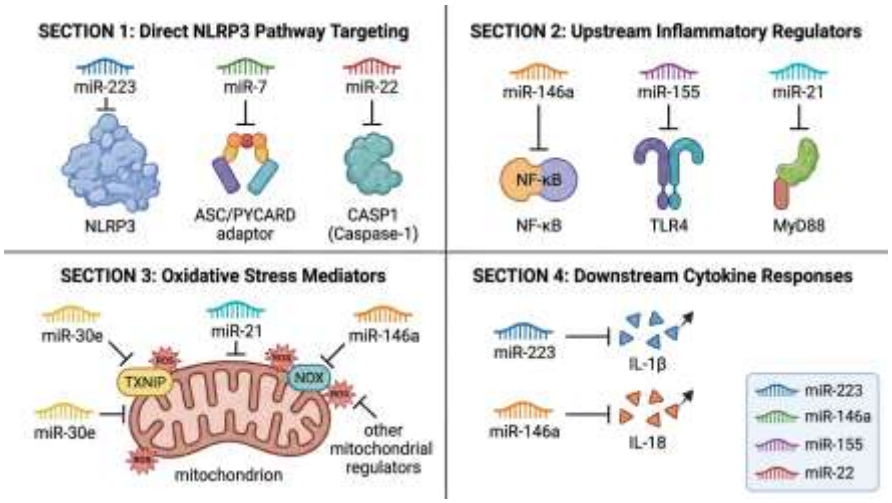

Figure 2. MicroRNA regulation of NLRP3 inflammasome signaling. MicroRNAs (miRNAs) regulate NLRP3 inflammasome activation at multiple levels through direct targeting of pathway components and upstream regulatory molecules. The diagram illustrates four major regulatory nodes: (1) Direct targeting of NLRP3 pathway components, where miR-223, miR-7, and miR-22 suppress expression of NLRP3, ASC/PYCARD, and caspase-1 (CASP1), thereby inhibiting inflammasome assembly and activation. (2) Regulation of upstream inflammatory regulators, where miR-146a, miR-155, and miR-21 target key signaling molecules including nuclear factor-κB (NF-κB), Toll-like receptor 4 (TLR4), and myeloid differentiation primary response 88 (MyD88), modulating transcriptional priming of NLRP3 and pro-IL-1β. (3) Control of oxidative stress mediators, where miR-30e, miR-21, and miR-146a target thioredoxin-interacting protein (TXNIP), NADPH oxidase (NOX), and mitochondrial regulators, reducing reactive oxygen species (ROS) production and mitochondrial dysfunction that trigger NLRP3 activation. (4) Modulation of downstream cytokine responses, where miR-223 and miR-146a suppress interleukin-1β (IL-1β) and interleukin-18 (IL-18) expression and signaling. Inhibitory interactions are depicted with blocking arrows (⊣). The coordinated action of multiple microRNAs provides multilayered control over NLRP3 inflammasome signaling, with dysregulation of these microRNA networks contributing to chronic inflammation in neurodegenerative and cardiovascular diseases. Therapeutic restoration of protective microRNAs or inhibition of pro-inflammatory microRNAs represents a promising strategy for modulating NLRP3-driven pathology.

Long non-coding RNAs

Long non-coding RNAs are transcripts exceeding 200 nucleotides that lack protein-coding potential but exert diverse regulatory functions including chromatin remodeling, transcriptional regulation, post-transcriptional processing, and competing endogenous RNA activity (Kopp and Mendell, 2018). Emerging evidence demonstrates that specific lncRNAs play critical roles in regulating NLRP3 inflammasome activation through multiple mechanisms, with particular emphasis on ceRNA networks that sequester microRNAs to de-repress NLRP3 pathway components (Hu et al., 2023; Wang et al., 2021).

LncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is a highly conserved nuclear-enriched lncRNA that regulates gene expression through chromatin modification and RNA processing (Gutschner et al., 2013). In cardiovascular disease contexts, MALAT1 promotes NLRP3 inflammasome activation by functioning as a competing endogenous RNA that sponges miR-22-3p and miR-133, leading to de-repression of NLRP3 expression (Che et al., 2020; Yu et al., 2018). In diabetic cardiomyopathy, MALAT1 upregulation sequesters miR-141, enhancing NLRP3 inflammasome-mediated cardiac fibrosis (Che et al., 2020). Melatonin treatment reduces MALAT1

expression, restoring miR-141 levels and attenuating NLRP3-driven fibrosis (Che et al., 2020). In myocardial ischemia-reperfusion injury, MALAT1 promotes cardiomyocyte pyroptosis through miR-133/NLRP3 axis activation (Yu et al., 2018). Genetic or pharmacological suppression of MALAT1 reduces infarct size and improves cardiac function by inhibiting NLRP3 inflammasome activation (Yu et al., 2018).

LncRNA HOTAIR (HOX transcript antisense intergenic RNA) is a well-characterized oncogenic lncRNA that also functions as a regulator of inflammatory responses (Rinn et al., 2007). In hyperuricemia-induced endothelial pyroptosis, HOTAIR upregulation promotes NLRP3 inflammasome activation by sponging miR-22, leading to enhanced caspase-1 activation and IL-1β secretion (Chi et al., 2021). Similarly, in Parkinson disease models, HOTAIR facilitates neuronal pyroptosis by sequestering miR-326, resulting in upregulation of ELAVL1 and subsequent NLRP3 activation (Zhang et al., 2022). Knockdown of HOTAIR attenuates dopaminergic neuronal loss and motor deficits in Parkinson disease models through inhibition of NLRP3-mediated pyroptosis (Zhang et al., 2022).

LncRNA NEAT1 (nuclear-enriched abundant transcript 1) is an essential structural component of paraspeckles, nuclear bodies involved in RNA processing and stress responses (Clemson et al., 2009). NEAT1 has emerged as a critical regulator of NLRP3 inflammasome activation in both neurodegenerative and cardiovascular diseases (Singh et al., 2024; Yao et al., 2022). In Alzheimer disease, NEAT1 expression is elevated in brain tissue and correlates with disease severity (Singh et al., 2024). NEAT1 promotes neuroinflammation by sequestering miR-124, leading to enhanced NLRP3 expression and microglial activation (Singh et al., 2024). In hypoxia-reoxygenation-induced endothelial injury, NEAT1 upregulation promotes NLRP3 inflammasome activation by sponging miR-204, resulting in increased BRCC3 expression and enhanced inflammasome assembly (Yao et al., 2022). Inhibition of NEAT1 protects endothelial cells from pyroptotic death by restoring miR-204 levels and suppressing NLRP3 activation (Yao et al., 2022).

LncRNA MEG3 (maternally expressed gene 3) exhibits tumor suppressor and anti-inflammatory properties in multiple disease contexts (Zhou et al., 2012). In viral myocarditis, MEG3 inhibits M2 macrophage polarization and attenuates inflammation by downregulating miR-223, leading to increased TRAF6 expression and modulation of downstream inflammatory signaling (Xue et al., 2020). In coronary microcirculatory dysfunction following myocardial infarction, the lncMEG3/miR-223/NLRP3 signaling axis plays a pivotal role in homocysteine-induced endothelial injury (Rao et al., 2025). Elevated homocysteine upregulates MEG3, which sequesters miR-223, resulting in NLRP3 de-repression and enhanced inflammasome activation (Rao et al., 2025).

LncRNA GAS5 (growth arrest-specific 5) functions as a tumor suppressor and regulator of cellular stress responses (Kino et al., 2010). In diabetic cardiomyopathy, GAS5 exerts cardioprotective effects by inhibiting NLRP3 inflammasome-mediated pyroptosis through targeting of the miR-34b-3p/AHR axis (Xu et al., 2020). GAS5 overexpression suppresses NLRP3 activation, reduces caspase-1 cleavage, and attenuates cardiomyocyte death in high glucose-treated cells (Xu et al., 2020).

Circular RNAs

Circular RNAs are covalently closed RNA molecules generated through back-splicing of pre-mRNA transcripts, resulting in exon-containing circles that resist exonuclease degradation and exhibit remarkable stability (Kristensen et al., 2019). CircRNAs function primarily as microRNA sponges, sequestering miRNAs through multiple binding sites and preventing their interaction with target mRNAs (Hansen et al., 2013). Emerging evidence demonstrates that specific circRNAs regulate NLRP3 inflammasome activation through ceRNA-mediated mechanisms (Figure 3).

CircHIPK3 (circular RNA HIPK3) is one of the most abundant circRNAs in mammalian cells and contains multiple miRNA binding sites (Zheng et al., 2016). In Parkinson disease, circHIPK3 promotes neuroinflammation by sponging miR-124-3p, leading to activation of the STAT3/NLRP3 signaling pathway (Zhang et al., 2022). CircHIPK3 upregulation in dopaminergic neurons enhances NLRP3 inflammasome activation, caspase-1 cleavage, and IL-1β secretion, contributing to neurodegeneration (Zhang et al., 2022). Knockdown of circHIPK3 attenuates neuroinflammation and improves motor function in Parkinson disease models by restoring miR-124-3p levels and suppressing NLRP3 activation (Zhang et al., 2022).

Additional circRNAs implicated in NLRP3 inflammasome regulation include circRNA_0054633 and other disease-specific circular transcripts identified through RNA sequencing studies (Wang et al., 2021). The high stability and tissue-specific expression patterns of circRNAs make them attractive biomarker candidates and therapeutic targets for modulating NLRP3-driven inflammation.

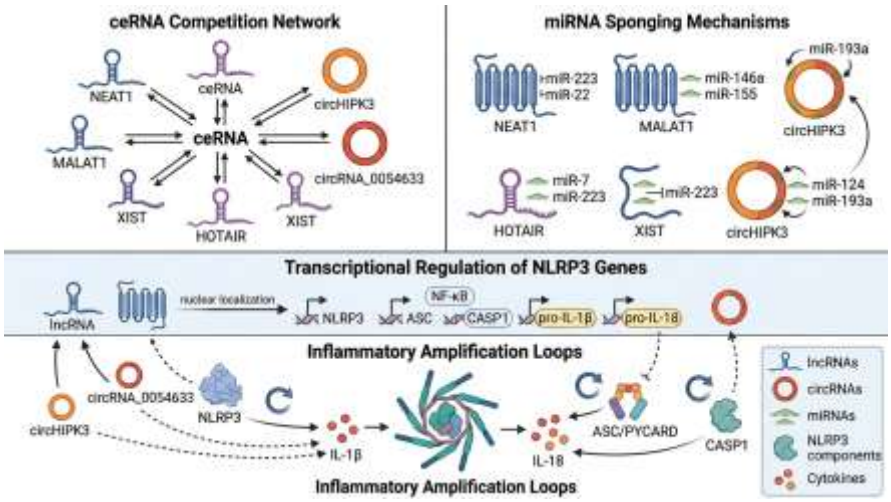

Figure 3. Long non-coding RNA and circular RNA networks regulating NLRP3 inflammasome activation. Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) regulate NLRP3 inflammasome signaling through competing endogenous RNA (ceRNA) networks and transcriptional regulatory mechanisms. The diagram illustrates four integrated regulatory layers: (1) ceRNA Competition Network, where lncRNAs (NEAT1, MALAT1, HOTAIR, XIST) and circRNAs (circHIPK3, circRNA_0054633) function as molecular sponges that sequester microRNAs through multiple miRNA response elements, preventing microRNA-mediated suppression of target mRNAs. (2) miRNA Sponging Mechanisms, showing specific examples of lncRNA/circRNA-miRNA interactions: NEAT1 sponges miR-124 and miR-204; MALAT1 sequesters miR-22, miR-133, and miR-141; HOTAIR binds miR-22 and miR-326; XIST sponges miR-223; MEG3 regulates miR-223; GAS5 targets miR-34b-3p; circHIPK3 sponges miR-124-3p; and other circRNAs sequester miR-223, miR-22, miR-146a, miR-155, and miR-7. By sequestering these protective microRNAs, lncRNAs and circRNAs de-repress NLRP3 pathway genes, amplifying inflammasome activation. (3) Transcriptional Regulation, where nuclear lncRNAs such as NEAT1, MALAT1, and HOTAIR modulate chromatin structure and transcription factor activity to directly regulate NLRP3 gene expression through interactions with nuclear factor-κB (NF-κB) and other transcriptional regulators. (4) Inflammatory Amplification Loops, demonstrating positive feedback mechanisms where NLRP3 inflammasome activation leads to increased production of interleukin-1β (IL-1β) and interleukin-18 (IL-18), which in turn upregulate expression of pro-inflammatory lncRNAs and circRNAs, creating self-amplifying inflammatory circuits. These complex ceRNA networks provide multilayered control over NLRP3 inflammasome signaling, with dysregulation contributing to chronic inflammation in neurodegenerative and cardiovascular diseases. Therapeutic targeting of pathogenic lncRNAs or circRNAs represents a promising strategy for breaking inflammatory amplification loops and modulating NLRP3-driven pathology.

NON-CODING RNA CONTROL OF NLRP3 IN NEURODEGENERATIVE DISEASES

Alzheimer disease

Alzheimer disease is characterized by progressive cognitive decline, accumulation of amyloid-β plaques and neurofibrillary tangles, and chronic neuroinflammation mediated by activated microglia (Heneka et al., 2015). NLRP3 inflammasome activation in microglia drives neuroinflammation through IL-1β and IL-18 production, contributing to synaptic dysfunction, neuronal loss, and disease progression (Heneka et al., 2018; Liang et al., 2022). Amyloid-β oligomers and fibrils activate the NLRP3 inflammasome through multiple mechanisms including lysosomal damage, potassium efflux, and mitochondrial ROS production (Halle et al., 2008).

Non-coding RNAs play critical roles in regulating NLRP3 inflammasome activation in Alzheimer disease pathogenesis (Saresella et al., 2020; Singh et al., 2024). MiR-223 expression is significantly reduced in peripheral blood mononuclear cells from Alzheimer disease patients compared to age-matched controls, correlating with elevated NLRP3 protein levels and enhanced IL-1β secretion (Saresella et al., 2020). The reduction in miR-223 impairs negative feedback regulation of NLRP3, resulting in sustained inflammasome activation and chronic neuroinflammation (Saresella et al., 2020). Restoration of miR-223 expression in microglia suppresses amyloid-β-induced NLRP3 activation and reduces neurotoxic cytokine production (Saresella et al., 2020).

LncRNA NEAT1 is upregulated in brain tissue from Alzheimer disease patients and in cellular models of amyloid-β-induced neuroinflammation (Singh et al., 2024). NEAT1 promotes microglial NLRP3 inflammasome activation by sequestering miR-124, a microRNA that targets NLRP3 mRNA (Singh et al., 2024). The NEAT1/miR-124/NLRP3 axis represents a critical regulatory circuit in Alzheimer disease pathogenesis, with NEAT1 upregulation amplifying neuroinflammatory responses (Singh et al., 2024). Genetic or antisense oligonucleotide-mediated suppression of NEAT1 reduces microglial activation, attenuates neuroinflammation, and improves cognitive function in Alzheimer disease models (Singh et al., 2024).

MiR-146a dysregulation has also been implicated in Alzheimer disease neuroinflammation (Lukiw et al., 2008). MiR-146a expression is altered in Alzheimer disease brain tissue, with regional variations reflecting different stages of disease progression (Lukiw et al., 2008). MiR-146a targets TRAF6 and IRAK1, key mediators of NF-κB activation, thereby modulating transcriptional priming of NLRP3 and pro-IL-1β (Taganov et al., 2006). Dysregulation of the miR-146a/TRAF6/NF-κB/NLRP3 axis contributes to sustained neuroinflammation in Alzheimer disease (Lukiw et al., 2008).

Parkinson disease

Parkinson disease is characterized by progressive loss of dopaminergic neurons in the substantia nigra, accumulation of α-synuclein aggregates in Lewy bodies, and chronic neuroinflammation mediated by activated microglia (Hirsch and Hunot, 2009). NLRP3 inflammasome activation in microglia contributes to dopaminergic neurodegeneration through IL-1β-mediated neurotoxicity and pyroptotic cell death (Liang et al., 2022). α-Synuclein fibrils activate the NLRP3 inflammasome through mechanisms involving lysosomal rupture and mitochondrial dysfunction (Zhou et al., 2016).

Non-coding RNAs regulate NLRP3 inflammasome activation in Parkinson disease through multiple mechanisms (Wu et al., 2023; Zhang et al., 2022). MiR-223 expression is reduced in dopaminergic neurons and microglia in Parkinson disease models, contributing to enhanced NLRP3 activation (Wu et al., 2023). Importantly, miR-223 not only directly targets NLRP3 but also regulates mitophagy, the selective autophagy of damaged mitochondria (Wu et al., 2023). Activation of mitophagy via the miR-223/NLRP3 axis ameliorates dopaminergic neuronal damage by clearing dysfunctional mitochondria that would otherwise trigger NLRP3 inflammasome activation (Wu et al., 2023). This dual mechanism highlights the interconnection between non-coding RNA regulation, mitochondrial quality control, and inflammasome signaling in Parkinson disease pathogenesis.

LncRNA HOTAIR is upregulated in Parkinson disease models and promotes neuronal pyroptosis through the miR-326/ELAVL1/NLRP3 pathway (Zhang et al., 2022). HOTAIR functions as a ceRNA that sequesters miR-326, leading to increased expression of ELAVL1 (also known as HuR), an RNA-binding protein that stabilizes NLRP3 mRNA (Zhang et al., 2022). The HOTAIR/miR-326/ELAVL1/NLRP3 axis amplifies inflammasome activation and pyroptotic neuronal death in dopaminergic neurons (Zhang et al., 2022). Knockdown of HOTAIR or overexpression of miR-326 attenuates NLRP3-mediated neurodegeneration in Parkinson disease models (Zhang et al., 2022).

CircHIPK3 plays a pro-inflammatory role in Parkinson disease by regulating the miR-124-3p/STAT3/NLRP3 signaling pathway (Zhang et al., 2022). CircHIPK3 is upregulated in dopaminergic neurons exposed to neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Zhang et al., 2022). CircHIPK3 sponges miR-124-3p, a neuroprotective microRNA that suppresses STAT3 activation and NLRP3 expression (Zhang et al., 2022). The circHIPK3/miR-124-3p/STAT3/NLRP3 axis promotes neuroinflammation and dopaminergic neurodegeneration, with circHIPK3 knockdown providing neuroprotection in Parkinson disease models (Zhang et al., 2022).

Stroke and neurovascular injury

Ischemic stroke results from cerebral artery occlusion, leading to acute neuronal injury, blood-brain barrier disruption, and robust inflammatory responses that contribute to secondary brain damage (Iadecola and Anrather, 2011). Cerebral ischemia-reperfusion injury is characterized by NLRP3 inflammasome activation in microglia, astrocytes, and neurons, driving neuroinflammation, pyroptosis, and expansion of infarct volume (Jiang et al., 2020). NLRP3 inflammasome activation during the reperfusion phase amplifies tissue damage through IL-1β and IL-18 production and pyroptotic cell death (Jiang et al., 2020).

Non-coding RNAs exert neuroprotective or neurotoxic effects in stroke by modulating NLRP3 inflammasome activation (Gui et al., 2023; Sha et al., 2019; Shi et al., 2022). MiR-223-3p is downregulated in brain tissue following cerebral ischemia-reperfusion injury (Gui et al., 2023). Overexpression of miR-223-3p attenuates neuronal pyroptosis by directly targeting NLRP3, caspase-1, and GSDMD, thereby inhibiting multiple steps in the pyroptotic pathway (Gui et al., 2023). Electroacupuncture, a traditional Chinese medicine intervention, provides neuroprotection in stroke models by upregulating miR-223 expression and suppressing NLRP3 inflammasome activation (Sha et al., 2019). The miR-223/NLRP3 pathway represents a therapeutic target for reducing ischemic brain injury (Sha et al., 2019; Gui et al., 2023).

In contrast, miR-155-5p upregulation exacerbates cerebral ischemia-reperfusion injury by promoting NLRP3 inflammasome activation (Shi et al., 2022). MiR-155-5p accelerates neuronal pyroptosis through the DUSP14/TXNIP/NLRP3 pathway, where miR-155-5p suppresses DUSP14 (dual-specificity phosphatase 14), leading to enhanced TXNIP expression and subsequent NLRP3 activation (Shi et al., 2022). Inhibition of miR-155-5p reduces infarct volume, attenuates neuroinflammation, and improves neurological outcomes in stroke models (Shi et al., 2022). These findings highlight the context-dependent and sometimes opposing roles of different microRNAs in regulating NLRP3 inflammasome activation during cerebral ischemia-reperfusion injury.

Table 1. Non-coding RNAs regulating NLRP3 inflammasome signaling in neurodegenerative diseases.

Disease context	Non-coding RNA	Direction of regulation	Main molecular target/pathway	Experimental model or evidence type	Functional outcome	Key reference
Alzheimer disease	miR-223	Downregulated (protective when restored)	Direct targeting of NLRP3 mRNA	Human PBMC; microglia cell culture	Reduced NLRP3 expression; decreased IL-1β secretion; attenuated neuroinflammation	Saresella et al., 2020
Alzheimer disease	lncRNA NEAT1	Upregulated (pathogenic)	Sponges miR-124 to de-repress NLRP3	Human brain tissue; amyloid-β-treated cells	Enhanced microglial activation; increased NLRP3 inflammasome activity; neuroinflammation	Singh et al., 2024
Parkinson disease	miR-223	Downregulated (protective when restored)	Direct targeting of NLRP3; activation of mitophagy	MPTP mouse model; dopaminergic neuron culture	Reduced NLRP3 activation; enhanced mitophagy; dopaminergic neuroprotection	Wu et al., 2023
Parkinson disease	lncRNA HOTAIR	Upregulated (pathogenic)	Sponges miR-326 to upregulate ELAVL1/NLRP3	MPTP mouse model; cell culture	Enhanced neuronal pyroptosis; dopaminergic neurodegeneration; motor deficits	Zhang et al., 2022
Parkinson disease	circHIPK3	Upregulated (pathogenic)	Sponges miR-124-3p to activate STAT3/NLRP3	MPTP mouse model; cell culture	Increased neuroinflammation; enhanced NLRP3 activation; neurodegeneration	Zhang et al., 2022
Cerebral ischemia-reperfusion	miR-223-3p	Downregulated (protective when restored)	Direct targeting of NLRP3, CASP1, GSDMD	Middle cerebral artery occlusion rat model	Inhibited neuronal pyroptosis; reduced infarct volume; improved neurological function	Gui et al., 2023
Cerebral ischemia-reperfusion	miR-223	Downregulated (protective when restored by electroacupuncture)	Direct targeting of NLRP3	Middle cerebral artery occlusion rat model	Reduced neuroinflammation; neuroprotection; improved outcomes	Sha et al., 2019
Cerebral ischemia-reperfusion	miR-155-5p	Upregulated (pathogenic)	Suppresses DUSP14 leading to TXNIP/NLRP3 activation	Oxygen-glucose deprivation cell model; MCAO mouse model	Accelerated neuronal pyroptosis; increased inflammation; expanded infarct volume	Shi et al., 2022

NON-CODING RNA CONTROL OF NLRP3 IN CARDIOVASCULAR DISEASES

Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the arterial wall characterized by lipid accumulation, endothelial dysfunction, macrophage infiltration, and formation of atherosclerotic plaques (Libby et al., 2019). NLRP3 inflammasome activation in macrophages and endothelial cells plays a central role in atherosclerosis pathogenesis by promoting IL-1β-mediated inflammation, endothelial activation, and plaque instability (Grebe et al., 2018; Tanase et al., 2023). Oxidized low-density lipoprotein (oxLDL) and cholesterol crystals are potent activators of the NLRP3 inflammasome in atherosclerotic lesions (Duewell et al., 2010).

Non-coding RNAs regulate NLRP3 inflammasome activation in atherosclerosis through multiple mechanisms affecting endothelial cells, macrophages, and smooth muscle cells (Wang et al., 2020; Peng et al., 2022; Silva et al., 2025). MiR-223 is downregulated in atherosclerotic plaques and oxLDL-treated endothelial cells (Wang et al., 2020; Xu et al., 2020). Upregulation of miR-223 abrogates NLRP3 inflammasome-mediated pyroptosis in human vascular endothelial cells exposed to oxLDL by directly targeting NLRP3 mRNA (Wang et al., 2020). MiR-223 overexpression reduces caspase-1 activation, IL-1β secretion, and pyroptotic cell death, protecting endothelial integrity (Wang et al., 2020). Similarly, miR-223-3p inhibits oxLDL-mediated NLRP3 inflammasome activation by targeting both NLRP3 and FOXO3, a transcription factor that regulates oxidative stress responses (Xu et al., 2020). The dual targeting of NLRP3 and FOXO3 by miR-223-3p provides multilayered protection against atherosclerotic inflammation (Xu et al., 2020).

MiR-155 exhibits pro-atherogenic effects by promoting NLRP3 inflammasome activation in carotid atherosclerotic plaques (Peng et al., 2022). In apolipoprotein E-deficient (ApoE−/−) mice, a well-established atherosclerosis model, miR-155 is upregulated in atherosclerotic lesions and activates the NLRP3 inflammasome by regulating the MEK/ERK/NF-κB pathway (Peng et al., 2022). MiR-155-mediated activation of this signaling cascade enhances transcriptional priming of NLRP3 and pro-IL-1β, amplifying inflammatory responses in atherosclerotic plaques (Peng et al., 2022). Inhibition of miR-155 reduces plaque size, decreases macrophage infiltration, and improves plaque stability in ApoE−/− mice (Peng et al., 2022).

The molecular mechanisms by which microRNAs regulate NLRP3 inflammasome activation in atherosclerosis have been comprehensively reviewed, highlighting the therapeutic potential of microRNA-based interventions for modulating vascular inflammation and plaque stability (Silva et al., 2025; Song et al., 2022). Circulating microRNAs, including miR-223 and miR-155, serve as potential biomarkers for atherosclerotic disease activity and cardiovascular risk stratification (Silva et al., 2025).

Myocardial infarction and ischemia-reperfusion injury

Myocardial infarction results from coronary artery occlusion, leading to cardiomyocyte death, inflammatory responses, and adverse cardiac remodeling (Frangogiannis, 2014). Myocardial ischemia-reperfusion injury, which occurs upon restoration of blood flow following ischemia, is characterized by NLRP3 inflammasome activation in cardiomyocytes, macrophages, and endothelial cells, driving pyroptosis, inflammation, and expansion of infarct size (Toldo et al., 2018). NLRP3 inflammasome activation during reperfusion amplifies tissue damage through IL-1β production and pyroptotic cardiomyocyte death (Toldo et al., 2018).

Non-coding RNAs play critical roles in regulating NLRP3 inflammasome activation during myocardial ischemia-reperfusion injury (Yu et al., 2018; Lu et al., 2025; Rao et al., 2025). LncRNA MALAT1 is upregulated in ischemic myocardium and promotes cardiomyocyte pyroptosis by sponging miR-133, leading to de-repression of NLRP3 expression (Yu et al., 2018). The MALAT1/miR-133/NLRP3 axis amplifies inflammasome activation during reperfusion, contributing to increased infarct size and cardiac dysfunction (Yu et al., 2018). Knockdown of MALAT1 using antisense oligonucleotides reduces NLRP3 inflammasome activation, attenuates cardiomyocyte pyroptosis, and improves cardiac function following ischemia-reperfusion injury (Yu et al., 2018).

MiR-155-5p upregulation in cardiomyocytes subjected to hypoxia-reoxygenation promotes pyroptosis through SIRT1-mediated NLRP3 inflammasome activation (Lu et al., 2025). SIRT1 (sirtuin 1) is a NAD+-dependent deacetylase that regulates cellular stress responses and inflammation (Howitz et al., 2003). MiR-155-5p directly targets SIRT1 mRNA, reducing SIRT1 protein levels and enhancing NLRP3 inflammasome activation (Lu et al., 2025). Inhibition of miR-155-5p alleviates cardiomyocyte pyroptosis by restoring SIRT1 expression and suppressing NLRP3 activation, providing cardioprotection during ischemia-reperfusion injury (Lu et al., 2025). The miR-155-5p/SIRT1/NLRP3 axis represents a therapeutic target for reducing reperfusion injury (Lu et al., 2025).

The lncMEG3/miR-223/NLRP3 signaling axis plays a pivotal role in homocysteine-induced coronary microcirculatory dysfunction following myocardial infarction (Rao et al., 2025). Elevated plasma homocysteine levels, a risk factor for cardiovascular disease, upregulate lncMEG3 expression in coronary microvascular endothelial cells (Rao et al., 2025). LncMEG3 functions as a ceRNA that sequesters miR-223, leading to de-repression of NLRP3 and enhanced inflammasome activation (Rao et al., 2025). The lncMEG3/miR-223/NLRP3 axis contributes to endothelial dysfunction, microvascular obstruction, and impaired myocardial perfusion following infarction (Rao et al., 2025). Targeting this axis through lncMEG3 knockdown or miR-223 supplementation improves coronary microcirculatory function and reduces adverse cardiac remodeling (Rao et al., 2025).

Heart failure and vascular inflammation

Heart failure is a complex clinical syndrome characterized by impaired cardiac function, neurohormonal activation, and chronic inflammation (Ponikowski et al., 2016). NLRP3 inflammasome activation contributes to heart failure progression through multiple mechanisms including cardiomyocyte pyroptosis, cardiac fibrosis, and adverse remodeling (Grebe et al., 2018). Chronic NLRP3 inflammasome activation in heart failure is driven by oxidative stress, mitochondrial dysfunction, and metabolic disturbances (Grebe et al., 2018).

Non-coding RNAs regulate NLRP3 inflammasome activation in heart failure through modulation of cardiomyocyte death, fibrosis, and inflammatory signaling (Che et al., 2020; Xu et al., 2020; Xue et al., 2020). In diabetic cardiomyopathy, a major cause of heart failure in diabetic patients, lncRNA MALAT1 promotes cardiac fibrosis by regulating the miR-141/NLRP3 inflammasome axis (Che et al., 2020). MALAT1 upregulation in diabetic hearts sequesters miR-141, leading to enhanced NLRP3 expression and inflammasome-mediated fibrosis (Che et al., 2020). Melatonin treatment alleviates diabetic cardiac fibrosis by suppressing MALAT1 expression, restoring miR-141 levels, and inhibiting NLRP3 inflammasome activation (Che et al., 2020). The MALAT1/miR-141/NLRP3 axis also regulates TGF-β1/Smad signaling, a key pathway in cardiac fibrosis, highlighting the interconnection between inflammasome activation and fibrotic remodeling (Che et al., 2020).

LncRNA GAS5 exerts cardioprotective effects in diabetic cardiomyopathy by inhibiting NLRP3 inflammasome-mediated pyroptosis (Xu et al., 2020). GAS5 targets the miR-34b-3p/AHR (aryl hydrocarbon receptor) axis to suppress NLRP3 activation (Xu et al., 2020). GAS5 overexpression reduces cardiomyocyte pyroptosis, attenuates cardiac dysfunction, and improves survival in diabetic cardiomyopathy models (Xu et al., 2020). The protective effects of GAS5 are mediated through inhibition of NLRP3 inflammasome assembly and reduction of caspase-1 activation (Xu et al., 2020).

In viral myocarditis, a leading cause of inflammatory cardiomyopathy and heart failure, lncRNA MEG3 regulates macrophage polarization and inflammatory responses through the miR-223/TRAF6 axis (Xue et al., 2020). MEG3 inhibits M2 macrophage polarization by downregulating miR-223, leading to increased TRAF6 expression and activation of NF-κB signaling (Xue et al., 2020). The MEG3/miR-223/TRAF6 axis modulates the balance between pro-inflammatory M1 and anti-inflammatory M2 macrophage phenotypes, influencing myocardial inflammation and cardiac function in viral myocarditis (Xue et al., 2020).

LncRNA HOTAIR promotes endothelial pyroptosis in hyperuricemia-induced vascular inflammation by regulating the miR-22/NLRP3 axis (Chi et al., 2021). Elevated uric acid levels upregulate HOTAIR expression in endothelial cells, leading to miR-22 sequestration and NLRP3 de-repression (Chi et al., 2021). The HOTAIR/miR-22/NLRP3 axis drives endothelial pyroptosis, vascular inflammation, and endothelial dysfunction in hyperuricemia (Chi et al., 2021). Knockdown of HOTAIR or overexpression of miR-22 protects endothelial cells from uric acid-induced pyroptosis by suppressing NLRP3 inflammasome activation (Chi et al., 2021).

LncRNA NEAT1 promotes endothelial pyroptosis during hypoxia-reoxygenation injury by regulating the miR-204/BRCC3 axis (Yao et al., 2022). NEAT1 upregulation in hypoxic endothelial cells sequesters miR-204, leading to increased expression of BRCC3 (BRCA1/BRCA2-containing complex subunit 3), a deubiquitinase that stabilizes NLRP3 protein (Yao et al., 2022). Inhibition of NEAT1 protects endothelial cells from hypoxia-reoxygenation-induced NLRP3 inflammasome activation and pyroptosis by restoring miR-204 levels and reducing BRCC3 expression (Yao et al., 2022).

Table 2. Non-coding RNAs regulating NLRP3 inflammasome signaling in cardiovascular diseases.

Disease context	Non-coding RNA	Direction of regulation	Main molecular target/pathway	Experimental model or evidence type	Functional outcome	Key reference
Atherosclerosis	miR-223	Downregulated (protective when restored)	Direct targeting of NLRP3 and FOXO3	Human endothelial cells; oxLDL treatment	Inhibited pyroptosis; reduced IL-1β secretion; endothelial protection	Wang et al., 2020; Xu et al., 2020
Atherosclerosis	miR-155	Upregulated (pathogenic)	Activates MEK/ERK/NF-κB pathway to prime NLRP3	ApoE−/− mice; carotid atherosclerotic plaques	Enhanced inflammasome activation; increased plaque inflammation; plaque instability	Peng et al., 2022
Myocardial ischemia-reperfusion	lncRNA MALAT1	Upregulated (pathogenic)	Sponges miR-133 to de-repress NLRP3	Rat ischemia-reperfusion model; cardiomyocyte culture	Increased cardiomyocyte pyroptosis; expanded infarct size; cardiac dysfunction	Yu et al., 2018

Myocardial hypoxia-reoxygenation	miR-155-5p	Upregulated (pathogenic)	Targets SIRT1 to activate NLRP3 inflammasome	Cardiomyocyte hypoxia-reoxygenation model	Enhanced pyroptosis; increased caspase-1 activation; cardiomyocyte death	Lu et al., 2025
Post-MI coronary microcirculatory dysfunction	lncMEG3	Upregulated (pathogenic)	Sponges miR-223 to de-repress NLRP3	Homocysteine-treated endothelial cells; MI model	Endothelial dysfunction; microvascular obstruction; impaired perfusion	Rao et al., 2025
Diabetic cardiomyopathy	lncRNA MALAT1	Upregulated (pathogenic)	Sponges miR-141 to activate NLRP3/TGF-β1 pathways	Diabetic mouse model; high glucose-treated cardiomyocytes	Cardiac fibrosis; inflammasome activation; cardiac dysfunction	Che et al., 2020
Diabetic cardiomyopathy	lncRNA GAS5	Downregulated (protective when restored)	Targets miR-34b-3p/AHR axis to suppress NLRP3	Diabetic cardiomyopathy model; high glucose treatment	Inhibited pyroptosis; reduced caspase-1 activation; cardioprotection	Xu et al., 2020
Viral myocarditis	lncRNA MEG3	Upregulated	Downregulates miR-223 to increase TRAF6/NF-κB signaling	Viral myocarditis mouse model	Inhibited M2 macrophage polarization; modulated inflammation	Xue et al., 2020
Hyperuricemia-induced endothelial injury	lncRNA HOTAIR	Upregulated (pathogenic)	Sponges miR-22 to de-repress NLRP3	Uric acid-treated endothelial cells	Enhanced endothelial pyroptosis; vascular inflammation; endothelial dysfunction	Chi et al., 2021
Hypoxia-reoxygenation endothelial injury	lncRNA NEAT1	Upregulated (pathogenic)	Sponges miR-204 to upregulate BRCC3/NLRP3	Endothelial cell hypoxia-reoxygenation model	Increased NLRP3 inflammasome activation; endothelial pyroptosis	Yao et al., 2022

THERAPEUTIC AND BIOMARKER IMPLICATIONS

The central role of non-coding RNA networks in regulating NLRP3 inflammasome activation across neurodegenerative and cardiovascular diseases provides multiple therapeutic opportunities and biomarker applications (Figure 4). The convergence of non-coding RNA dysregulation and NLRP3 inflammasome hyperactivation in diverse pathological contexts suggests that targeting these regulatory networks could yield broad therapeutic benefits (Wang et al., 2021; Hu et al., 2023).

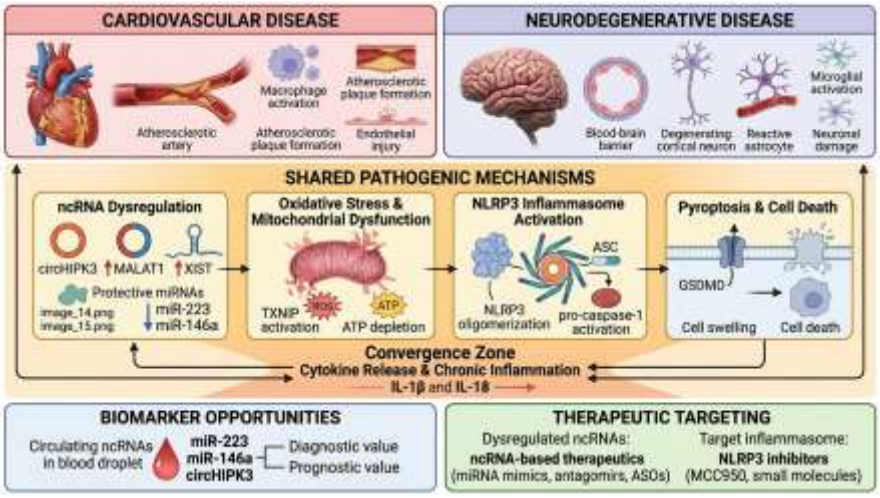

Figure 4. Translational model linking non-coding RNA-NLRP3 signaling to neurodegenerative and cardiovascular disease. This schematic illustrates the convergence of non-coding RNA (ncRNA) dysregulation and NLRP3 inflammasome activation in both neurodegenerative and cardiovascular disease pathogenesis, highlighting shared molecular mechanisms and translational opportunities. In neurodegenerative diseases (left pathway, purple/blue), pathological protein aggregates (amyloid-β in Alzheimer disease, α-synuclein in Parkinson disease) and cerebral ischemia trigger microglial activation and neuroinflammation. Dysregulated ncRNAs (upregulation of circHIPK3, MALAT1, HOTAIR, NEAT1, XIST; downregulation of miR-223, miR-146a, miR-124) promote NLRP3 inflammasome activation in microglia and neurons, leading to enhanced production of interleukin-1β (IL-1β) and interleukin-18 (IL-18), neuronal pyroptosis, synaptic dysfunction, and progressive neurodegeneration. In cardiovascular diseases (right pathway, red/pink), metabolic stressors (oxidized LDL, cholesterol crystals, hyperglycemia, hypoxia) trigger macrophage activation and endothelial inflammation. Similar ncRNA dysregulation patterns promote NLRP3 inflammasome activation in macrophages, endothelial cells, and cardiomyocytes, driving IL-1β and IL-18 secretion, pyroptotic cell death, atherosclerotic plaque formation, myocardial infarction, and heart failure. Both disease pathways converge on shared pathogenic mechanisms (center, orange/yellow): ncRNA dysregulation, oxidative stress and mitochondrial dysfunction, NLRP3 inflammasome assembly and activation, caspase-1-mediated pyroptosis, and chronic inflammatory cytokine production. These shared mechanisms create positive feedback loops that amplify and sustain inflammation. The translational implications section (bottom, green) highlights therapeutic targeting opportunities including ncRNA-based therapeutics (microRNA mimics to restore protective miRNAs such as miR-223 and miR-146a; antagomirs to inhibit pathogenic miRNAs such as miR-155; antisense oligonucleotides (ASOs) to suppress pathogenic lncRNAs such as MALAT1, HOTAIR, and NEAT1) and NLRP3 inhibitors (small molecule inhibitors such as MCC950 that directly block NLRP3 inflammasome assembly). Biomarker opportunities include circulating ncRNAs (plasma/serum levels of miR-223, miR-146a, miR-155, lncRNA MALAT1, lncRNA HOTAIR) for diagnostic, prognostic, and therapeutic monitoring applications. The parallel disease pathways, shared molecular mechanisms, and common therapeutic targets underscore the translational potential of modulating ncRNA-NLRP3 networks for treating chronic inflammatory diseases across multiple organ systems.

MicroRNA-based therapeutics represent a promising approach for modulating NLRP3 inflammasome activation (Rupaimoole and Slack, 2017). MicroRNA mimics, which are synthetic double-stranded RNA molecules that recapitulate endogenous microRNA function, can restore expression of protective microRNAs such as miR-223 and miR-146a that are downregulated in disease states (Saresella et al., 2020; Hou et al., 2021). Conversely, microRNA inhibitors (antagomirs) can suppress pathogenic microRNAs such as miR-155 that promote NLRP3 inflammasome activation (Peng et al., 2022; Lu et al., 2025). Chemical modifications including 2'-O-methyl, 2'-fluoro, and phosphorothioate linkages enhance microRNA therapeutic stability, cellular uptake, and target engagement while reducing off-target effects and immunogenicity (Rupaimoole and Slack, 2017).

Long non-coding RNA-targeted therapeutics, particularly antisense oligonucleotides (ASOs), provide opportunities to suppress pathogenic lncRNAs that amplify NLRP3 inflammasome signaling (Bennett and Swayze, 2010). ASOs are short single-stranded DNA molecules that hybridize to target lncRNAs, recruiting RNase H to degrade the lncRNA or blocking its function through steric hindrance (Bennett and Swayze, 2010). ASO-mediated knockdown of MALAT1, HOTAIR, and NEAT1 has demonstrated efficacy in reducing NLRP3 inflammasome activation and improving disease outcomes in preclinical models of cardiovascular and neurodegenerative diseases (Yu et al., 2018; Zhang et al., 2022; Singh et al., 2024). GapmeR ASOs, which contain a central DNA gap flanked by modified RNA wings, exhibit enhanced potency and specificity for lncRNA targeting (Stein et al., 2010).

Small molecule NLRP3 inhibitors represent an alternative or complementary therapeutic approach to non-coding RNA-based interventions (Coll et al., 2015). MCC950 is a potent and selective small molecule inhibitor of NLRP3 that directly binds NLRP3 to prevent inflammasome assembly (Coll et al., 2015). MCC950 has demonstrated efficacy in preclinical models of neurodegenerative and cardiovascular diseases, reducing IL-1β production, attenuating pyroptosis, and improving functional outcomes (Coll et al., 2015; van Hout et al., 2017). Combination therapies targeting both non-coding RNA networks and NLRP3 protein may provide synergistic therapeutic benefits by addressing multiple regulatory nodes simultaneously (Wang et al., 2021).

Circulating non-coding RNAs serve as accessible biomarkers for disease diagnosis, prognosis, and therapeutic monitoring (Condorelli et al., 2014). MicroRNAs are remarkably stable in blood due to packaging in extracellular vesicles or association with RNA-binding proteins, and their expression profiles reflect tissue-specific pathological processes (Mitchell et al., 2008). Circulating miR-223, miR-146a, and miR-155 levels correlate with disease activity, inflammatory burden, and clinical outcomes in neurodegenerative and cardiovascular diseases (Saresella et al., 2020; Silva et al., 2025). Long non-coding RNAs including MALAT1 and HOTAIR are also detectable in circulation and show promise as biomarkers for cardiovascular disease and neurodegeneration (Che et al., 2020; Zhang et al., 2022). Circular RNAs, due to their exceptional stability conferred by covalent closure, represent particularly attractive biomarker candidates (Kristensen et al., 2019). Longitudinal monitoring of circulating non-coding RNAs could enable early disease detection, risk stratification, and assessment of therapeutic responses to NLRP3-targeted interventions (Condorelli et al., 2014; Silva et al., 2025).

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite significant advances in understanding non-coding RNA regulation of NLRP3 inflammasome activation, several critical knowledge gaps remain that warrant future investigation. First, the cell-type-specific and context-dependent functions of non-coding RNAs in regulating NLRP3 signaling require further elucidation (Wang et al., 2021). Many non-coding RNAs exhibit opposing effects in different cell types or disease contexts, as exemplified by miR-155 promoting inflammation in atherosclerosis while exhibiting complex effects in ischemia-reperfusion injury (Peng et al., 2022; Lu et al., 2025). Single-cell RNA sequencing and spatial transcriptomics approaches will be essential for dissecting cell-type-specific non-coding RNA-NLRP3 regulatory networks in diseased tissues (Liang et al., 2022).

Second, the temporal dynamics of non-coding RNA expression and NLRP3 inflammasome activation during disease progression remain poorly characterized (Hu et al., 2023). Longitudinal studies examining non-coding RNA profiles at different disease stages are needed to identify critical windows for therapeutic intervention and to understand how non-coding RNA networks evolve as diseases progress from acute to chronic phases (Song et al., 2022). Time-resolved transcriptomic analyses in preclinical models could reveal stage-specific regulatory mechanisms and therapeutic targets (Liang et al., 2022).

Third, the mechanistic details of competing endogenous RNA networks involving lncRNAs, circRNAs, and microRNAs in NLRP3 regulation require further investigation (Hu et al., 2023). While numerous lncRNA-miRNA-NLRP3 axes have been identified, the stoichiometric requirements, subcellular localization, and quantitative contributions of individual ceRNA interactions to overall NLRP3 regulation remain incompletely understood (Kopp and Mendell, 2018). Genome editing approaches to disrupt specific miRNA binding sites in lncRNAs and circRNAs will be valuable for validating ceRNA mechanisms and determining their functional significance (Thomson and Dinger, 2016).

Fourth, the translational potential of non-coding RNA biomarkers for clinical applications requires rigorous validation in large, well-characterized patient cohorts (Condorelli et al., 2014). Most studies to date have examined circulating non-coding RNA profiles in relatively small patient populations, and standardized protocols for sample collection, processing, and analysis are needed to ensure reproducibility across studies (Silva et al., 2025). Multicenter prospective studies with standardized methodologies will be essential for establishing the clinical utility of circulating non-coding RNAs as biomarkers for neurodegenerative and cardiovascular diseases (Condorelli et al., 2014).

Fifth, the development of safe and effective delivery systems for non-coding RNA therapeutics remains a major challenge (Rupaimoole and Slack, 2017). While lipid nanoparticles, exosomes, and conjugate delivery approaches have shown promise in preclinical studies, achieving tissue-specific and cell-type-specific delivery of microRNA mimics, antagomirs, and antisense oligonucleotides to diseased tissues in humans remains technically challenging (Bennett and Swayze, 2010). Advances in delivery technologies, including brain-penetrant nanoparticles for neurodegenerative diseases and cardiac-targeted delivery systems for cardiovascular diseases, will be critical for translating non-coding RNA therapeutics to clinical applications (Rupaimoole and Slack, 2017).

Sixth, potential off-target effects and unintended consequences of modulating non-coding RNA networks require careful evaluation (Thomson and Dinger, 2016). MicroRNAs typically regulate hundreds of target mRNAs, and lncRNAs participate in complex regulatory networks affecting multiple cellular processes (Bartel, 2018; Kopp and Mendell, 2018). Comprehensive transcriptomic and proteomic analyses are needed to assess the broader impact of non-coding RNA therapeutics on cellular phenotypes and to identify potential adverse effects (Thomson and Dinger,

2016). Conditional and inducible genetic models will be valuable for determining the consequences of long-term non-coding RNA modulation in vivo (Wang et al., 2021).
Finally, the integration of non-coding RNA-targeted therapies with existing and emerging treatments for neurodegenerative and cardiovascular diseases requires systematic investigation (Liang et al., 2022; Tanase et al., 2023). Combination therapies targeting non-coding RNAs, NLRP3 protein, and upstream or downstream inflammatory pathways may provide synergistic benefits (Wang et al., 2021). Preclinical studies evaluating combination regimens and identifying optimal therapeutic windows will be essential for maximizing therapeutic efficacy while minimizing adverse effects (Grebe et al., 2018).

CONCLUSION

Non-coding RNAs, including microRNAs, long non-coding RNAs, and circular RNAs, function as master regulators of NLRP3 inflammasome activation in both neurodegenerative and cardiovascular diseases. These non-coding RNA networks modulate NLRP3 signaling through direct targeting of inflammasome components, regulation of upstream activators including NF-κB and oxidative stress pathways, and competing endogenous RNA mechanisms that fine-tune inflammatory responses. Dysregulation of protective microRNAs such as miR-223 and miR-146a, combined with upregulation of pathogenic long non-coding RNAs such as MALAT1, HOTAIR, and NEAT1, amplifies NLRP3 inflammasome activation, driving chronic inflammation, pyroptosis, and tissue damage in Alzheimer disease, Parkinson disease, stroke, atherosclerosis, myocardial infarction, and heart failure. The convergence of non-coding RNA dysregulation and NLRP3 inflammasome hyperactivation across diverse disease contexts highlights shared molecular mechanisms and provides multiple therapeutic opportunities. MicroRNA mimics, antagomirs, and antisense oligonucleotides targeting pathogenic lncRNAs represent promising therapeutic modalities for modulating NLRP3-driven inflammation. Circulating non-coding RNAs offer accessible biomarkers for disease diagnosis, risk stratification, and therapeutic monitoring. Future research addressing cell-type-specific regulatory mechanisms, temporal dynamics of non-coding RNA expression, delivery system optimization, and integration with existing therapies will be essential for translating these insights into precision medicine approaches for chronic inflammatory diseases. Understanding and harnessing non-coding RNA networks that govern NLRP3 inflammasome activation holds significant promise for developing novel therapeutic strategies to combat neurodegenerative and cardiovascular diseases.

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