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REVIEW

Novel Insights into the Emerging Role of Neat1 and Its Effects Downstream in the Regulation of Inflammation

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Abstract: Nuclear paraspeckle assembly transcript 1 (Neat1) located at chromosome 11 is a long non-coding RNA that is widely expressed in mammalian cell types, and which is overexpressed in several inflammation-related disorders. Inflammation implies a plethora of mutual interactions between both soluble factors and cells due to various stimuli including tissue injury. Although there is no doubt that inflammation is critically involved in multiple biological and pathological processes alike, the precise mechanisms being involved are still open for debate. In this context, the role of Neat1 as a regulator of inflammation, microglial activation, and lipid accumulation under various inflammatory conditions remains elusive. Herein, we review the regulation of Neat1 and how it modulates the expression of its target genes. Thereafter, we will review the impact of Neat1 on inflammation by activating or inhibiting various signaling pathways, such as microRNAs, AKT, TLR4, TRAF6, and NF-κB.

Keywords: Neat1, inflammation, microglia, lipids, microRNA, NF-κB

Introduction

Inflammation is an adaptive pathological response initiated after bacterial or viral infection,[1,2] and it is a normal defense mechanism that the body uses to protect itself from tissue injury. In response to these stimuli, immune cells migrate to the site of infection and/or injury prompting tissue repair/wound healing.[3] Thus, it is necessary to understand the mechanisms under the inflammation so that we can seek effective anti-inflammatory resolutions.[4] However, up to now, our understanding of inflammation is largely based on the central dogma of molecular biology.[5] Long non-coding RNAs (lncRNAs) are defined as a class of RNA transcripts with a length of longer than 200 nucleotides, by far the largest fraction of non-coding transcripts,[6,7] which can be transcribed from different genomic regions including intergenic regions, mitochondrial regions, specific chromosomal regions, and intergenic.[8,9] Nuclear paraspeckle assembly transcript 1 (Neat1), a nuclear lncRNAs, a vital component of paraspeckles, plays critical roles in multiple cellular physiology and pathophysiology,[10,11] such as the innate immune reaction,[12] organ development,[13,14] cancer[15–17] and neurodegenerative diseases.[18–21] There are two isoform transcripts of Neat1, Neat1_1 (3.7 kb) and Neat1_2 (23 kb), respectively, both of which are localized to nuclear paraspeckles.[22] Paraspeckles are a type of subnuclear body built on the Neat1 and enriched

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with various proteins, RNAs, which are involved in regulating gene expression by a process called nuclear retention.[23] Accumulating evidence has shown that Neat1is dysregulated during the progression of a variety of diseases. For example, Zhou et al and Zhang et al found that Neat1 is aberrantly expressed in glioma and colorectal cancer, while its expression is closely related to tumor cell viability, migration, and invasion, as well as for the overall patient survival.[24,25] Neat1 dysregulation has also been shown to be involved in non-cancerous diseases, for instance, Huntington's Disease (HD), Parkinson's disease (PD), multiple sclerosis and Hantavirus infection.[26] Sunwoo et al identified upregulation of Neat1 in the human HD brain and revealed the neuroprotective function without the precise mechanism in HD pathogenesis.[20] Likewise, 1-Methyl-4-phenylpyridinium (MPP+) induced PD was protected by the knockdown of Neat1, and the protect mechanism might relate to α-synuclein expression.[27] Notably, the role and mechanism of Neat1 in disorders related to the inflammatory cytokines and mediators are poorly understood and have not been systematically reviewed. Herein, in this study, we discuss and summarize the function and mechanism of Neat1 specific to inflammation and propose potential signaling pathways.

The Course of Inflammation

Inflammation is programmed progress initiated to protect tissue from injury stimuli, which can cause the release of pathogen or danger-associated molecular patterns (PAMP), and promote tissue recovery via suppressing bacteria, viruses, toxins, and infections by fighting pathogens.[28–30] Inflammatory responses have the potential to initially inhibit the release of inflammatory mediators, which appear when with an insult and elapse once the injury is eliminated.[30,31] Upon the initial stage of the inflammatory response, PAMPs can be identified by macrophages or mast cells, which in turn promote the release of a pro-inflammation-related mediator such as cytokines, chemokines, and eicosanoids, therefore, enhancing vascular permeability and activating the immune response.[1,31,32] Besides that, the neutrophils and monocytes immediately move to the lesion region by a series of pathways and molecules like cytokines and adhesion molecules.[32] With the signs of progress of inflammation, monocytes and lymphocytes are recruited and migrate to the lesion site to eliminate the harmful substances, which are finally cleared by macrophages through the cell apoptosis pathway.[31] When it comes to the final stage of inflammation, the inflammatory process is replaced by the tissue repair process. In addition, inflammatory reaction normally involves the rapid induction of pro-inflammatory response, closely followed by an anti-inflammatory process.[33] To regain homeostasis, resolution of inflammation represents a turning point, since the progression from acute-resolving to persistent-chronic inflammation can appear due to a failure in resolving inflammatory processes.[33] Herein, for the sake of promoting tissue to restore homeostasis, the inflammatory reaction must be immediately inhibited to prevent the organ from further damage,[31] and a great deal of signal pathways is included in the inflammatory process, providing novel insight into the treatment of inflammation-related disorders.

The Course of Neat1

Although ncRNAs do not encode for proteins, they participate in various biological processes and thus play a vital role in transcriptional and post-transcriptional modulation.[34,35] They can be divided into two categories according to the length of the RNA chain, involving lncRNA with lengths of more than 200 nucleotides and small ncRNAs with lengths of less than 200 nucleotides.[35,36] Discovered in 2007 by Hutchinson et al,[37] Neat1 lncRNA is—as indicated in the name, nuclear enriched abundant transcript— one of the most abundant lncRNAs localized within paraspeckles in the mammalian nucleus and abundantly expressed in a variety of cell types.[38–40] Additionally, it is suggested that Neat1 can target numerous genomic regions in various cells, mainly involving active genes, revealing that it is a regulator for plenty of active genes and signal pathways.[41] Structured illumination microscopy detecting RNA and protein components of paraspeckles simultaneously revealed the structural arrangement of Neat1 within paraspeckles; that is, the paraspeckle compositions are located at the core-shell spheroidal structure; however, Neat1', 5' and 3' ends are in paraspeckle around, and the central sequence is present at the core site.[42,43] Paraspeckle is a complex consisting of subnuclear ribonucleoprotein within interchromatin, which plays a vital role in modulating transcription and RNA processing mainly via regulating RNA and protein editing and serving as a sponge targeting to various microRNAs.[19] There are two subtypes of mono-exonic isoforms transcribed from the Neat1 locus from chromosome 11, known as shorter Neat1_1 with 3684 nucleotides and longer Neat1_2 with 22,743 nucleotides.[19,44] The shorter Neat1_1 isoform (3.7 kb in human)

is polyadenylated,[23] whereas the longer 23 kb subtype of Neat1_2 is not polyadenylated. Neat1_1 is high abundance and exhibits a high expression in a wide range of tissues.[19] Nonetheless, in contrast to the Neat1_2 isoform, the shorter Neat1_1 isoform has no an integral element of paraspeckles; however, it appears as microspeckles and thus may contain other effects that have not been discovered.[43] Additionally, Sasaki et al[45] indicated that the knockdown of the production of Neat1_2 can lead to paraspeckle elimination even in the presence of intact Neat1_1. Likewise, Neat1_2 defect female mice have a loss function of reproductive tissue development; however, no external or histological abnormalities are observed in Neat1_1 knockout mouse.[13,46]

NEAT1 Directly Regulates Inflammation in the Central Nervous System

Inflammatory response, in the central nervous system (CNS), is generally recognized as an essential component of the CNS to restrain abnormal protein aggregates, infection, ischemia, and toxins.[47,48] Neat1 has been identified as dysregulated in cell growth, differentiation, apoptosis, cells migration, metastasis, and invasion in neurological disorders,[26,49] where regulation of inflammation plays a vital role. Although the fundamental role of Neat1 in terms of inflammation in CNS is becoming increasingly evident,[50,51] it is urgent to summarize the inflammatory effect of Neat1 upon inflammatory conditions of the CNS owing to diverse interaction pathways in various neurological disorders with disparate efficiency. The electronic databases, including Cochrane Library, Medline, PubMed, Embase, ScienceDirect, and other databases were retrieved to identify the literature exploring the regulation of Neat1 on inflammation upon various neurological diseases from the inception of electronic databases to September 2021. We retrieved studies using the following keywords in accordance with Boolean logic: ("Neat1" OR "nuclear paraspeckle assembly transcript 1") AND ("inflammatory" OR "inflammation" OR "microglia"). Beyond this, research on the appraisal reference list was manually checked to determine other potential qualification trials that may have been missed by the database searches. The process was iterated until no more publications would be obtained. A total of 15 publications were identified in this section,[50–64] which were performed between 2017 and 2021. The most widely used species and related inflammatory models are mice and middle cerebral artery occlusion (MCAO), respectively. The most common identification method and inflammatory markers are quantitative real-time polymerase chain reaction and interleukin, respectively. Of these 15 studies, 5 on stroke, 6 on PD, 2 on spinal cord injury (SCI), and 1 on traumatic brain injury with the last one on epilepsy study, suggesting that it is sufficient to illustrate that Neat1 can modulate inflammation in the CNS disorders. Up on stroke condition, an upregulation of Neat1 was uncovered in ischemic stroke patients' blood,[61] animals with an MCAO,[60] and in vitro cells with hypoxia.[50] Similarly, the upregulation of Neat1 has a detrimental effect and accelerates disease progression in PD via regulating inflammation.[19] Moreover, the knockdown of Neat1 could inhibit microglia polarization towards the M1 phenotype in various neurological disorders.[62] Nevertheless, concerning the differences between diseases (dosage and delivery time), the studies used heterogeneous experimental paradigms meeting their own applied study purposes. More details are shown in Table 1.

Neat1 Directly Regulates Inflammation in the Peripheral System

Peripheral inflammation is a non-specific, adaptive response to infections or noxious stimuli aiming to limit injury and enhance recovery.[65] Systemic inflammation is characterized by an up-regulated expression of circulating cytokines, chemokines, and acute-phase proteins, as can be seen in multiple chronic disorders, such as obesity, diabetes, and metabolic syndrome, can lead to serious health risks.[66] It is of interest that peripheral inflammatory stimuli that circulate in the blood may lead to the release of cytokines in the CNS mainly via regulating the integrity of the blood–brain barrier and activation of microglia,[67,68] suggesting that peripheral and central inflammation can be mutually modulated.[65] Indeed, Neat1 can regulate inflammation in CNS; therefore, the effect of Neat1 on peripheral inflammation deserves more attention. The aforementioned literature search strategy with the keywords of "Neat1" OR "nuclear paraspeckle assembly transcript 1" was also applied in this section and yielded a total of 53 studies,[69–121] suggesting broad regulatory effect of Neat1 on peripheral inflammation. Sepsis is a systemic inflammatory response syndrome triggered by infection, with a global incidence of approximately 437 per 100,000 person-years.[70] Ten of these included studies, respectively, demonstrated that circulating Neat1 correlated with an increased risk of sepsis, elevated severity, and unfavorable prognosis, as well as higher expression of pro-inflammatory cytokines in sepsis patients, and knockdown of Neat1

Table 1 Preclinical and Clinical Studies Assessing the Effect of NEAT1 on the Regulation of Inflammation in Central Nervous System

Author, Year	Disease's Type	Diseases Model	Organism	Expression	Identify	Inflammatory Marker	Mechanism	Ref.
Han et al 2019	Stroke	OGD/R	Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	Wnt/β-catenin	[50]
Li et al 2020	Stroke	Patients	Human	Up	qRT-PCR	TNF-α, IL-1β, 6, 8, 10, 17, 22	miR-124, miR-125a	[61]
Ni et al 2020	Stroke	Patients, OGD/R	Human, Cells	Up	qRT-PCR	NA	AKT/STAT3	[62]
Zhang et al 2021	Stroke	MCAO, OGD/R	Rats, Cells	Up	qRT-PCR	IL-1β, 18	miR-22-3p	[59]
Jin et al 2021	Stroke	MCAO	Mice	Up	qRT-PCR	TNF-α, IL-1β, 6, NF-κB	NA	[60]
Ban et al 2020	SCI	LPS treat	Cells	Up	qRT-PCR	IL-1β, 6, 10, TNF-α	miR-29a/BCL2L11	[57]
An et al 2021	SCI	LPS treat	Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	miR-211-5p/MAPK1	[58]
Xie et al 2019	PD	MPP^+ treat	Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	miR-124	[54]
Zhou et al 2020	PD	MPP^+ treat	Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	miR-1277-5p/ ARHGAP26	[55]
Liu et al 2020	PD	MPTP, MPP^+ treat	Mice, Cells	Up	qRT-PCR	IL-1β, 6	miR-212-3p/AXIN1	[56]
Liu et al 2020	PD	MPP^+ treat	Cells	Up	qRT-PCR	IL-1β, TNF-α	miR-212- 5p/RAB3IP	[51]
Chen et al 2021	PD	MPP^+ treat	Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	miR-124-3p/PDE4B/ mTOR	[52]
Sun et al 2021	PD	MPP^+ treat	Cells	Up	qRT-PCR	IL-1β	miR-1301-3p	[53]
Zhong et al 2017	TBI	OGD/R, ICVI AVV	Mice, Cells	Up	ChIP-qPCR	IL-1, TNF-α	Pidd1	[63]
Wan et al 2020	Epilepsy	Patients, IL-1β treat	Human, Cells	Up	qRT-PCR	IL-1β, 6, TNF-α	miR-129-5p/notch	[64]

Abbreviations: NA, not available; qRT-PCR, quantitative real-time polymerase chain reaction; IL, interleukin; TNF, tumor necrosis factor; OGD/R, oxygen-glucose deprivation/re-oxygenation; MCAO, middle cerebral artery occlusion; AIS, acute ischemic stroke; AKT, protein kinase B; STAT3, signal Transducer And Activator Of Transcription 3; NF-κB, nuclear factor-κB; SCI, spinal cord injury; LPS, lipopolysaccharides; BCL2L11, Bcl-2-like protein 11; MAPK1, mitogen-activated protein kinase 1; PD, Parkinson's disease; AXIN1, axis inhibition protein 1; MPTP, 1-methyl- 4-phenyl-1, 2, 3, 6-tetrahydropyridine injection; MPP^+, 1-methyl- 4-phenyl pyridine; RAB3IP, RAB3A-interacting protein; PDE4B, phosphodiesterase 4B; mTOR, mechanistic target of rapamycin; TBI, traumatic brain injury; ICVI, intracerebroventricular injection; AVV, adenovirus; ChIP-qPCR, chromatin immunoprecipitation polymerase chain reaction; Pidd1, p53-induced death domain-containing protein 1.

promoted viability and reduced the expression of inflammatory cytokines in lipopolysaccharide (LPS)-induced cells.[69–78] Additionally, inflammation is a vital driver of atherosclerosis and myocardial infarction, and besides various proteins and microRNAs, Neat1 has been involved in inflammation regulation.[79–85] Fu et al,[83] Chen et al,[84] and Wang et al[85] indicated that silencing of Neat1 can suppress lipid uptake inflammation-related molecules including interleukin (IL)-6, reactive oxygen species, IL-1β, and tumor necrosis factor (TNF)-α. Meanwhile, Gast et al[79] applied a Neat1 -/- mice and showed the first direct illustration that Neat1 was involved in the regulation of T cell and monocyte-macrophage lineage differentiation and functions via serving as a novel lncRNA-type immunoregulator in myocardial infarction. The characters and primary mechanism of some of these studies are summarized in Table 2, demonstrating Neat1 may offer a promising strategy to treat the disorders with peripheral inflammation.

Table 2 Preclinical and Clinical Studies Assessing the Effect of NEAT1 on the Regulation of Inflammation in Peripheral System

Author, Year	Diseases	Model	Organism	Expression	Identification	Inflammatory	Main Action	Ref.
					Method	Marker	Mechanism	
Xia et al 2020	Sepsis	LPS	Mice, Cells	Up	qRT-PCR	TNF-α, IL-6, 10, MCP-1	miR-211/PI3K/AKT	[69]
He et al 2019	Sepsis	Patients	Human	Up	qRT-PCR	TNF-α, IL-1β, 6, 17	miR-124	[71]
Huang et al 2018	Sepsis	Patients	Human	Up	qRT-PCR	CRP, TNF-α, IL-1β, 6, 8, 10	NA	[70]
Chen et al 2019	Sepsis	CLP	Mice	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-125/MCEMP1	[72]
Liu et al 2020	Sepsis	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 9	miR-590-3p	[74]
Wu et al 2020	Sepsis	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8	miR-370-3p/TSP-1	[76]
Xiao et al 2020	Sepsis	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8	miR-370-3p/Irak2	[77]
Yang et al 2021	Sepsis	LPS	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-31-5p/ POU2F1	[78]
Li et al 2020	Sepsis	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-17-5p/TLR4	[73]
Wang et al 2020	Sepsis	LPS	Cells	Up	qRT-PCR	TNF-α, IL-1β, 4, 6, 10	miR-125a-5p/ TRAF6/ TAK1	[75]
Chen et al 2020	MI	As_2O_3	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-124/NF-κB	[80]
Gast et al 2019	MI	Patients, LPS	Human, Mice, Cells	Up	RNA-sequencing	TNF-α, IL-6, 10, IFN-γ,	NA	[79]
Wang et al 2019	MI	LPS	Mice	Up	qRT-PCR	TNF-α, IL-1, 6, MCP1	TLR2/NF-κB	[81]
Wei et al 2020	MI	LPS	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-144-3p	[82]
Liu et al 2019	OA	Patients	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8	miR-193a-3p/SOX5	[105]
Wang et al 2019	OA	Patients	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8, COX-2	miR-181a/GPD1L	[106]
Tu et al 2019	OA	Patients, IL-1β	Human, Cells	Up	qRT-PCR	IL-1β	miR-377-3p/ITGA6	[107]
Wang et al 2017	OA	Patients	Human, Cells	Up	qRT-PCR	IL-6, 8	miR-181c	[110]
Huang-Fu et al 2018	AS	ox-LDL	Cells	Up	qRT-PCR	NF-κB	CD36, p65	[83]
Chen et al 2018	AS	ox-LDL	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-128	[84]
Wang et al 2018	AS	ox-LDL	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, COX-2	miR-342-3p	[85]
Guo et al 2019	AS	Patients, ox-LDL	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-30c-5p/TCF7	[91]
Feng et al 2020	AKI	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8	miR-22-3p	[93]
Gao et al 2020	AKI	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	let-7b-5p/TRAF6	[102]
Wang et al 2020	AKI	Sepsis-induced AKI, LPS	Rats, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-27a-3p/TAB3	[94]
Wang et al 2018	IBD	Acute colitis	Mice	Up	Bioinformatics	TNF-α, IL-7, 12a, 17a	miR204-5p-PI3K-AKT	[89]
Liu et al 2018	IBD	5% DSS	Mice, Rats, Cells	Up	qRT-PCR	TNF-α, IL-23	Polarization of macrophages	[90]

(*Continued*)

Table 2 (Continued).

Author, Year	Diseases	Model	Organism	Expression	Identification	Inflammatory	Main Action	Ref.
					Method	Marker	Mechanism	
Pan et al 2021	IBD	Patients, DSS, TNF-α	Human, Mice, Cells	Up	qRT-PCR	IL-8, TNF-α, MCP1	TNFSF1B	[112]
Zhou et al 2020	ALI	Sepsis-evoked ALI, LPS	Mice, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	HMGB1-RAGE	[86]
Chen et al 2020	ALI	LPS	Mice, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-944/TRIM37	[101]
Zhang et al 2019	ALI	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	Let-7a/TLR4	[95]
Li et al 2019	Asthma	Patients	Human	Up	qRT-PCR	TNF-α, IL-1β, 6, 17	miR-124	[87]
Wang et al 2021	Asthma	PDGF	Cells	Up	qRT-PCR	IL-4, 6, 13	MiR-9-5p/SLC26A2	[88]
Zhang et al 2016	SLE	Patients, LPS	Human, Cells	Up	qRT-PCR	TNF-α, IL-6	MAPK	[103]
Zhang et al 2019	SLE	LPS	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, IFN-γ	miR-146b/TRAF6/NF-κB	[104]
Wang et al 2020	RA	Patients, TNF-α	Human, Cells	Up	qRT-PCR	TNF-α	miR-410-3p/YY1	[119]
Rao et al 2021	RA	Bovine type II collagen	Mice, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-23a/MDM2/SIRT6	[120]
Shao et al 2020	DR	Patients, diabetic animal	Human, Rats, Cells	Up	qRT-PCR	COX-2, TNF-α, IL-6	TGF-β1, VEGF	[92]
Li et al 2020	Renal fibrosis	UUO, TGF-β1	Mice, Cells	Up	qRT-PCR	IL-1β, 6	miR-129	[111]
Jin et al 2019	NAFLD	Free fatty acid	Cells	Up	qRT-PCR	TNF-α, MCP1, IL-1β, 6	miR-506/GLI3	[96]
Ye et al 2020	ASH	Patients	Human, Mice, Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-129-5p/SOCS2	[97]
Wang et al 2021	ALF	Patients, D-galactosamine	Human, Mice	Up	qRT-PCR	TNF-α, IL-1β, 6	miR-139/PUMA	[98]
Xu et al 2019	ACLF	Patients, LPS	Human, Rats, Cells	Up	qRT-PCR	IL-1, 6, 22	TRAF6	[99]
Zhang et al 2021	NASH	MCD diet	Mice, Cells	Up	qRT-PCR	NF-κB	miR-129-5p/PEG3	[100]
Sun et al 2020	TB	Patients, H37Ra	Human, Cells	Up	qRT-PCR	TNF-α, IL-6, IFN-γ	miR-377–3p	[114]
Sheng et al 2020	AP	Caerulein	Mice, Cells	Up	qRT-PCR	TNF-α, IL-6, 10	miR-216b/MAP2K6	[108]
Zhu et al 2021	CSF	Patients, OGD	Human, Cells	Up	qRT-PCR	TNF-α, IL-6, sICAM-1	miR-148b-3p/ICAM-1	[109]
Wang et al 2018	HCC	Transfection	Cells	Up	qRT-PCR	IL-6	IL-6/STAT3	[113]
Wang et al 2021	I/R	I/R	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6	NA	[115]
Wang et al 2021	AR	Patients	Human	Up	qRT-PCR	IL-4, 6, 10, 17	miR-21, 124, 125a	[116]
Nong et al 2019	Pneumonia	LPS	Cells	Up	qRT-PCR	TNF-α, IL-1β, 6, 8	miR-193a-3p/TLR4/NF-κB	[117]

(*Continued*)

Table 2 (Continued).

Author, Year	Diseases	Model	Organism	Expression	Identification	Inflammatory	Main Action	Ref.
					Method	Marker	Mechanism	
Dai et al 2021	Bone	LPS	Cells	Up	qRT-PCR	IL-1β, 6	NLRP3 inflammasome	[118]
Zhan et al 2020	DN	STZ, HG	Rats, Cells	Up	qRT-PCR	IL-1β	miR-34c/NLRP3	[121]

Abbreviations: NA, not available; qRT-PCR, quantitative real-time polymerase chain reaction; IL, interleukin; TNF, tumor necrosis factor; PDGF, platelet-derived growth factor; IBD, inflammatory bowel disease; AS, atherosclerosis; MCP-1, monocyte chemoattractant protein-1; DSS, dextran sulfate sodium; HUVECs, human umbilical vein endothelial cells; ox-LDL, oxidized low-density lipoprotein; TCF7, transcription factor 7; UUO, unilateral ureteral obstruction; CRP, C-reactive protein; MCEMP1, mast cell expression membrane protein 1; CLP, cecal ligation and puncture; TSP-1, thrombospondin-1; Irak2, interleukin 1 receptor associated kinase 2; POU2F1, POU domain class 2 transcription factor 1; ALI, acute lung injury; HMGB1, high-mobility group box1; DR, diabetic retinopathy; COX-2, cyclooxygenase-2; hRECs, human retinal endothelial cells; VEGF, vascular endothelial growth factor; TGF-β1, transforming growth factor-β1; AKI, acute kidney injury; TRAF6, tumor necrosis factor receptor-associated factor 6; TLR4, toll-like receptor 4; NAFLD, non-alcoholic fatty liver disease; ASH, alcoholic steatohepatitis; SOCS2, suppressor of cytokine signaling 2; ALF, acute liver failure; PBMCs, peripheral blood mononuclear cells; PUMA, p53-upregulated modulator of apoptosis; ACLF, acute-on-chronic liver failure; PEG3, paternally expressed gene 3; NASH, non-alcoholic steatohepatitis; MCD diet, methionine choline-deficient diet; NF-κB, nuclear factor-κB; SLE, systemic lupus erythematosus; MAPK, mitogen-activated protein kinase; SLE, systemic lupus erythematosus; IFN-γ, interferon γ; TB, tuberculosis; TRAF6, TRAF6, tumor necrosis factor receptor-associated factor 6; TAK1, transforming growth factor-activated kinase 1; As_2O_3, arsenic trioxide; MI, myocardial infarction or cardiomyocyte injury; OA, osteoarthritis; SOX-5, sex-determining region Y-box protein 5; GPD1L, glycerol-3-phosphate dehydrogenase 1-like; AP, acute pancreatitis; CSF, coronary slow flow; sICAM-1, soluble intercellular adhesion molecule-1; TNFSF1B, tumor necrosis factor superfamily member 1B; HCC, hepatocellular carcinoma; STAT3, signal Transducer And Activator Of Transcription 3; I/R, ischemia/reperfusion; AR, allergic rhinitis; NLRP3, Nod-like receptor protein 3; RA, rheumatoid arthritis; YY1, Yin Yang1; MDM2, murine double minute-2; SIRT6, Sirtuin 6; DN, diabetic nephropathy; NLRP3, Nod-like receptor protein-3; STZ, streptozotocin; HG, high glucose.

Neat1 Can Regulate the Activation of Microglia

Microglia cells serve as "brain-resident macrophages" that comprise approximately 10% of all the cells in the CNS,[122] which play a key role in phagocytic elimination of influencing brain development and maintenance of the neural environment. Normally, the microglia are in the rest state to keep homeostasis in the fields around microglia cells.[123] Upon an inflammatory condition, the activation of microglia is the first step of response to inflammation, and then other immune cells like neutrophils, T cells, natural killer cells, and so on were activated in the brain.[123–125] Stimuli results in the activation of microglia, which represents the first step of an inflammatory response, followed by four distinct phenotypes, such as ramified, intermediate, amoeboid, and round phenotypes.[123,126] Based on the morphological progression and its substance secretion, microglia are characterized as M1-type and M2-type.[123] M1-type, the pro-inflammatory phenotype, produces various pro-inflammatory factors such as IL-1β, IL-6, interferon-α, motif chemokine ligand, cyclooxygenase-2, and inducible nitric oxide synthase.[123,127–130] M2, anti-inflammatory phenotype, microglia involve the states of both alternative activation and acquired deactivation, which are accompanied by IL-4/IL-13 and IL-10/transforming growth factor (TGF)-β, respectively.[123,131,132] Ni et al[62] exposed Neat1 knockdown BV-2 cells to oxygen–glucose deprivation/reoxygenation (OGD/R) and then detected the various levels of markers of M1 (CD16, CD32, and CD86) and M2 (BDNF, PDGF, and Arg-1) microglia, demonstrating that Neat1 knockdown suppresses M1microglial polarization but does not promote M2 microglial polarization. Jin et al[60] revealed that microglia had shorter ramifies and larger cell bodies after MCAO; however, the antisense oligonucleotides (ASO)-Neat1 group (Neat1 knockdown) was associated with significantly fewer activated microglia. Also, pyknotic nuclei and vacuolated cytoplasm were markedly reduced in the cortex and striatum of ASO-Neat1 mice. Similarly, Han et al[50] suggested that Yin Yang 1 (YY1)-induced upregulation of Neat1 contributed to the OGD/R injury and neuroinflammation damage to microglial cells. Neat1 knockdown might therefore contribute to suppressing microglia activation, and information regarding this aspect, however, is scarce.

Neat1 Can Regulate the Expression of Lipids

Lipids are a kind of hydrophobic or amphiphilic small molecules that are insoluble in water and soluble in nonpolar solvents.[133] They are an essential structural component of cell membranes and play a vital role in regulating important biological processes that support multiple biological functions, and dysregulation of lipid metabolism has been revealed to be involved in inflammation-related disorders, such as atherosclerosis, cancer, and neurodegenerative diseases.[134]

Since bioactive lipids emerged as vital factors during all phases of the inflammatory process, we also explored the effect of paraspeckles of Neat1 on lipid uptake. Atherosclerosis has been recognized as a chronic inflammation process induced by lipid accumulation in the vessel wall.[135] Neat1 was significantly increased in human macrophages THP-1 cells incubated with oxidized low-density lipoprotein (ox-LDL). To investigate the role of Neat1 in foam cells formation, Neat1 was downregulated in THP-1 cells by transfection of Neat1 small interfering RNA (siRNA), as demonstrated by Wang et al,[85] knockdown of Neat1 restrained CD36 protein expression, triglyceride, and oil-red staining levels, suggesting that Neat1 could modulate the formation of foam cells triggered by ox-LDL in vitro. Therein, abnormality of triglyceride metabolism is a lipid metabolism disorder and includes hypertriglyceridemia and liver triglyceride accumulation.[136] Using rapamycin after transplantation can cause hypertriglyceridemia and liver triglyceride accumulation.[137] Fan et al indicated that the down-regulation of the expression of hsa-miR-372–3p contributes to triglyceride accumulation induced by rapamycin, further using dual-luciferase reporter assay and bioinformatics to determine the relationship between hsa-miR-372–3p and Neat1.[137] In vivo, Neat1 was upregulated in non-alcoholic fatty liver disease patients, and besides that, knockdown of Neat1 can inhibit lipid accumulation in mice with a high-fat diet.[138] Although Neat1 has been illustrated to be collectively effective in regulating lipids and inflammation, information regarding this aspect is scarce. Herein, more evidence-based information is provided in this respect.

Neat1 Correlates with the Level of Inflammatory Cytokines in Clinical Studies

Liquid biopsy is a new diagnostic tool conducted on blood or other biofluids to evaluate the inflammation-derived components and their genomic or proteomic profiles. In clinical practice, it is widely accepted that Neat1 is identified as a potential contributor to the increased secretion of multiple pro-inflammatory factors in diverse inflammatory disorders.[103,139] For instance, in patients with systemic lupus erythematosus, the expression level of Neat1 is upregulated in the blood and correlates with the increased expression of pro-inflammatory chemokines and cytokines, such as IL-1β, IL-6, and CXC chemokine ligand 10 (CXCL10), exacerbating the severity of disorder.[103] In asthma, Neat1 exhibits the potential to differentiate patients with asthma or not, especially in predicting exacerbation risk and severity of asthma. Neat1 relative expression was positively correlated with TNF-α, IL-1β, and IL-17, while negatively correlated with miR-124 expression in patients with asthma in exacerbation. Interestingly, miR-124 relative expression was positively correlated with TNF-α, IL-1β, IL-17, and exacerbation severity as well.[87] Likewise, sepsis patients were associated with a higher incidence of plasma Neat1 expression than those in healthy control and further disclosed that Neat1 revealed a good predictive value for sepsis risk and was positively associated with levels of TNF-α, IL-1β, IL-6, and IL-8, while negatively correlated with level of IL-10.[74,76] Hence, Neat1 expression is aberrantly-mostly upregulated in inflammatory pathological conditions, indicating that it may serve as a potential diagnostic and prognostic biomarker to monitor disease activity and treatment outcome in multiple inflammatory disorders; however, the potential of Neat1 as a biomarker and as a therapeutic target for clinical CNS inflammation highly warrants further research to elucidate its exact role due to limited clinical data, moreover, different liquid biopsy is deserved to be performed to detect the expression of Neat1 since most studies use blood samples.

The Mechanism of Neat1 in the Effect of Regulating Inflammation

Neat1-miRNA-mRNA Axis is the Key Player in Regulating Inflammation

MicroRNAs (miRNAs) are small non-coding RNAs with lengths of approximately 18–24 nucleotides and can post-transcriptionally modulate gene expression through binding to 3′-untranslated regions of mRNAs, which further induce degradation or suppression of mRNAs, and then inhibit gene translation.[85,140,141] MiRNAs can regulate various target genes via serving as mediators, and one target gene may be regulated by multiple miRNAs.[141,142] MiRNAs are involved in crucial cellular functions of inflammatory progression, such as miR-195 and miR-146b-5p, which can regulate inflammatory profile in affecting the crosstalk with smooth muscle cells and foam cell formation via targeting different mRNA, respectively.[85] lncRNAs play a key role in multiple human diseases by regulating miRNA since they have direct ‘sponging-like effects’ on miRNAs,[141,143] which in turn modulate target genes via imperfect complementarity binding to

the 3-UTR of mRNA.[141] In addition, some lncRNAs can compete with miRNAs directly through targeting mRNA.[140,141] That shows the lncRNA–microRNA–mRNA axis, herein, contributes to the regulation of inflammatory disorders, and the emerging evidence has been identified that the anti- or proinflammatory effects of specific miRNAs are highly modulated by Neat1.[114,117] As downstream of Neat1, the top two miRNA reported in frequency were miRNA-124 and miRNA-129 as shown in Table 2. MiR-124, a tumor inhibitor, has recently been reported to be involved in the inhibition of inflammatory responses by diverse pathways, for instance, it plays a crucial role in traumatic brain injury and intestine by regulating inflammation processes and reduces skin inflammation by inhibiting the innate immune response.[144–146] Chen et al[80] reported that the overexpression of Neat1 markedly increased H9c2 cells inflammation, while the miR-124 could reverse the effects by repressing the NF-κB signaling pathway. With regard to miR-129, Li et al[111] uncovered that Neat1 was upregulated, while miR-129 was distinctly downregulated in vitro and in vivo in renal fibrosis models, what is more, Neat1 knockdown and miR-129 overexpression can suppress renal fibrosis, as shown by a decreased expression of inflammatory factor release. Likewise, Zhang et al[100] performed the luciferase reporter assay and RNA pull-down and illustrated a direct interaction between miR-129-5p and NEAT1, which in turn interacted with NF-kB signaling pathway. Besides that, Table 2 provides more miRNAs involved in the interaction between Neat1 and inflammatory regulation, hence, a plethora of miRNAs is found in the downstream of Neat1 of which the precise signaling cascades that are regulated under inflammatory conditions are also diverse.

Neat1 Regulates Inflammation Through the NF-κB Pathway

Nuclear factor-kB (NF-κB) is present in almost all types of cells and primarily serves as a transcription factor implicated in various biological processes, such as apoptosis, cell proliferation, tumorigenesis, inflammation, and various autoimmune disorders.[147] It is revealed to promote multiple proinflammatory mediators, and suppression of NF-κB signaling correlates with beneficial effects in inflammatory conditions. For instance, LncRNA Snhg8 acts as a competitive endogenous RNA (ceRNA) by binding to miR-425–5p, which was revealed to boost microglial inflammation by targeting the sirtuin1 (SIRT1)-mediated NF-κB pathway.[148] Furthermore, microglia can mediate experimental autoimmune encephalomyelitis, a neuroinflammatory disorder, and pathogenesis progression, therein, T cells activate the microglial noncanonical NF-κB pathway plays a crucial role.[149] As aforementioned, LncRNA can act on mRNA indirectly through miRNA or mRNA, and there is such a relationship between Neat1 and NF-κB. Xiao et al[150] demonstrated that Neat1 was up-regulated in rheumatoid arthritis, a chronic inflammatory disease, and the knockdown of it attenuated TNF-α-induced cell proliferation and inflammatory cytokine production while promoting cell apoptosis by targeting miR-204-5p through activating the NF-κB signaling pathway. Likewise, Nong et al[117] indicated Neat1 functioned as a ceRNA by sponging to reversed miR-193a-3p overexpression and alleviated inflammatory injury of normal human fibroblast cell-line WI-38 cells induced by LPS via regulating the activation of NF-κB signaling. Of note, Neat1 is able to interact indirectly with NF-κB via mRNA as well as to regulate inflammation, as indicated by Wang et al that Neat1 knockdown by tail vein injection of siRNAs has the potential to inhibit the expression levels of pro-inflammatory factor by inhibiting the Toll-like receptor 2/NF-κB signaling pathway in myocardial injury.[81] Hence, Neat1 appears to interact with NF-κB indirectly via miRNA and mRNA, however, the same signaling pathways that are regulated under other inflammatory conditions (except for the disorders described in the Tables) are not fully known due to currently limited evidence, yet.

Neat1 Regulate Inflammation Through AKT, TLR4, and TRAF6 Pathway

Despite the NF-κB pathway being involved downstream of Neat1, the following question remains: how can Neat1 achieve this pro-inflammatory effect through the NF-κB signaling pathway? The activation of Toll-like receptor 4 (TLR4)/NF-κB pathway has been widely studied for its involvement in inflammation. It is the main receptor of inflammation and activated in stimuli-challenged macrophages (such as LPS) which further leads to immune cells to release inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, inducing a systemic inflammatory response, followed by the activation of NF-κB.[73,117] Zhang et al[151] disclosed that Juglanin, a natural compound derived from the crude Polygonum aviculare, could ameliorate LPS induced neuroinflammatory injury through impeding activation of TLR4/NF-κB-mediated inflammatory response, and Neat1 was involved in the TLR4-mediated inflammatory process as identified by Zhang et al.[103] Consecutively, Nong et al[117] illustrated that knockdown of Neat1 promoted cell viability and ameliorated inflammatory response; besides, it exerted its role through regulating TLR4/

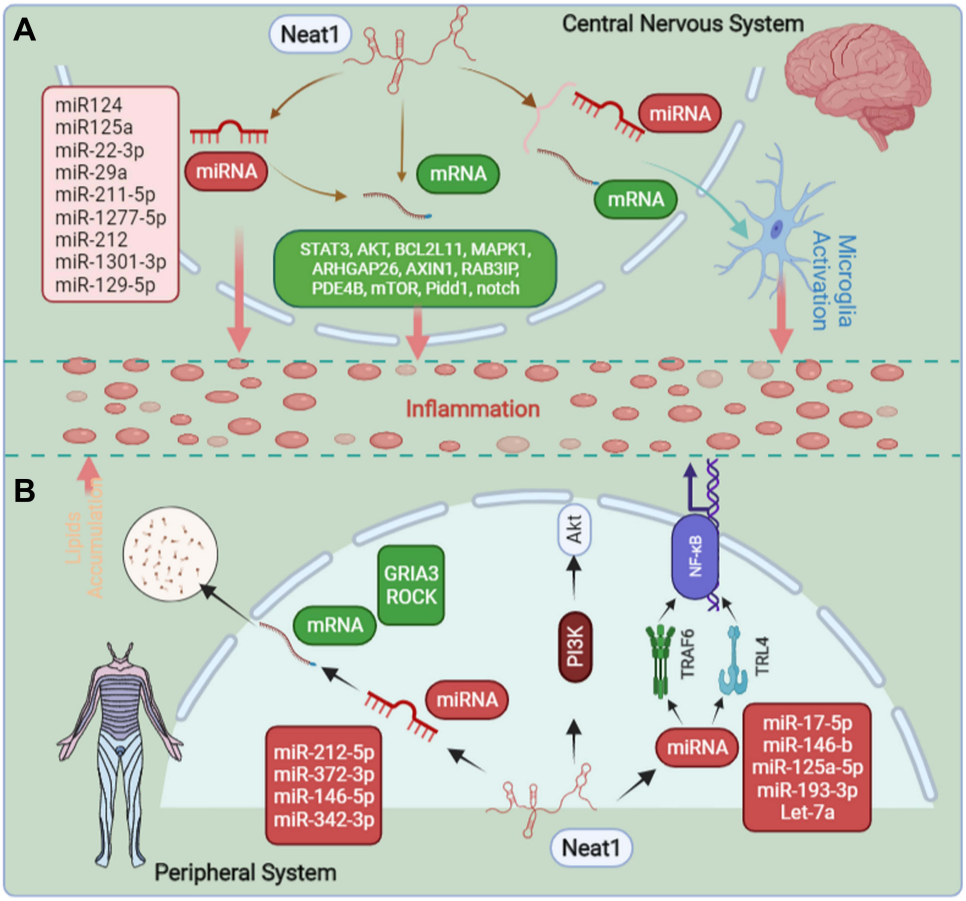

Figure 1 The overview of mechanisms of how Neat1 regulates inflammation. (**A**) In the central nervous system, Neat1 can regulate inflammation and the activation of microglia. (**B**) In the peripheral system, Neat1 can regulate inflammation and liposome deposition. The completion of all the above effects, mainly through the interaction with various miRNA and mRNA, and thus achieve the regulation of inflammation.

NF-κB signaling pathway. TNF receptor-associated factor 6 (TRAF6), an E3 ubiquitin ligase, is a signal transduction molecule shared by the IL-1 receptor/TLR family and the TNFR superfamily.[152] To identify that TRAF6 is involved in NF-κB activation, using the TRAF6-deficient mice, Yamamoto et al demonstrated that TRAF6 plays an irreplaceable role in many pathophysiological processes by activating the NF-κB pathway.[152] Several previous studies had indicated that down-expression of Neat1 could interact with TRAF6 and decrease its expression level, and significantly inhibited the expression levels of anti-inflammatory cytokines,[75,102,104] and Zhang et al[104] further hinted that TARF6 could promote the inflammatory injury via activating the NF-κB signaling. Downregulated Neat1 might therefore contribute to suppressing inflammation by regulating TNFR6 and TLR4, which further modulate NF-κB activation. Information regarding this aspect, however, is still scarce. Of note, Akt kinases, also known as protein kinase B, are signaling molecules of cell growth and differentiation and serve as a well-characterized effector of phosphoinositide 3-kinase (PI3K), involved in diverse cellular processes, especially for inflammation.[141,153,154] As indicated by Xia et al[69] and Wang et al,[89] given that Neat1 can modify miRNA/PI3K/AKT axis in cell and animal models exposed to inflammation, it exhibited great potential in inflammatory conditions treatment. Herein, it suggests that pharmacological upregulation of Akt signaling might be a potential target as well for inhibiting inflammation. Besides that, there are, of course, many other pathways that are involved downstream of Neat1 to regulate inflammation as shown in Table 2 and Figure 1.

Conclusion

Inflammation usually leads to an aberrant expression of Neat1 that exerts crucial functions in epigenetic and transcriptional regulation of gene expression. The regulation of Neat1 offers a great opportunity for adjuvant

treatment of neurological and peripheral disorders, for which inflammation is an excellent target. There is abundant evidence that Neat1 is directly involved in the regulation of inflammation in both the central nervous system and the peripheral system. Furthermore, inhibiting the activation of microglia and accumulation of lipids has practical implications in regulating inflammation, and a great amount of evidence demonstrates that, for now, the regulation of Neat1 appears to suppress microglial activation, lipid accumulation, and inflammatory responses in clinical and preclinical studies. Among the mechanism of Neat1 in the effect of regulating inflammation, the Neat1-miRNA-mRNA network plays a key role, additionally, it can modify various signaling pathways, such as AKT, TLR4, TRAF6, and NF-κB as well.

Disclosure

The authors declare that they have no competing interests.

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