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miRNAs: Role of Post-Transcriptional Regulation of NLRP3 Inflammasomes in The Treatment of Neurodegenerative Disorders

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1. Introduction

Inflammasomes are multiprotein complexes consist of having nucleotide binding domain and leucine rich repeat with the pyrin and HIN domain family. The NLRP3 inflammasome one of these members of family. It is activated upon sensing microbes or danger associated molecular pattern. NLRP3 inflammasome activation leads to activation of caspase 1 which is in turn activate proinflmmatory cytokines/chemomokines.

The role of NLRP3 inflammasome in Alzheimer's disease has recently being identified. NLRP3 inflammasome activation is necessary for maturation of IL-1β, IL-18 these cytokines/chemokines. Prolong activation of NLRP3 inflammasome and release of these cytokines/chemokines, and neuronal cell death serve as danger signal to further excitation of NLRP3 activation in this way, neuronal cell death provides feedback loop and deteriorate the pathological condition.

Deficiency or inhibition of NLRP3 inflammasome can be beneficial to reduce the deleterious effect of neuroinflammation in pathophysiology of AD. It has been described that NLRP3 inflammasome activity is under additional transcriptional regulation. In this study, I would like to identify the role of microRNA such as miR-223 in the regulation of NLRP3 inflammasome. micR223 is a critical regulator of NLRP3 inflammasome activity. miR-223 suppresses NLRP3 expression through a conserved binding site within the 39 untranslated region of NLRP3, translating to reduced NLRP3 inflammasome activity. It is interested to note that miR-223 itself is not regulated by proinflammatory signals, its expression varies among different myeloid cell types. Therefore, given the tight transcriptional control of NLRP3 message itself, miR-223 functions as an important rheostat controlling NLRP3 inflammasome activity. Therefore, induction of therapeutic treatment target to NLRP3 inflammasome may be beneficial to neurodegenerative disease such as Alzheimer's disorder.

2. NLRP3 Inflammasomes Molecular Mechanism of Activation

NLRP3 inflammasome is not active in resting state. Upon activation it can sense pathogen ligand or danger signals. NLRP3 inflammasome activation require internal stimuli such as ATP, toxins Postassium efflux such as reactive oxygen species (Cicolari, S., et al., 2021) (Jin, C. et al., 2010) [1,2]. Two steps activation of NLRP3 are 1) priming and 2) activation of NLRP3 inflammasome. The priming step include identification of Toll Like Receptor (TLRs) and activation of NLRP3 required second stimulus which are provided by multiple pathogens and danger associated ligand that promote assembly of NLRP3 inflammasome (Figure 1) (Jo, E. et al.,2016) [3].

3. Increasing complexity of NLRP3 inflammasome regulation role of epigenetic Factors and Post-Transcriptional Mechanisms

Recent studies have revealed role of epigenetic factors in pathogenesis of acute and chronic inflammation such as:

3.1. DNA Methylation

Epigenetic factors have their role during embryonic development. Detection of DNA demethylation near promoter's region of gene suggesting overexpression of that gene. Similarly, demethylation also participate in NLRP3 inflammasome overexpression (Dabin, L.et al., 2020) [4].

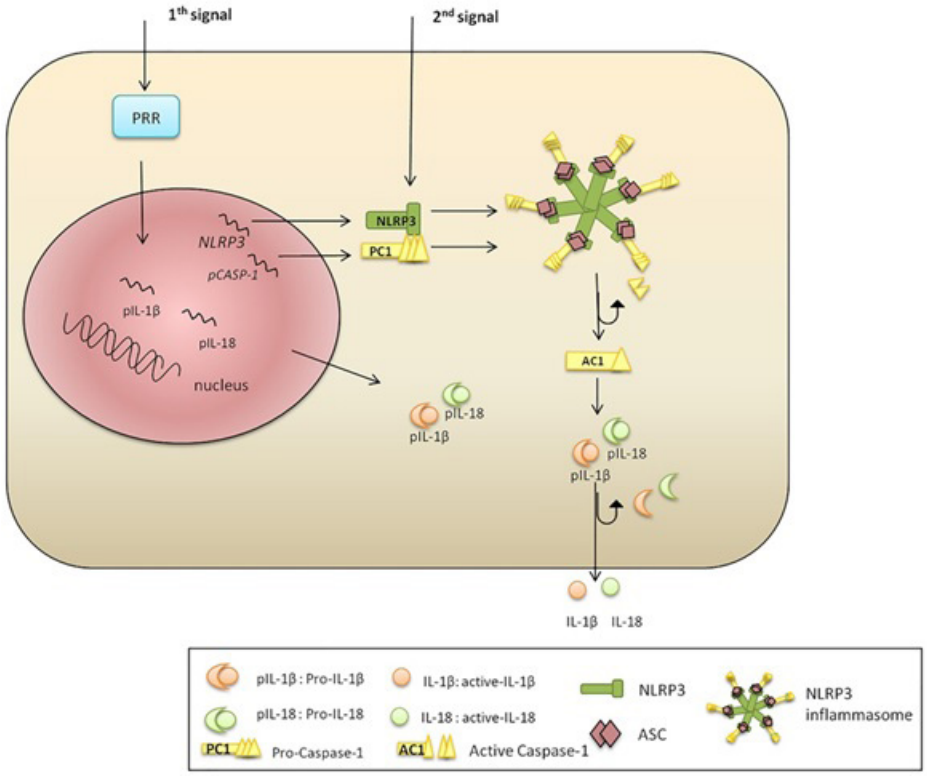

Figure 1: NLRP3 inflammasome activation. There are two signals required for NLRP3 inflammasome. Signal 1 ligands priming signal. It regulates the NLRP3 and pro IL-1β transcription and protein synthesis. Signal 2 activate trigger such trigger are ATP, toxins viral RNA. Second signal promotes NLRP3, proILβ and IL-18 synthesis.

3.2. Histone Modifications

Up regulation of NLRP3 inflammasome is associated with histone modification thus accelerate neuroinflammation diagnosed in patient with neuropathy (Liu, C. et al., 2018) [5].

3.3. Non-coding RNA

Non-coding RNAs are also involved in NLRP3 regulation as was demonstrated in the setting of inflammation caused by microbial and viral infection. Non coding RNAs targets inflammasome where mRNA stability and inhibition of translation were most commonly affected (Chen, I. et al., 2015) [6].

4. Post-transcriptional Regulation of NLRP3 Inflammasomes:

4.1. MicroRNA (miRNA)

Micro RNA belongs to class of non-coding RNA. It is single stranded endogenous conservative 19-24 nucleotides long. miRNA are transcribed from DNA sequence into primary miRNA proceed to precursor then to mature miRNA. miRNA interact with untranslated regions 3' UTRs of target mRNA induced mRNA degradation and translational repression. miRNA also interact with other regions of mRNA such 5'UTRs, coding regions and at gene promoter region (O'Brien, et al.,2018) Coll, R. et al.,2010) [7,8]. miRNA has role in modulation of histone deacetylases and DNA methytransferases which result in modulation of histone modifications and DNA methylation (Fabbri, M., et al.,2007) [9].

4.2. Post-transcriptional Regulation of NLRP3 Inflammasomes: MicroRNA (miRNA)

NLRP3 inflammasome activation is a two steps procedure which include priming of TLR ligand activation. Indirect regulation of TLR expression associated includes modulation of downstream pathways molecules, is shown to have role in inflammation, injuries and in cancer. There are several TLRs have been studied. However, TLR4 is widely studied receptor ligand for NLRP3 activation (Zhi, H., et al., 2018) [10].

Increased levels of miRNA such as miR-155, miR-146a, miR-21, and miR-132, are linked with TLR4 ligand binding. Upregulation of miRNA is a component of a negative feedback mechanism which were linked to inhibition of TLR4/MyD88/NF-κB signaling (Anzola, A., et al., 2018) [11]. This negative feedback mechanism of miRNA thus down modulate the inflammatory cytokines production after response to stimulus (Ceppi, M., et al.,2009) [12]. let -7 family miRNA has role in regulation on TLR4. TLR4 down regulation via let- 7 family miRNA can be beneficial to survival of cell or organism (Figure 2) (Urena-Peralta, J. et al., 2020) [13]. NLRP3 transcription is considered to be a second signal in the formation of active NLRP3 inflammasome. NLRP3 transcription can be regulated by miRNA during active phase such as my miRNA-223(Bauernfeind, F., et al., 2012) [14]. miRNA binds to

3'UTR region of NLRP3 transcripts and subsequently interfere with protein translation (Figure3) (Lewis, B. et al.,2005) [15]. miRNA has role regulation of inflammation decreased production of pro inflammation cytokines or chemokineses was demonstrated cells treated with miRNA (Ding, Q., et al., 2018) [16]. These data suggest that miR-223 could be a potential target for regulation of NLRP3 expression. Whereas, increased miRNA could reduce inflammasome activation and, subsequently, abrogate the inflammation (Figure 2) (Moretti, J.,et al.,2021) [17].

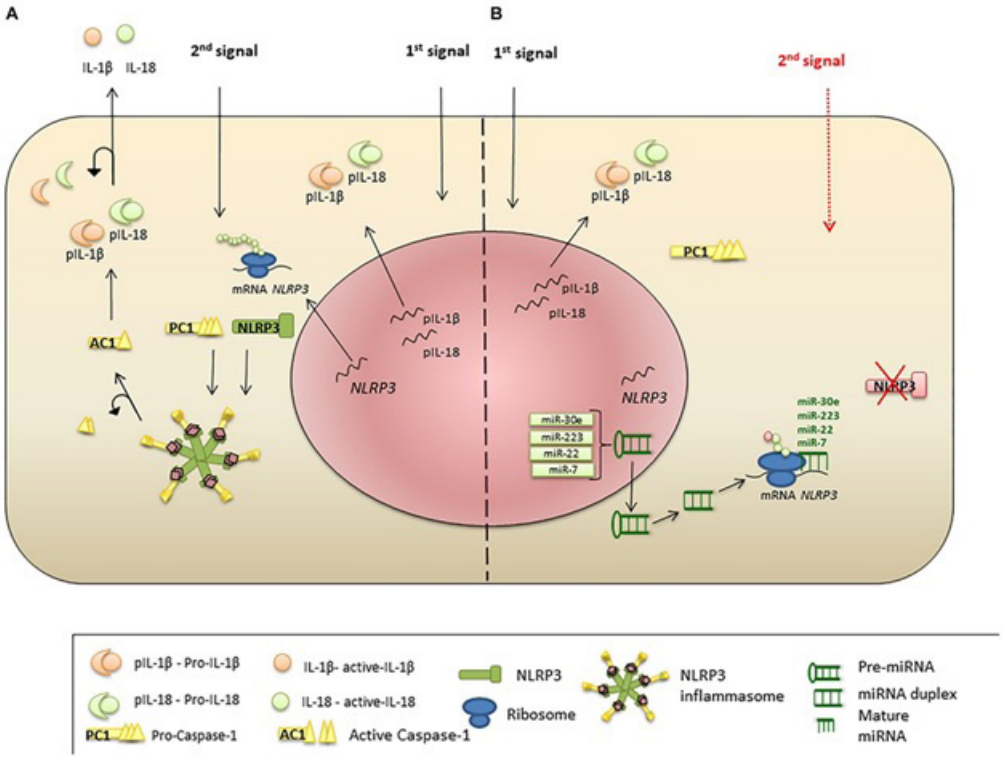

Figure2: miRNA regulation of NLRP3 inflammasome expression. A) Priming signal triggers NLRP3, PC1, IL-1β and IL-18 transcription and protein synthesis. B) Suppression of NLRP3 inflammasome translation and inflammasome formation by miRNA.

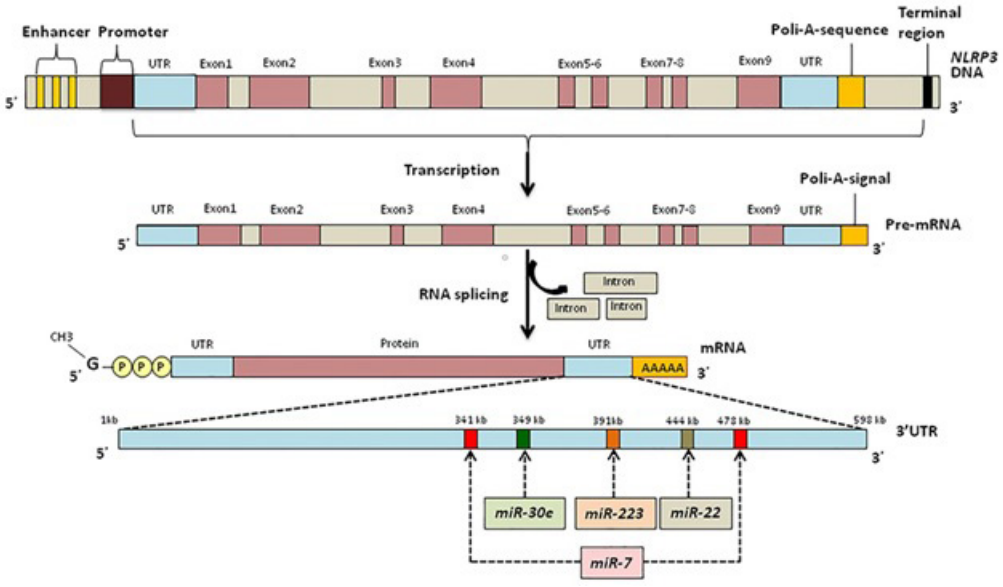

Figure 3: 'UTR binding sites of NLRP3 for miRNAs responsible for the regulation of inflammasome.

5. miRNA Regulation of Inflammasome in Neurodegenerative Disorders

5.1. Future Aspects for Clinical Approaches

Several preclinical and clinical studied have done on miRNA as therapeutic potential in prevention of NLRP3 inflammation. miRNA and/or miRNA targeting oligonucleotides approaches multiple gene target(Li, Z., and Rana, T. M. 2014) [18]. Let-7, miR-10b, miR-21, miR-34, miR-155, miR-221, and others were extensively used in several phases in clinical trial and shown positive results (Moles, R. et al., 2017) [19]. It is also studied that miRNA targets almost all genes on post transcriptional level (Hassan, M. K., et al., 2021) [20]. miRNA are predicted to regulate the expression of at least 30% of all human protein encoding gens and therefore it has role in almost all cellular function. It is also interesting that miRNA has specific sequences and that's why single miRNA has able to modify expression of several mRNA. These feature of miRNAs makes them valuable as therapeutic candidates (Çakmak, H. A.,et al.,2020) [21]. Although there are some limitations are reported associated with the use of miRNA such as when it is administered without any carrier molecules, their effect may be limited and can be cleared by kidney or liver. Other limitation of their usage is anti miRs can be sensed and removed by body's immune receptors. To overcome this limitation, tissue specific antibody coated chemically engineered polymer-based nanoparticles and carrier proteins have been developed to improve the specificity and efficacy of delivery. To improve therapeutic efficacy of miR223 was used with nanoparticle lipid emulsions as a delivery method, applied on animal model (Neudecker, V., et al., 2017) [22]. Therefore, on basis of their therapeutic advantages miRNAs have shown great potential for the disease linked with NLRP3 dysfunction. Our understanding of the role of the inflammasome in disease pathogenesis is still limited and is hampering development of the miRNA targeting therapeutics against the inflammasome. However, exciting discoveries in fundamental and preclinical research in recent years have demonstrated great potential for miRNA targeting in the treatment of diseases linked to NLRP3 dysfunction.

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