



MicroRNA Post-transcriptional Regulation of the NLRP3 Inflammasome in Immunopathologies

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Inflammation has a crucial role in protection against various pathogens. The inflammasome is an intracellular multiprotein signaling complex that is linked to pathogen sensing and initiation of the inflammatory response in physiological and pathological conditions. The most characterized inflammasome is the NLRP3 inflammasome, which is a known sensor of cell stress and is tightly regulated in resting cells. However, altered regulation of the NLRP3 inflammasome is found in several pathological conditions, including autoimmune disease and cancer. *NLRP3* expression was shown to be post-transcriptionally regulated and multiple miRNA have been implicated in post-transcriptional regulation of the inflammasome. Therefore, in recent years, miRNA based post-transcriptional control of NLRP3 has become a focus of much research, especially as a potential therapeutic approach. In this review, we provide a summary of the recent investigations on the role of miRNA in the post-transcriptional control of the NLRP3 inflammasome, a key regulator of pro-inflammatory IL-1 β and IL-18 cytokine production. Current approaches to targeting the inflammasome product were shown to be an effective treatment for diseases linked to NLRP3 overexpression. Although utilizing NLRP3 targeting miRNAs was shown to be a successful therapeutic approach in several animal models, their therapeutic application in patients remains to be determined.

Keywords: NLRP3, inflammasome, microRNA, inflammation, disease

INFLAMMASOME

Structure

In 2002, the ground breaking work published by Martinon et al. (2002) has demonstrated the role of the inflammasome, a multi-protein complex, in the activation of pro-inflammatory caspases. The authors described the multistep process of the inflammasome assembly which is initiated by the detection of pathogen-associated molecular patterns (PAMPs) or danger signals released by damaged cells (Duncan et al., 2009; Ichinohe et al., 2010; Costa et al., 2012). Several inflammasome sensors were later identified including the nucleotide-binding oligomerization domain (NOD) like receptors (NLRs), the absent in melanoma-2 like receptors (ALRs) and pyrin (Ting et al., 2008).

In the past decade our understanding of NLR containing inflammasomes structure and assembly mechanisms has advanced considerably, largely due to their potential involvement in pathogenesis of several diseases (Hoffman et al., 2001; Alexander So and Borbála Pazár, 2010; Song et al., 2017). NLRs contain three domains, an N-terminal domain, a NOD, and a C-terminal leucine-rich repeat (LRR) (Inohara and Nunez, 2003). The N-terminal domain contains a caspase recruitment domain (CARD) or pyrin domain (PYD), which function to interact with downstream molecules, such as apoptosis-associated speck-like protein containing (ASC) (Inohara and Nunez, 2003; Schroder and Tschopp, 2010). The NOD domain is linked to LRR detecting PAMPs (Boekhout et al., 2011). Upon sensing PAMPs, the NLRs polymerize followed by the interaction between the PYD or CARD domains of LLR and ASC (Stutz et al., 2013). Once activated the inflammasome adopts a wheel-like structure (Hu et al., 2015), where CARD-CARD interactions are essential for recruiting pro-caspase 1 (PC1) into close proximity with the complex (Faustin et al., 2007). PC1 becomes proteolytically cleaved by the CARD domain releasing an active caspase 1 (AC1) p10/p20 tetramer (Martinon et al., 2002; Kanneganti et al., 2006; Boucher et al., 2018).

NLR Inflammasomes

This family of inflammasomes includes two subgroups based on the presence of CARD or pyrin in the N terminus. Only nucleotide-binding domain leucine-rich repeats proteins (NLRP)1, NLRP3, and NLRC4 were shown to form inflammasomes that produce AC1 (Mao et al., 2014). In contrast, NLRP6, NLRP9b, and NLRP12 are believed to form inflammasomes, but their roles as inflammasome sensors are less recognized (Anand et al., 2012; Vladimer et al., 2012; Zhu et al., 2017).

NLRP1

NLRP1 was the first identified cytosolic receptor capable of forming active inflammasomes (Martinon et al., 2002). PYD, NBD, and LRR domains, a 'function-to find' domain (FIIND) and a C-terminal CARD are the structural components of NLRP1 (Jin et al., 2013b). Our knowledge of NLRP1 function comes largely from studying animal models. It appears that NLRP1 senses and protects against microbial pathogens, as was shown using a mouse model of *Bacillus anthracis* and *Shigella flexneri* infection (Boyden and Dietrich, 2006; Sandstrom et al., 2019). Additionally, NLRP1 inflammasomes facilitate parasite clearance and protection as demonstrated in *Toxoplasma gondii* infection in mouse and rat models (Cirelli et al., 2014; Gorfú et al., 2014). The clinical relevance of NLRP1 inflammasomes against *Toxoplasma gondii* is also evident in individuals with specific single-nucleotide polymorphisms in the *NLRP1* gene, which are linked to congenital toxoplasmosis (Witola et al., 2011).

Aberrant activation of NLRP1 is linked to a pathogenesis of inflammatory diseases. Polymorphisms in the *NLRP1* gene are linked to Crohn's disease, rheumatoid arthritis (RA) and systemic sclerosis (Finger et al., 2012). Although the mechanism of NLRP1 activation remains largely unknown, recently, the failure of inflammasome inhibition by dipeptidyl dipeptidase 9

(DDP9), linked to antigen processing (Zhong et al., 2018), was demonstrated to play role in pathogenesis of an autoimmune diseases (Zhong et al., 2018). The authors identified that a single mutation in the FIIND domain of NLRP1 abrogates binding to DPP9, triggering over activation of the inflammasome in autoinflammatory disease AIADK.

NLRC4

Similar to NLRP1, NLRC4 establishes protection against infectious pathogens (Mariathasan et al., 2004; Franchi et al., 2006; Zhao et al., 2011). In the absence of stimulus, NLRC4 remains inactive, where its NBD domain retains a closed conformation by binding to the winged helix domain (Tenthorey et al., 2014). NLRC4 activation is indirect, and it requires NLR family apoptosis inhibitory proteins (NAIPs) for the initial sensing of the microbial ligand (Rayamajhi et al., 2013; Yang et al., 2013; Kortmann et al., 2015). NAIPs trigger NLRC4 oligomerization, which is essential for inflammasome activation (Hu et al., 2015). Loss of the control over NLRC4 expression and subsequent production of AC1 and release of IL-1 β by macrophages was suggested to play role in the pathogenesis of inflammasome linked autoinflammation (von Moltke et al., 2012; Canna et al., 2014). Also, a missense mutation in the NLRC4 gene was found in familial cold autoinflammatory syndrome (Kitamura et al., 2014). Multiple mutations in NLRC4 were identified in several autoinflammatory diseases including atopic dermatitis, periodic fever, and fatal or near-fatal episodes of autoinflammation (Nakamura et al., 2010; Canna et al., 2014; Bonora et al., 2015). These data suggest that NLRC4 plays role in protection against microbial pathogens and autoinflammation.

NLRP6

NLRP6 is an inflammasome which plays a role in gut health and maintaining mucosal response to pathogens (Elinav et al., 2011; Anand et al., 2012). A microbial metabolite, taurine, was identified as an NLRP6 activator (Levy et al., 2015). The NLRP6-taurine axis appears to be essential for the health of the gut mucosa and microbiome. Taurine produced by the normal microbiota activates NLRP6 which prevents dysbacteriosis by promoting production of antimicrobial peptides (Levy et al., 2015).

NLRP12

NLRP12 is intracellular protein expressed in cells of myeloid lineages (Arthur et al., 2010). NLRP12 inflammasome expression can be downregulated by microbial ligands (Williams et al., 2005; Lich et al., 2007) via canonical and non-canonical inhibition of NF- κ B (Zaki et al., 2011; Allen et al., 2012). Several ligands were identified as NLRP12 activators including microbes (Allen et al., 2012; Vladimer et al., 2012).

ALR Family Inflammasomes

ALR family inflammasomes contain an N-terminal PYD and a C-terminal hematopoietic interferon-inducible nuclear protein with 200-amino acid repeat (HIN200) domain (Cridland et al., 2012). ALR inflammasomes sense cytosolic double stranded DNA (dsDNA) (Burckstummer et al., 2009; Ferreri et al., 2010). Absent

in melanoma 2 (AIM2) is the best characterized member of ALR inflammasomes. Similar to other ALR family members, AIM2 senses dsDNA; however, it appears that dsDNA recognition is independent of nucleic acid sequence as it could bind to both, microbial and host genomic material (Jin et al., 2012). dsDNA binding to HIN200 causes its dissociation from the PYD domain (Jin et al., 2012), allowing the freed PYD domain to interact with ASC, and inflammasome assembly (Jin et al., 2013c). AIM2 was implicated in the recognition of microbial, host and tumor derived dsDNA (Davis B.K. et al., 2011; Choubey, 2012; Dihlmann et al., 2014).

Pyrin

Pyrin is an inflammasome sensor complex, which contains a N-terminal PYD, central B-box and coiled-coil domain, and a C-terminal B30.2/SPRY domain (Heilig and Broz, 2018). Pyrin was proposed to sense the changes in actin cytoskeletal dynamics as it was found co-localized with stress actin filaments (Xu et al., 2014). Microtubules promote ASC recruitment and the oligomerization (Gao et al., 2016); however, the physiological relevance of this interaction remains largely unknown. Also, microbial toxins which cause impairment of Rho GTPase activity were identified as strong activators of the pyrin inflammasome (Dumas et al., 2014; Xu et al., 2014).

Several monogenic autoinflammatory syndromes were linked to pyrin inflammasome dysregulation including familial Mediterranean fever (FMF), pyrin-associated autoinflammation with neutrophilic dermatosis, pyogenic arthritis, pyoderma gangrenosum, acne, etc. (Jamilloux et al., 2018). FMF is the most investigated pyrin inflammasome disease, characterized by repeating, self-limited, episodes of fever and polyserositis (Bernot et al., 1998). FMF is linked to a mutation in the Mediterranean Fever (MEFV) gene in a region encoding the B30.2 domain of pyrin (Omenetti et al., 2014). Also, the high prevalence of FMF within certain populations could indicate a selective pressure to preserve this mutation (Schaner et al., 2001).

Pyroptosis

Pyroptosis is an inflammatory form of programmed cell death linked exclusively to PC1 activation (Hilbi et al., 1998). AC1 is a product of several inflammasomes: NLRP1, NLRP3, NLRC4, and AIM2. Therefore, pyroptosis is often associated with inflammasome activation. Pyroptosis differs from apoptosis in many respects including lack of DNA fragmentation (Watson et al., 2000) and sustained structural integrity of the nucleus (Zychlinsky et al., 1992). Also, pyroptosis is characterized by cell membrane pore formation, which causes cell swelling in contrast to apoptosis, where cells shrink (Fink and Cookson, 2006). Additionally, an increased intracellular osmotic pressure generates large spherical protrusions of the membrane in pyroptotic cells, which coalesce and rupture (Ona et al., 1999). Multiple studies revealed the role of pyroptosis in clearance of microbial pathogens (Sansonetti et al., 2000; Tsuji et al., 2004; Lara-Tejero et al., 2006). However, over activation of AC1 could lead to pyroptosis associated tissue damage

and autoimmunity (Ona et al., 1999; Siegmund et al., 2001; Frantz et al., 2003).

NLRP3 INFLAMMASOMES

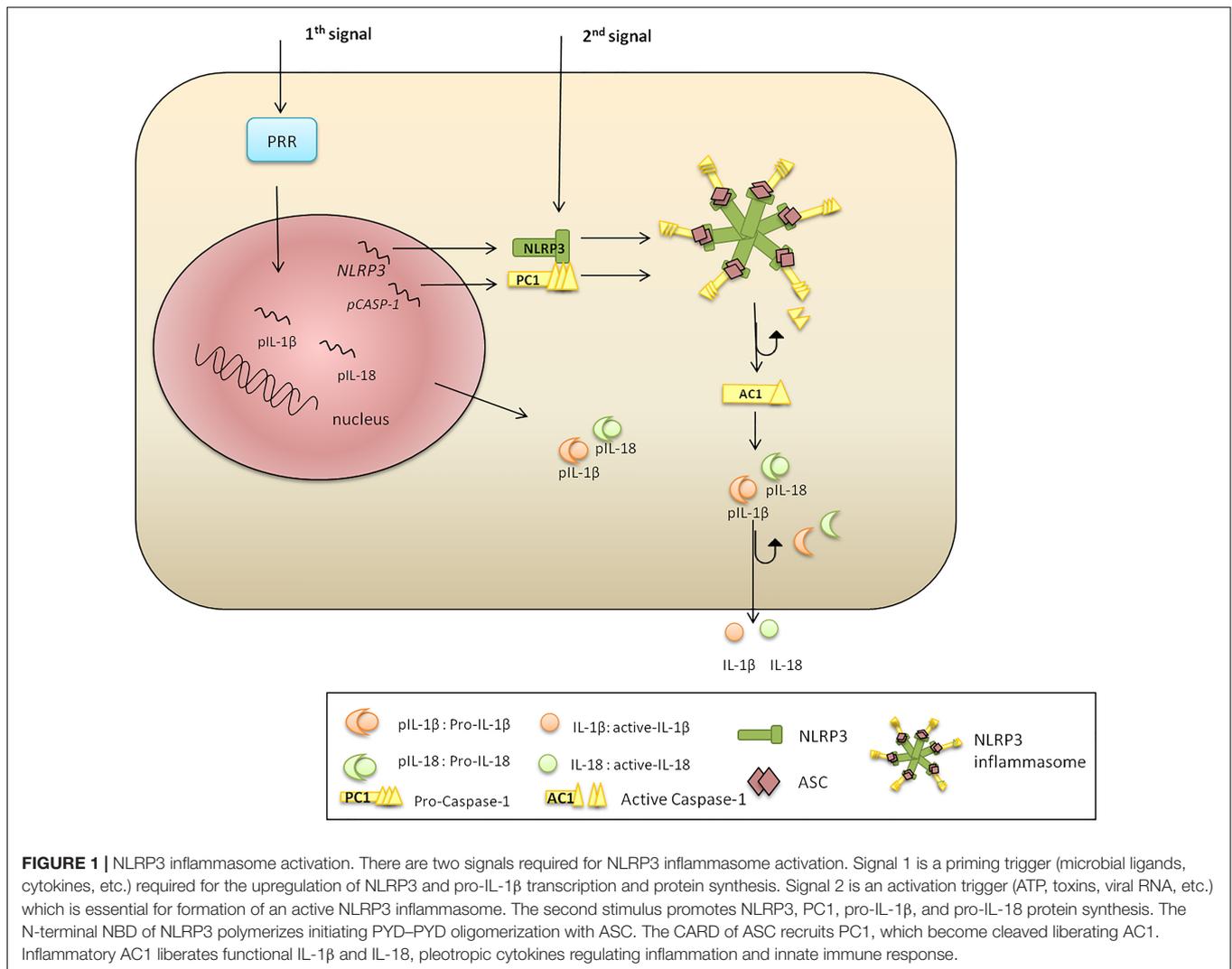
Molecular Mechanism of Activation

NLRP3 is the most characterized inflammasome, and its expression is tightly regulated in resting cells (Bauernfeind et al., 2009). While NLRP3 levels in unstimulated cells are insufficient to trigger assembly of an active inflammasome complex, sensing of pathogen ligands or danger signals, triggers complex formation and pro-inflammatory cytokine production. There are multiple stimuli shown to activate NLRP3 including ATP, toxins, K⁺ efflux, reactive oxygen species and mitochondrial dysfunction (Dostert et al., 2008; Piccini et al., 2008). Upon sensing the stimulus, the nucleotide binding domain (NBD) polymerizes initiating PYD–PYD oligomerization with ASC (Lu A. et al., 2014). The CARD of ASC recruits PC1, which becomes cleaved liberating AC1 (Boucher et al., 2018). It appears that within the large family of inflammasomes, NLRP3 is the main PC1 activator (Agostini et al., 2004; Davis E.E. et al., 2011). Inflammatory AC1 liberates functional IL-1 β and IL-18 (Afonina et al., 2015), pleiotropic cytokines regulating inflammation and innate immune response (Garlanda et al., 2013).

The classic pathway of NLRP3 activation requires two steps: priming and activation (**Figure 1**). Toll-like receptor (TLR), FAS-associated death domain protein and IL-1R ligands were identified as NLRP3 priming stimuli (Allam et al., 2014; Gurung et al., 2014; He Y. et al., 2016). The priming step includes transcriptional activation of NLRP3 via NF- κ B signaling (Bauernfeind et al., 2009; Costa et al., 2012); however, it fails to initiate functional inflammasome formation, which requires a second stimulus (Jo et al., 2016). The second signal can be provided by multiple pathogen and danger associated ligands (Franchi et al., 2012; Koizumi et al., 2012), promoting the assembly of an adaptor (ASC) and PC1. The formed complex cleaves the PC1, which subsequently processes and releases functional IL-1 β and IL-18 (Alnemri et al., 1996).

EPIGENETIC FACTORS AND POST-TRANSCRIPTIONAL MECHANISMS REGULATING NLRP3 INFLAMMASOME ACTIVATION

The term “epigenetic” was originally presented by Waddington (1956) to describe regulation of gene expression during the embryogenesis. Since then, definition of “epigenetic” has changed, and now refers to a stably heritable modulation of gene expression without altering DNA sequence (Berger et al., 2009). Epigenetic factors include DNA methylation at cytosine followed by guanine (CpGs) nucleotide and histone posttranslational modifications (Peschansky and Wahlestedt, 2014). Initially, epigenetic control was demonstrated in normal development and differentiation; however, its role in pathogenesis of acute



and chronic inflammation has become increasingly recognized (Bayarsaihan, 2011).

DNA Methylation

DNA methylation is dynamic and changes during the embryonic development and differentiation (Berger, 2007). It was shown that DNA methylation silences genes to ensure monoallelic expression, prevent endogenous retrovirus expression and transposon actions (Walsh et al., 1998; Bourc'his et al., 2001; Bourc'his and Bestor, 2004). DNA methylation is essential for normal cell function; however, its role in the pathogenesis of several diseases has also been confirmed (Wei et al., 2016; Vento-Tormo et al., 2017). DNA demethylation is often detected near promoters, suggesting that gene overexpression could play role in pathogenesis of many pathologies (Ryan et al., 2010; Bierne et al., 2012). NLRP3 inflammasome expression can also be regulated by changes in gene methylation status. For example, *NLRP3* gene expression is silenced in health which appears to be essential for inhibiting inflammation (Ryan et al., 2010; Bierne et al., 2012; Wei et al., 2016).

However, demethylation and, subsequent, overexpression of *NLRP3* was linked to pathogenesis of cryopyrin-associated periodic syndromes (CAPS) (Vento-Tormo et al., 2017) and *Mycobacterium tuberculosis* infection (Wei et al., 2016).

Histone Modifications

The effect of epigenetic modification of histones was studied using several inflammatory models (Bayarsaihan, 2011). Histone acetylation is essential for initiation of an activation phase of inflammation, which is characterized by the release of pro-inflammatory cytokines via CREB, mitogen-activated protein kinases (MAPKs), nuclear factor-κB (NF-κB) and signal transducer and activator of transcription (STAT) factors (Escobar et al., 2012). In contrast, histone deacetylations regulate the late, an attenuation phase of inflammation (Villagra et al., 2010). It appears that inflammasome activation can also be regulated by affecting the acetylation status of histones, as it was recently shown by Liu C.C. et al. (2018). The authors demonstrated upregulation of NLRP3 in patients diagnosed with

(Coll and O'Neill, 2010; Sheedy et al., 2010; Nahid et al., 2011; Anzola et al., 2018; Tan et al., 2018; Zhi et al., 2018). TLR4 ligands are the most studied priming signals of NLRP3 activation (Gros Lambert and Py, 2018). It was shown that the TLR4 ligand binding increases the level of several miRNAs, including *miR-155*, *miR-146a*, *miR-21*, and *miR-132*, which were linked to inhibition of TLR4/MyD88/NF- κ B signaling (Coll and O'Neill, 2010; Sheedy et al., 2010; Nahid et al., 2011; Anzola et al., 2018; Tan et al., 2018; Zhi et al., 2018). It appears that upregulation of miRNAs is a component of a negative feedback mechanism designed to down-modulate inflammatory cytokine production after response to microbial stimuli (Ceppi et al., 2009).

A direct inhibitory effect of *let-7* family miRNAs on *TLR4* mRNA has been demonstrated (Chen et al., 2007). *Let-7* miRNA regulation of *TLR4* was shown to occur via post-transcriptional suppression (Androulidaki et al., 2009). It was suggested that *let-7* miRNA downregulation of *TLR4* could have detrimental effect on host defense against microbes, promoting microbial survival and propagation (Chen et al., 2005; Muxel et al., 2018). Post-transcriptional regulation of TLR signaling and its impact on diseases are reviewed by Nahid et al. (2011).

Active inflammasome complex formation requires a second signal, initiating substantial NLRP3 transcription (Dostert et al., 2008; Piccini et al., 2008). During this transcriptionally active phase, *NLRP3* mRNA could be regulated by miRNA, as was shown by *miR-223* (Bauernfeind et al., 2012). According to an *in silico* analysis, *miR-223* can bind to a highly conserved region of the 3'UTR of *NLRP3* mRNA and subsequently interfere with protein translation (Lewis et al., 2005). Interestingly, *miR-223* appears to be an important NLRP3 regulator in

leukocytes (Bauernfeind et al., 2012; Haneklaus et al., 2012), where the miRNA levels have been shown to vary in different leukocyte subsets. For example, this miRNA was found absent in T and B lymphocytes (Bauernfeind et al., 2012; Haneklaus et al., 2012). In contrast, the *miR-223* was demonstrated in myeloid cells, where it was highest in neutrophils, followed by macrophages and dendritic cells (Bauernfeind et al., 2012). It has been suggested that this miRNA plays role in granulocyte production and regulation of inflammation (Johannidis et al., 2008; Neudecker et al., 2017). Decreased production of pro-inflammatory cytokines such as IL-1 β and IL-18 was demonstrated in cells treated with *miR-223* or its mimics (Neudecker et al., 2017; Ding Q. et al., 2018). These data suggest that *miR-223* could be a potential target for regulation of *NLRP3* expression, where increased miRNA could reduce inflammasome activation and, subsequently, abrogate the inflammation (Bauernfeind et al., 2012; Haneklaus et al., 2012).

Since several miRNAs could regulate expression of a single transcript (Krek et al., 2005), it is likely that in addition to *miR-223*, other miRNAs can alter NLRP3 transcription (Figure 3).

Numerous studies have identified that pathogens, trauma and cancer can cause abnormal expression of miRNAs which impair NLRP3 inflammasome function disrupt the functional complex formation and its signaling (Table 1).

miRNA in Regulation of Inflammasome in Infections

Inflammasome activation is an important component of infectious pathogens surveillance and antimicrobial immune and inflammatory responses. This inflammasome was shown to be activated by several bacterial pathogens including

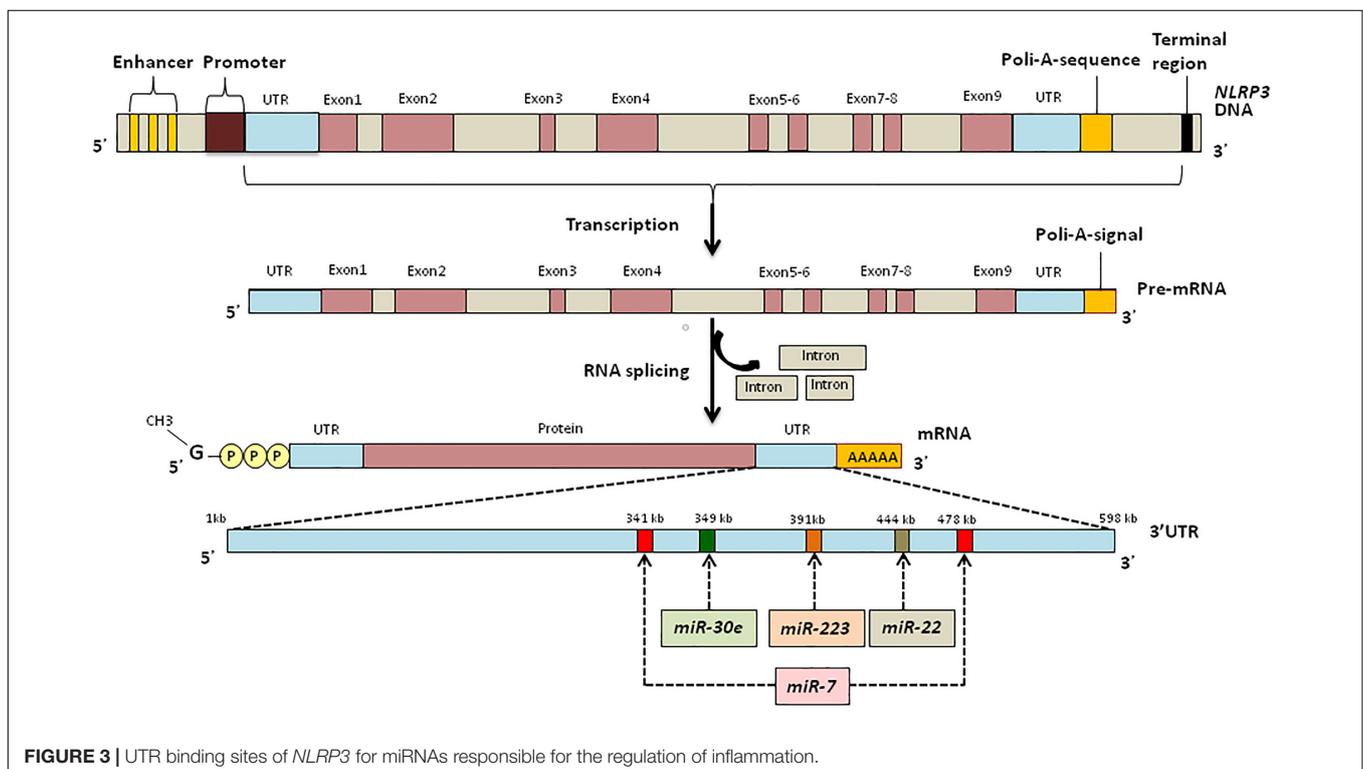


TABLE 1 | Aberrant miRNA expressions linked to inflammasome related diseases.

Disease	miRNA	Regulation of miRNA	Target cell	Target gene	References
Inflammatory bowel diseases	miR-223	↑ ↑	Intestinal biopsies Circulating monocytes, neutrophils	NLRP3	Neudecker et al., 2017 Johannidis et al., 2008; Bauernfeind et al., 2012; Neudecker et al., 2017
Rheumatoid arthritis	miR-33	↓ ↑	Macrophages Macrophages	PGC1- α	Karunakaran et al., 2015; Xie Q. et al., 2018
Type 1 diabetes	miR-146a	↓	Macrophages	TLR2, TLR4	Bhatt et al., 2016; Xie Z. et al., 2018
Type 2 diabetes	miR-146a	↓	Macrophages	TLR2, TLR4	Balasubramanyam et al., 2011
Systemic lupus erythematosus	miR-23b	↓	Inflammatory lesions	TAB2, TAB3, IKK- α	Zhu et al., 2012
Parkinson's disease	miR-7	↓	Microglia	NLRP3	Zhou Y. et al., 2016
	miR-30e	↓		NLRP3	Li D. et al., 2018
Atherosclerosis	miR-22	↓	Monocytes, macrophages	NLRP3	Huang W.Q. et al., 2017
	miR-9	↓		JAK1	Wang F. et al., 2017
	miR-30e-3p	↓		FOXO3	Li P. et al., 2018
Acute lung injury/acute respiratory distress syndrome	miR-223	↑	Ly6G+ neutrophils	NLRP3	Feng et al., 2017
Hepatocellular carcinoma	miR-223	↑	Tumor cell line	NLRP3, EPB41L3, FOXO1	Li X. et al., 2011; Kim et al., 2017
	miR-223	↓	Patient's sera	NLRP3	Bhattacharya et al., 2016
	miR-30e	↓		NLRP3	Bhattacharya et al., 2016
Colorectal cancer	miR-223	Tumor type specific	Tumor tissue, tumor cell line	NLRP3, FoxO3a	Ju et al., 2018
	miR-22	↓		SP-1	Xia et al., 2017
Gastric cancer	miR-223	↑	Tumor tissue	NLRP3	Haneklaus et al., 2012
	miR-22	↓	Macrophages	NLRP3	Li S. et al., 2018
Oral squamous cell carcinoma	miR-223	↑	Tumor tissue	RHOB	Manikandan et al., 2016
	miR-22	↓		NLRP3	Feng et al., 2018
Cervical cancer	miR-223	↓	Tumor tissue, tumor cell line	FOXO1	Wu et al., 2012
	miR-22	↓		HDAC6	Wongjampa et al., 2018
Glioblastoma	miR-223	Controversial	Tumor tissue, tumor cell line	NFIA, PAX6	Fazi et al., 2005; Glasgow et al., 2013; Cheng et al., 2017; Ding Q. et al., 2018
	miR-22	↓		SIRT1	Li W.B. et al., 2013

Staphylococcus aureus, *Salmonella typhimurium*, *Listeria monocytogenes*, *Mycobacterium*, *Streptococcus pyogenes*, *Neisseria gonorrhoeae* as well as fungi such as *Candida albicans* and *Aspergillus fumigatus* (Franchi et al., 2006; Mariathasan et al., 2006; Miao et al., 2006; Craven et al., 2009; Duncan et al., 2009; Harder et al., 2009; Hise et al., 2009; Joly et al., 2009; Munoz-Planillo et al., 2009; Broz et al., 2010; Carlsson et al., 2010; McElvania Tekippe et al., 2010; Said-Sadier et al., 2010). NAIP/NLRC4 inflammasome can protect against *Salmonella Typhimurium* and *C. rodentium* invasion by bacteria expulsion from intestinal epithelial cells together with IL-18 and eicosanoid lipid mediators release (Nordlander et al., 2014; Sellin et al., 2014; Rauch et al., 2017). It appears that NLRP3 activation is essential for establishing the inflammatory milieu in the target tissue and augmenting the phagocytic capacity of

the local macrophages (Master et al., 2008; Melehani and Duncan, 2016; Cohen et al., 2018). Enhanced macrophage bactericidal activity is the most commonly identified mechanism of inflammasome antimicrobial effect (Master et al., 2008; Cohen et al., 2018). Additionally, NLRP3 activation induced death of macrophages was described as an effort to prevent microbial propagation and spread (Miao et al., 2010; Sagulenko et al., 2013). However, there is a growing body of evidence suggesting that there is a threshold of NLRP3 activity, which acts as a safeguard mechanism to prevent inflammasome over-activation. It appears that aberrant NLRP3 activation could have a detrimental effect on tissues homeostasis and compromise barrier integrity (Bortolotti et al., 2018; McKenzie et al., 2018). It is this detrimental effect of the inflammasome over-activation that is often employed by microbes to ensure

spread and propagation (Duncan et al., 2009; Harder et al., 2009; Carlsson et al., 2010).

Microbial virulence factors often act as NLRP3 activators. For example, it was shown that the detrimental (to the host) role of Esx1, a membrane lysis factor of *Mycobacterium* (Stanley et al., 2003), is linked to inflammasome activation (Carlsson et al., 2010). Two virulence factors of group A *Streptococcus* (GAS), M protein and streptolysin O, were also identified as contributing into NLRP3 activation and IL-1 β production (Harder et al., 2009; Valderrama et al., 2017). Both virulence factors are commonly detected in association with invasive GAS infections, including necrotizing fasciitis and toxic shock syndrome. Therefore, NLRP3 activation by virulent factors could promote microbe propagation and aid their escape from immune clearance.

Restoring the NLRP3 activation threshold could be a novel therapeutic approach for treatment of invasive infections. In this respect, miRNA may be a tool to regain control over NLRP3. It has been shown that *miR-223* expression is consistently high in NLRP3 responsive cells, suggesting the high efficacy of this miRNA in prevention of inflammasome over-activation (Bauernfeind et al., 2012). Dorhoi et al. (2013) demonstrated that *miR-223* is upregulated in the blood and lung parenchyma of patients diagnosed with tuberculosis. Also, data collected using animal models confirmed the link between deletion of *miR-223* and increased susceptibility to *Mycobacterium tuberculosis* infection (Dorhoi et al., 2013). Similarly, a protective role of *miR-223* in *Staphylococcus aureus* infection was demonstrated by Fang et al. (2016). Additionally, the effect of targeting TLR4 for NLRP3 regulation in *Listeria monocytogenes* infection was demonstrated by Schnitger et al. (2011). The authors identified that, *miR-146a* can directly inhibit TLR4 receptor expression, which can downregulate inflammasome activity (Schnitger et al., 2011).

Many viruses can activate inflammasomes, including Influenza virus, Hepatitis C virus, Herpes simplex virus-1, etc. (Delaloye et al., 2009; Ichinohe et al., 2010; Ito et al., 2012; Kaushik et al., 2012; Negash et al., 2013; Triantafilou et al., 2013a,b; Wu et al., 2013; Ermler et al., 2014; Chen and Ichinohe, 2015). Inflammasome activation appears to be essential for anti-viral protection, serving as viral genome sensors and triggering innate immune response (Muruve et al., 2008; Lupfer et al., 2015). The protective role of inflammasomes was shown in influenza virus infection as an increased viral clearance was NLRP3 dependent (Allen et al., 2009). Also, inflammasome activation improved the survival rate in an animal model of influenza (Ichinohe et al., 2009). Thomas et al. (2009) demonstrated that, the innate immune response activation by NLRP3 inflammasomes is essential for animal protection. However, our understanding of the mechanisms of inflammasome antiviral defense remains limited (Anand et al., 2011).

Some viruses were shown to post-transcriptionally regulate inflammasome expression to benefit self-replication and propagation (Kieff and Rickinson, 2007; Rickinson and Kieff, 2007). For example, miRNA suppression of inflammasomes was shown in Epstein Barr Virus (EBV) infected cells (Kieff and

Rickinson, 2007; Rickinson and Kieff, 2007). It appears that, EBV can avert NLRP3 inflammasome activation by expressing miRNAs encoded by three *BHRF1*-regions and 40 *BART*-regions of the viral genome (Albanese et al., 2016; Tagawa et al., 2016; Farrell, 2018). Additionally, two miRNAs encoded by EBV, *miR-BART11-5p* and *miR-BART15*, were identified by Haneklaus et al. (2012), which could bind to the 3'-UTR of *NLRP3*, the same site targeted by *miR-223*, and inhibit the inflammasome. It remains to be determined whether these viral miRNA could be used as therapeutic targets.

miRNA Regulation of Inflammasome in Autoimmune Diseases

Autoimmune diseases are often the result of a dysregulated immune response, characterized by inflammation and organ damage (Chang, 2013; Yang and Chiang, 2015). Chronic inflammation is frequently identified as a predisposing factor for an autoimmune reaction (Yang and Chiang, 2015). Multiple mechanisms were suggested to explain prolonged inflammation leading to autoimmunity; where failure to control inflammasome activation was recently identified in some autoimmune conditions (Yang and Chiang, 2015). It has been established that in addition to inflammation, an increased secretion of IL-1 β and IL-18, can stimulate proliferation and organ distribution of the effector T cells, which can cause tissue damage (Oyanguren-Desez et al., 2011; Celhar et al., 2012). Therefore, targeting the inflammasome could be suggested to restore control over the inflammatory and immune response. Therapeutic potentials of several *NLRP3* targeting miRNAs were investigated in autoimmune diseases such as inflammatory bowel diseases (IBDs) (Neudecker et al., 2017), RA (Xie Z. et al., 2018), type 1 diabetes (T1D) (Yang and Chiang, 2015), type 2 diabetes (T2D) (Yang and Chiang, 2015), and systemic lupus erythematosus (SLE) (Zhu et al., 2012).

Inflammatory bowel diseases (IBDs)

Inflammatory bowel diseases are characterized by chronic inflammation of the intestine and comprise two disorders Crohn's disease and ulcerative colitis. It is believed that the pathogenesis of IBDs is associated with dysregulation of innate and adaptive immune responses, triggered by microbial antigens. This could result in chronic inflammation of the digestive tract and damage to the intestinal mucosa (Fiocchi, 1998). The role of the inflammasome in intestinal inflammation is controversial. Zaki et al. (2010) reported that, NLRP3 induced production of IL-18 in intestinal epithelial cells can be protective, and contributes to epithelium integrity in experimental colitis. In contrast, Seo et al. (2015) have demonstrated the role of inflammasome in exacerbation of an intestinal pathology. The damaging effect of the inflammasome was also confirmed by Shouval et al. (2016), who identified that IL-1 β inhibition improves the course of IBDs. It appears that increased IL-1 β levels and tissue damage in IBDs are linked to NLRP3 activation in myeloid leukocytes infiltrating the gut tissue (Neudecker et al., 2017). The role of the inflammasome in IBDs pathogenesis was also confirmed by using a *miR-223* deficient animal model of colitis (Neudecker et al., 2017). *miR-223* deficient mice

develop experimental colitis manifesting with colonic ulceration, inflammatory leukocyte infiltration and tissue injury which resembles closely IBDs (Neudecker et al., 2017). Tissue injury in these mice was linked to an enhanced NLRP3 expression and elevated IL-1 β (Neudecker et al., 2017). Treatment of animals with *miR-223* mimetics alleviated symptoms of the colitis which coincided with reduced *NLRP3* RNA and IL-1 β levels (Neudecker et al., 2017). This data presents *miR-223* as a novel biomarker and therapeutic target in subsets of IBDs and colitis (Polytarchou et al., 2015).

Rheumatoid arthritis (RA)

Rheumatoid arthritis is a chronic, systemic inflammatory disease affecting joints as well as skin, eyes, lungs, heart, and blood vessels (Scott et al., 2010). It was suggested that RA pathogenesis is related to activation of the NLRP3/IL-1 β axis, where inflammasome activation was linked to worsening symptoms of the disease (Xie Q. et al., 2018). It was shown that activation of NLRP3 leads to an abundant expression of IL-1 β (Guo et al., 2018), which can trigger T helper type 17 (Th17) cell differentiations and osteoclasts activation in RA (Dayer, 2003; McInnes and Schett, 2011; Zhang et al., 2015b). Th17 cells play a central role in RA pathogenesis, by maintaining chronic inflammation, recruiting neutrophils and promoting joint degradation (Cai et al., 2001; Shahrara et al., 2009; Leipe et al., 2010). Recently, an indirect effect of *miR-33* on NLRP3 activation was demonstrated in RA (Xie Q. et al., 2018), which could be explained by miRNA controlled dysregulation of mitochondrial function (Schroder et al., 2010; Zhou et al., 2011; Miao et al., 2014; Ouimet et al., 2015). Xie Q. et al. (2018) suggested that *miR-33* increases mitochondrial oxygen consumption and accumulation of reactive oxygen species which upregulates expression of NLRP3 and PCA1 in RA. Also, both *miR-33* expression and NLRP3 inflammasome activity were found to be higher in RA monocytes as compared to controls (Xie Q. et al., 2018). These findings indicate that *miR-33* could play an indirect role in pathogenesis of RA through NLRP3 inflammasome activation. Additional studies will provide more insight into the miRNA regulation of NLRP3 in RA and its therapeutic and prognostic implications.

Type 1 diabetes (T1D)

Type 1 diabetes is caused by autoimmune targeted elimination of pancreatic β cells islet (Kloppel et al., 1985). It was shown that TLRs play an essential role in the pathogenesis of T1D (Xie Z. et al., 2018). Upregulated expression of TLR4 as well as increased activity of the downstream targets was demonstrated in monocytes from T1D (Devaraj et al., 2008). Increased expression of activated TLRs was explained as a reaction to a high levels of circulating ligands in T1D (Devaraj et al., 2009). Also, epigenetic regulation was associated with an aberrant TLR signaling and an increased IL-1 β expression in T1D (Grishman et al., 2012). Several miRNAs were found altered in pre-T1D patients, where levels of nine miRNAs (*miR-146a*, *miR-561*, and *miR-548a-3p*, *miR-184*, and *miR-200a*) were decreased, and two miRNAs (*miR-30c* and *miR-487a*) were increased (Grieco et al., 2018). Supporting these results was data published by Wang G. et al.

(2018) demonstrating lower levels of *miR-150*, *miR-146a*, and *miR-424* compared to controls. One of the most consistent findings was the decreased *miR-146a* levels in T1D. It appears that *miR-146a* deficiency could play role in T1D exacerbation and increased IL-1 β and IL-18 expression (Bhatt et al., 2016). Increased IL-1 β levels could indicate inflammasome activation in T1D, although the role of inflammasome in the disease pathogenesis remains largely unknown.

Type 2 diabetes (T2D)

Circulating autoantibodies to β cells, self-reactive T cells and the glucose-lowering efficacy of some immunomodulatory therapies are suggestive of the autoimmune nature of the T2D (Itariu and Stulnig, 2014). Interestingly, a role for miRNA regulation of gene expression was demonstrated in T2D, where Balasubramanyam et al. (2011) have shown reduced *miR-146a* which was associated with increased *NF- κ B*, *TNF- α* and *IL-6* mRNA levels. It is the same miRNA, which was found implicated to pathogenesis of T1D (Xie Z. et al., 2018), indicating potential similarities in the pathogenesis of both diseases. Recently *in vivo* studies demonstrated that *miR-146a* deficiency could increase expression of M1 and suppress expression of M2 markers in macrophages collected from patients with diabetes (Bhatt et al., 2016). Macrophage polarization occurs in the presence of IFN γ (M1) or IL-4 (M2) (Nathan et al., 1983; Stein et al., 1992) and is linked to pro-inflammatory and anti-inflammatory activities, respectively. M1 macrophages were shown to support inflammation by producing pro-inflammatory cytokines, including the inflammasome product IL-1 β (Bhatt et al., 2016). Therefore, a link could be suggested between low *miR-146a* levels and inflammasome activation in M1 cells. More investigation is required to identify the connection between *miR-146a* and inflammasome activation and the role of this in T2D pathogenesis.

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus is an autoimmune disease caused by the loss of immune tolerance to ubiquitous autoantigens (Tsokos, 2011). Inflammation plays essential role in SLE pathogenesis (Yang et al., 2014; Rose and Dornier, 2017), where high levels of circulating proinflammatory cytokines are commonly detected (Yao et al., 2016; Mende et al., 2018). Inflammasome activation is proposed as one of the mechanisms underlying increased proinflammatory cytokine level in SLE (Kahlenberg and Kaplan, 2014). This assumption is supported by a report where IL-1 β deficient mice were found to be resistant to experimental SLE (Voronov et al., 2006). Also, an increased expression of NLRP3 and AC1 have been reported in SLE nephritis biopsies (Kahlenberg et al., 2011). Kahlenberg and Kaplan (2014) have shown that SLE macrophages are highly reactive to innate immune stimuli, often leading to inflammasome activation. Therefore, targeting inflammasome activity could be a novel approach for SLE treatment. The expression of several miRNAs targeting the inflammasome and its products were found differentially expressed in SLE. For example, Wang et al. (2012) have demonstrated high levels of circulating *miR-223*, which was shown to inhibit *NLRP3*, in SLE.

Also, reduced levels of circulating *miR-146a*, which regulates priming of TLRs, was found in SLE plasma (Wang et al., 2012). Interestingly, expression of *miR-23b*, which indirectly inhibits IL-1 β responses, was shown to be downregulated in inflammatory lesions of SLE patients and animal model (Zhu et al., 2012). More studies are required to determine the role of miRNAs in pathogenesis of SLE and their therapeutic potential.

miRNA Regulation of Inflammasome in Neurodegenerative Disorders

Inflammasome products, IL-1 β and IL-18, were shown to be essential for the health and functional competence of the nervous system (McAfoose and Baune, 2009; Dinarello et al., 2012). NLRP3 expression was demonstrated in microglia and astrocytes, which could explain the constitutive level of these cytokines in the brain (McAfoose and Baune, 2009; Dinarello et al., 2012; Savage et al., 2012; Minkiewicz et al., 2013; Cho et al., 2014; Lu M. et al., 2014). Interestingly, higher than normal levels of IL-1 β and IL-18 were found in several neurodegenerative disorders, suggesting that over-activation of inflammasomes may play a role in pathogenesis of these diseases (Cho et al., 2014; Lu M. et al., 2014; Denes et al., 2015; Mamik and Power, 2017; Song et al., 2017). The significance of miRNA in the regulation of inflammasome activation in the pathogenesis of neurodegenerative diseases remains largely unknown. However, the role of an aberrant miRNA in regulation of *NLRP3* expression was previously demonstrated in Parkinson's disease (PD).

Parkinson's disease is a neurodegenerative disease which is characterized by progressive loss of dopaminergic neurons in substantia nigra compacta (Gasser, 2009). It is believed that accumulation of α -Syn fibrillary aggregates in the brain, most notably in the nigral dopaminergic neurons, induces the neuroinflammation (Eriksen et al., 2003). According to Zhou Y. et al. (2016), α -Syn can activate NLRP3 inflammasomes in microglia leading to an increased production of IL-1 β . The authors also demonstrated that, *miR-7* and *miR-30e* analogs can inhibit NLRP3 inflammasome mediated neuroinflammation in the brain and protect dopaminergic neurons (Zhou Y. et al., 2016). It appears that the anti-inflammatory effects of *miR-7* and *miR-30e* are associated with their targeting of *NLRP3* mRNA in microglial cells. Interestingly, decreased *miR-7* and *miR-30e* expression was demonstrated in PD, which could lead to the loss of the regulatory control of α -Syn induced NLRP3 activation (Li D. et al., 2018).

miRNA Regulation of the Inflammasome in Cardiovascular Diseases (CVDs)

The physiological significance of inflammation is confirmed as it facilitates elimination of destructive stimuli and pathogens. However, aberrant inflammatory responses could cause tissue damage, tissue fibrosis and chronic diseases (Liu D. et al., 2018). Inflammation is recognized as a major risk factor for CVDs (Zhou et al., 2018), where chronic inflammasome activation was shown to contribute to the pathogenesis of atherosclerosis, ischemic and non-ischemic heart diseases (Zhou et al., 2018). Therefore, regulation of inflammasome activity using miRNA could be used for treatment and prevention of CVDs. Currently, strong

evidence for the role of NLRP3 activation has been demonstrated in pathogenesis atherosclerosis.

Atherosclerosis is a form of CVD characterized by narrowing of the blood vessel lumen due to plaque formation, continuous dyslipidemia and inflammation (Ross, 1993). Chronic inflammation is commonly found in and around the atherosclerotic plaques which has an adverse effect on the arterial wall structure and function (Bernhagen et al., 2007). It is believed that atherogenic lipid mediators, involved in the formation of chronic inflammation in atherosclerotic plaque (Chen et al., 2006), can trigger peripheral blood monocytes migration and differentiation into macrophages within the intima of the arterial wall (Chen et al., 2006). T cells were also detected in atherosclerotic lesions (Kleemann et al., 2008), where, together with activated macrophages, they were shown to secrete proinflammatory mediators such as interferons, interleukins, and proteases (Østerud and Bjørklid, 2003; Shashkin et al., 2005; Tabas, 2005; Chen et al., 2006). IL-1 β expression was identified in the early phase of atherosclerotic plaque formation and this stimulates secretion of additional cytokines and chemokines (Kleemann et al., 2008). Therefore, inflammasome activation in macrophages and T cell within the atherosclerotic lesion contributes to the pathogenesis of chronic inflammation.

miR-22, a miRNA inhibiting *NLRP3*, is decreased in peripheral blood mononuclear cells from coronary atherosclerosis (Chen B. et al., 2016), suggesting that upregulation of this miRNA could have therapeutic potential in CVD. Supporting this assumption, Huang W.Q. et al. (2017) investigated the effect of *miR-22* on the NLRP3 inflammasome and endothelial cell damage in an *in vivo* model of coronary heart disease. The authors demonstrated that *miR-22* mimics could decrease the release of inflammatory cytokines such as IL-1 β and IL-18 by suppressing *NLRP3* expression in monocytes and macrophages (Huang W.Q. et al., 2017). Two additional miRNAs, *miR-9* and *miR-30e-5p* were found to indirectly affect inflammasome activation in atherosclerosis (Wang Y. et al., 2017; Li P. et al., 2018). It appears that *miR-9* could indirectly suppress inflammasome activation by targeting an atherogenic lipid mediator, oxidized low-density lipoprotein (oxLDL), in atherosclerosis (Liu W. et al., 2014). In another report, Wang Y. et al. (2017) reported that *miR-9* inhibits NLRP3 inflammasome activation induced by oxLDL in human THP-1 derived macrophages and peripheral blood monocytes in an *in vitro* atherosclerosis model. *miR-9* targets *Janus kinase 1 (JAK1)* pathway (Wang Y. et al., 2017) inhibiting expression of NF- κ B p65 which is required for the first step of NLRP3 inflammasome activation (Wang Y. et al., 2017). In addition, *miR-30c-5p* was linked to an indirect regulation of *NLRP3* expression in atherosclerosis (Li P. et al., 2018). Li P. et al. (2018) reported that *miR-30c-5p* protects human aortic endothelial cells (HAECs) from the oxLDL insult by targeting *FOXO3*. The authors showed that *miR-30c-5p* can suppress *FOXO3* expression and, consequently, decrease levels of NLRP3, AC1, IL-18 and IL-1 β in HAECs (Li P. et al., 2018). As evidence emerges supporting the role of NLRP3 in the pathogenesis of atherosclerosis, targeting the inflammasome becomes an attractive therapeutic approach, where miRNAs could be suitable novel tools.

miRNA in Regulation of Inflammasome in Cancer

The role of the inflammasome in tumorigenesis remains controversial. Some reports indicate that NLRP3 inflammasome activation and IL-18 signaling protect against colorectal cancer (Karki et al., 2017), whereas progression of breast cancer, fibrosarcoma, gastric carcinoma, and lung metastasis were shown to be supported by the inflammasome (Okamoto et al., 2010; Kolb et al., 2014). Inflammasome regulation is complex, where multiple factors are implicated, making identification of the key regulatory elements challenging. As the inflammasome involvement in pathogenesis of some malignancies becomes more evident, understanding the regulatory mechanisms could lead to the discovery of novel therapeutic targets for cancer treatment.

Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is a frequent sequelae of hepatitis B and hepatitis C viral infection (Perz et al., 2006). It is understood that these viruses activate NLRP3 inflammasomes causing hepatocyte pyroptosis, apoptosis and fibrosis (Kofahi et al., 2016). However, HCC tissue analysis failed to detect inflammasome activation; in fact, it was found to be significantly down-regulated when compared to the adjacent normal tissue (Zhu et al., 2011; Wei et al., 2014). To explain this inconsistency, Wei et al. (2014) suggested that *NLRP3* expression is dynamic changing during the progression of HCC. It appears that *NLRP3* expression was increased in liver cells at the early stages of transformation, while inflammasome levels were decreased in malignant cells when compared to adjacent normal tissue (Wei et al., 2014). Interestingly, levels of *miR-223*, a negative regulator of *NLRP3*, were found to be increased in Hep3B cells derived from HCC (Wan et al., 2018). Increased *miR-223* was shown to coincide with tumor growth, suggesting a role in post-transcriptional mechanisms in malignant progression. In addition to *NLRP3*, *miR-223* was shown to target *erythrocyte membrane protein band 4.1 like 3 (EPB41L3)* and *FOXO1* (Li and Rana, 2014; Kim et al., 2017). *FOXO1* transcription factor binds to the thioredoxin-interacting protein (TXNIP) and regulates genes involved in cell death as well as the oxidative stress responses (Kim et al., 2017). TXNIP interacts with the NLRP3 inflammasome and activates AC1 in murine β -cells (Zhou et al., 2010). In addition, *miR-223* appears to be released systemically, where the level of this miRNA in the plasma was significantly lower in HCC cases (Giray et al., 2014). In addition to *miR-223*, decreased circulating *miR-30e*, which also targets *NLRP3*, was found in HCC cases (Bhattacharya et al., 2016). Therefore, it could be suggested that analysis of serum levels of *miR-223* and *miR-30e* could be used for diagnosis of HCC as well as an indicator of the efficacy of anticancer therapeutics.

Colorectal cancer (CRC)

Data on the role of NLRP3 in colorectal cancer (CRC) pathogenesis is inconsistent, where some evidence suggests a pro-tumorigenic role for the inflammasome, while others identified that the inflammasomes protects against tumor (Allen et al., 2010; Huber et al., 2012; Guo et al., 2014; Wang et al., 2016). Inflammasome expression analysis also demonstrated

contradicting results where Wang et al. (2016) reported high NLRP3 in mesenchymal-like colon cancer cells, while Allen et al. (2010) demonstrated decreased inflammasome expression in colitis-associated cancer. Inflammasome contribution to tumorigenesis varies depending on the target cell type in the intestinal tissue (Lissner and Siegmund, 2011). According to Lissner and Siegmund (2011), inflammasome activation is required to maintain integrity of the epithelium. However, aggravated activation of the inflammasome stimulates intestinal inflammation, which could have a detrimental effect on epithelium permeability and increase its leakage (Lissner and Siegmund, 2011). It was identified that damage to the intestinal epithelium could trigger NLRP3 activation and secretion of IL-18, a proinflammatory cytokine (Huber et al., 2012). Subsequently, it was shown that IL-18 could reduce the expression of IL-22 binding protein (IL-22BP) and increase levels of IL-22 (Huber et al., 2012). Although IL-22 is protective against malignancies, aberrant over expression of IL-22 could trigger gut epithelial cell transformation and CRC development (Huber et al., 2012). Therefore, it is believed that IL-18, a NLRP3 product, has a promoting role in CRC development (Huber et al., 2012).

Targeting the inflammasome was suggested as a potential approach for treatment of CRC (Guo et al., 2014). NLRP3 expression was shown to be regulated by multiple miRNAs in various diseases (Haneklaus et al., 2012; Feng et al., 2018; Wan et al., 2018; Xie Q. et al., 2018). However, the role of miRNAs in cancer pathogenesis is not straight forward. There are inconsistent results regarding the expression status of *miR-223*, a known regulator of NLRP3 expression, in CRC cell lines and primary tumors. In a clinical study, the expression of *miR-223* was found to be significantly higher in stage III/IV patients (Ding J. et al., 2018). However, levels of *miR-223* vary significantly in colon tumor derived cell lines (Ding J. et al., 2018). Wu et al. (2012) reported reduced expression of *miR-223* in a HCT116, a CRC cell line. In contrast, several research groups demonstrated up-regulation of *miR-223* in CRC cell lines and primary tissues (Wang F. et al., 2017; Ju et al., 2018; Wei et al., 2018). Similar to these results, Ju et al. (2018) demonstrated up-regulation of *miR-223* in SW620, a CRC cell line. It was identified that high expression of *miR-223* suppresses *FoxO3a* and enhances cancer cell proliferation (Ju et al., 2018). It appears that the protumorigenic effect of *Foxo3a* is via NF- κ B activation, which is essential for upregulation of the inflammasome linked proinflammatory signaling pathways (Thompson et al., 2015).

Unlike *miR-223*, data on *miR-22* expression status in CRC consistently demonstrates that *miR-22* expression is significantly lower in CRC tissues and cell lines (Zhang et al., 2012, 2015a; Li B. et al., 2013; Xia et al., 2017; Liu Y. et al., 2018). Also, absence of *miR-22* was shown to positively correlate with increased cancer cell proliferation, migration, invasion, and metastasis (Zhang et al., 2012, 2015a; Li B. et al., 2013; Xia et al., 2017; Liu Y. et al., 2018). Multiple genes were identified as targets for *miR-22* including *TIAM1* (Li B. et al., 2013), *BTG1* (Zhang et al., 2015a), *HuR* (Liu Y. et al., 2018), and *SP-1* (Xia et al., 2017). Among these genes, only *SP-1* gene expression was linked to inflammasome regulation (Hofmann et al., 2015). According to Hofmann et al. (2015), Sp-1 protein could contribute to

NLRP3 inflammasome activation in monocytes in chronic recurrent multifocal osteomyelitis. However, the role of Sp-1 in activation of the NLRP3 inflammasome in CRC tumor tissues and monocytes remains largely unknown. Recent finding revealed that, in addition to *miR-22*, another negative regulator of NLRP3, *miR-30e*, is absent in CRC tumors as compared to normal colon tissues (Laudato et al., 2017). However, the role of *miR-30e* in CRC pathogenesis remains unknown.

Gastric cancer (GC)

It was shown that NLRP3 inflammasome activation promotes gastric cancer (GC) cells proliferation (Li S. et al., 2018). Over expression of *miR-223* supports GC invasion and metastasis in primary GC tumors (Haneklaus et al., 2012). Additionally, Li S. et al. (2018) reported that increased NLRP3 expression in GC tumors and macrophages negatively correlates with *miR-22* expression. The authors also demonstrated that constitutive expression of *miR-22* dramatically decreases *NLRP3* mRNA expression and IL-1 β secretion in macrophages (Li S. et al., 2018). Therefore, the effect of targeting *NLRP3* expression with miRNAs in tumors and immune cells may vary depending on tumor and/or cell type.

Oral squamous cell carcinoma (OSCC)

High *NLRP3* expression was found in oral squamous cell carcinoma (OSCC) cells and tissues (Wang H. et al., 2018). A role for *NLRP3* supporting OSCC proliferation and growth was demonstrated in several reports. Wang G. et al. (2018) demonstrated a positive correlation between *NLRP3* expression and tumor size, lymph node status and IL-1 β expression in OSCC tissue specimens and *in vivo* models of OSCC. Also, the authors showed that, silencing of *NLRP3* in OSCC cell lines reduced cell proliferation, migration, and invasion *in vitro* (Wang H. et al., 2018). Additionally, high expression of the NLRP3 inflammasome mediates chemoresistance in OSCC (Feng et al., 2018). Therefore, downregulation of *NLRP3* could have a therapeutic potential in OSCC.

Surprisingly, high expression of *miR-223*, which targets *NLRP3*, was found in primary OSCC tissue (Manikandan et al., 2016). *In silico* analysis identified a *Ras Homolog Family Member B (RHOB)* as a potential target for *miR-223* in OSCC (Manikandan et al., 2016). It appears that *miR-223* could indirectly suppress NLRP3 and TLR4/NF- κ B signaling via RHOB (Yan et al., 2019). These data provide a novel potential target for OSCC treatment, where *miR-223* inhibition of NLRP3 could be attained through RHOB.

Overexpression of *miR-22* in OSCC was shown to reduce NLRP3 activation and decrease OSCC malignancy (Feng et al., 2018). *miR-22* levels were shown to be inversely correlated with NLRP3 expression and *miR-22* levels were significantly lower in OSCC compared to adjacent non-cancerous tissue (Feng et al., 2018). The inhibitory effect of *miR-22* on OSCC migration was confirmed using a lentiviral expression system. As expected an inhibitor of *miR-22* promoted OSCC spread (Feng et al., 2018). The 3'-UTR of the *NLRP3* gene was identified as a *miR-22* target site (Feng et al., 2018). It appears that

NLRP3 promotes OSCC growth and tumor spread, which makes *miR-22* a potential therapeutic target for cancer treatment. Two miRNAs, *miR-223* and *miR-22*, were identified as inhibiting the inflammasome and, subsequently, suppressing tumor growth. Therefore, the anti-tumor effect of these molecules in OSCC warrants further investigation.

Cervical cancer (CC)

Human papillomavirus (HPV) infection and persistent chronic inflammation were identified as fundamental for the pathogenesis of cervical cancer (CC) (de Castro-Sobrinho et al., 2016; Kriek et al., 2016). HPV can cause chronic inflammation by inducing TLR4 expression and impairing the TLR4-NF- κ B pathway (Wang et al., 2014; He A. et al., 2016).

Wu et al. (2012) reported reduced expression of *miR-223*, which targets *NLRP3*, in the CC cell line HeLa. The authors also demonstrated that over-expression of *miR-223* inhibits tumor cell proliferation by targeting *FOXO1* (Wu et al., 2012). In addition, another direct post-transcriptional regulator of *NLRP3*, *miR-22*, was found to be down-regulated in CC cell lines and tissues (Xin et al., 2016; Wongjampa et al., 2018). Furthermore, Wongjampa et al. (2018) reported an inverse correlation between histone deacetylase 6 (HDAC6) and *miR-22*. It was previously shown that HDAC6 directly binds to NLRP3 via its ubiquitin-binding domain to regulate NLRP3 inflammasome expression (Hwang et al., 2015). As NLRP3 plays a role in the pathogenesis of HPV induced chronic inflammation, *miR-223* and *miR-22*, both of which regulate inflammasome activation, could be potential therapeutic tools for the treatment of CC.

Glioblastoma (GBM)

High NLRP3 inflammasome activation and high levels of inflammasome products are found in malignant glioblastoma (GBM) (Basu et al., 2004; Tarassishin et al., 2014). Increased IL-1 β , a major NLRP3 inflammasome product, was linked to the release of VEGF and MMPs, angiogenic factors, in human astrocytes and GBM cells (Suh et al., 2013). Therefore, it could be suggested that inflammasome activation favors GBM growth and spread.

Several miRNAs were shown to regulate inflammasome expression, where decreased miRNA levels could promote GBM growth and invasion. Ding Q. et al. (2018) demonstrated that *miR-223*, which is effective at reducing NLRP3 inflammasome levels in several tumors (Wu et al., 2012), was decreased in GBM tissues (Ding Q. et al., 2018). However, a conflicting report from Cheng et al. (2017) indicated that *miR-223* is overexpressed in GBM cell lines. Similar findings were also reported in GBM stem like cells and GBM tissues (Huang B.S. et al., 2017). Similarly there are conflicting data regarding *miR-223* targets and phenotypic impacts. A *miR-223-3p* mimic inhibited tumor cell proliferation and migration, effects that were due to a reduction in proinflammatory cytokines IL-1 β and IL-18 in GBM cell lines (Ding Q. et al., 2018). Also, nuclear factor I-A (NFIA) was a target of *miR-223* in GBM cell lines and was found to decrease tumorigenesis in the CNS (Glasgow et al., 2013). The pro-tumorigenic effect of *miR-223* was linked to suppression

of the tumor suppressor *paired box 6* (*PAX6*) (Cheng et al., 2017). By targeting *PAX6*, *miR-223* could promote GBM stem cell chemotherapy resistance (Huang B.S. et al., 2017). The mechanism underlying the diverse effects of *miR-223* on GBM growth and metastasis remains largely unknown. However, it could be suggested that the stage of tumorigenesis plays a role in the effect of *miR-223* in GBM.

Levels of *miR-22* and *miR-30e*, two post-transcriptional regulators of *NLRP3*, are low in GBM tissues (Li W.B. et al., 2013; Chakrabarti et al., 2016; Chen H. et al., 2016). In addition to targeting *NLRP3*, *miR-22* can also directly target the 3'-UTRs of *SIRT1* (Li W.B. et al., 2013), and *miR-22* mimics decrease the expression of *SIRT1* protein in GBM cell lines (Li W.B. et al., 2013). Interestingly, several studies have demonstrated that *SIRT1* can suppress *NLRP3* (Ma et al., 2015; Jiang et al., 2016; Zhou C.C. et al., 2016). It could be proposed that the decreased levels of *miR-22* could fail to control *NLRP3* expression, which could enable GMB tumorigenesis.

FUTURE ASPECTS FOR CLINICAL APPROACHES

The role of the *NLRP3* inflammasome in the pathogenesis of several diseases was demonstrated, including CAPS, autoimmune disorders and cancers (Aganna et al., 2002; Martinon et al., 2006; Masters et al., 2009; Bauer et al., 2010; Wen et al., 2011). An increased IL-1 β level, commonly found in these diseases, is a strong indicator of *NLRP3* inflammasome activation. Also, the body of evidence suggests that IL-1 β plays a central role in disease pathogenesis. Therefore, targeting IL-1 β , a *NLRP3* inflammasome product, appears to be a rational therapeutic approach. The efficacy of anti-IL-1 β therapy was demonstrated in CAPS, where both the symptoms and severity of the disease were alleviated using either an IL-1 β receptor antagonist or anti-IL-1 β antibodies (Hoffman et al., 2008; Dinarello, 2009; Lachmann et al., 2009). A similar approach targeting IL-1 β was successfully applied to treat *NLRP3* inflammasome associated autoimmune diseases and cancer (Larsen et al., 2007; Lust et al., 2009). These data provide compelling evidence for the *NLRP3* inflammasome as a potential therapeutic target for treatment of the diseases associated with an elevated level of IL-1 β . In this respect, miRNAs have therapeutic potentials as they could target *NLRP3* preventing its expression and, consequently, averting IL-1 β production.

miRNA based replacement and silencing therapeutic approaches were tested in several preclinical and clinical studies (Li and Rana, 2014). miRNAs and miRNA-targeting oligonucleotides approaches (mimic and/or anti-miR technologies) appear to be more effective when compared to small-molecule drugs due to their ability to effect concurrently multiple gene targets (Li and Rana, 2014). Anti-*miR-122* oligonucleotide, Miravirsin, was the first miRNA-based therapeutic used to treat hepatitis c infection (Lindow and Kauppinen, 2012; van der Ree et al., 2016). Currently Miravirsin is in a phase II clinical trial (van der Ree et al., 2016). Several phase

I clinical trials and pre-clinical studies using miRNA-targeting oligonucleotide technologies targeted to *Let-7*, *miR-10b*, *miR-21*, *miR-34*, *miR-155*, *miR-221*, and others, have demonstrated positive results (Moles, 2017). miRNA-targeting oligonucleotides are designed to bind to their targeted miRNA (Li and Rana, 2014). miRNAs generally target more than one gene in the same signaling pathway (Li Z. et al., 2011; Li and Rana, 2014). This feature of miRNAs makes them valuable as therapeutic candidates (Li and Rana, 2014).

However, there are still multiple obstacles to overcome, including target specificity and the potential toxicity of miRNA-targeting oligonucleotides (Merhautova et al., 2016). First, the limited specificity, anti-miRs generally target nucleotide sequences on miRNAs which can be present on multiple miRNAs within the same family (Hogan et al., 2014). Chemical modifications of anti-miRs have been suggested to improve their specificity (Hogan et al., 2014). Second, when administered without a carrier molecule, their effect may be limited and they can be cleared by the liver and kidney (Bennett and Swayze, 2010). Third, anti-miRs can be sensed and eliminated by receptors of the innate and adaptive immune responses (Diebold et al., 2004; Heil et al., 2004). 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. For example, the therapeutic efficiency of *miR-223* was improved by using nanoparticle lipid emulsions as a delivery method, in animal model of colitis (Neudecker et al., 2017). These exciting results demonstrate great potential for miRNA-based treatments of diseases linked to *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.

AUTHOR CONTRIBUTIONS

GT and SK contributed to the conception and design of the study. ZG organized the database. SK wrote the first draft of the manuscript. GT, EM, ZG, AM, AR, and SK wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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