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MicroRNAs in Shaping the Resolution Phase of Inflammation

Raza Ali Naqvi[1], **Meenal Gupta**[2], **Anne George**[3], **Afsar R. Naqvi**[1,*]

[1]Department of Periodontics, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois, USA

[2]Department of Department of Human Genetics, University of Utah, Salt Lake City, Utah, USA

[3]Department of Oral Biology, College of Dentistry, University of Illinois at Chicago, Chicago, Illinois, USA

Abstract

Inflammation is a host defense mechanism orchestrated through imperative factors - acute inflammatory responses mediated by cellular and molecular events leading to activation of defensive immune subsets - to marginalize detrimental injury, pathogenic agents and infected cells. These potent inflammatory events, if uncontrolled, may cause tissue damage by perturbing homeostasis equilibrium towards immune dysregulation. A parallel host mechanism operates to contain inflammatory pathways and facilitate tissue regeneration. Thus, resolution of inflammation is an effective moratorium on the pro-inflammatory pathway to avoid the tissue damage inside the host and leads to reestablishment of tissue homeostasis. Dysregulation of the resolution pathway can have a detrimental impact on tissue functionality and contribute to the diseased state. Multiple reports have suggested peculiar dynamics of miRNA expression during various pro- and anti-inflammatory events. The roles of miRNAs in the regulation of immune responses are well-established. However, understanding of miRNA regulation of the resolution phase of events in infection or wound healing models, which is sometimes misconstrued as anti-inflammatory signaling, remains limited. Due to the deterministic role of miRNAs in pro-inflammatory and anti-inflammatory pathways, in this review we have provided a broad perspective on the putative role of miRNAs in the resolution of inflammation and explored their imminent role in therapeutics.

Keywords

MicroRNA; Post-transcriptional regulation; Inflammation; Resolution; Pathogenesis; Wound healing

[*]**Corresponding Author**: Dr. Afsar R. Naqvi, University of Illinois at Chicago, College of Dentistry, Department of Periodontics, 461A Dent MC 859, 801 South Paulina, Chicago, IL 60612, afsarraz@uic.edu.

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CONFLICT OR INTEREST

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1. Introduction

Inflammation is a tightly regulated host response against a diverse gamut of biological and non-biological factors (*viz.*, pathogens, damaged cells and toxic compounds, pathogenic insult) to reinstate tissue homeostasis [1, 2]. Typically, inflammation involves the following sequence of events: 1) induction phase, 2) inflammatory phase, and 3) resolution. The induction phase is comprised of activation of tissue resident innate immune subsets (macrophages and dendritic cells) after recognition of the biological/non-biological threat. Various lipid and protein mediators are released to recruit innate immune cells (polymorphonuclear cells {PMNs}) at the site of damage [1–4]. This is followed by the inflammatory phase during which the pathogen is phagocytosed, the derived antigens are presented to adaptive immune cells for further amplification of inflammatory processes, and antibody-producing B cells are activated. Upon removal of the danger signal, the resolution phase ensues and tissue homeostasis is restored. Each phase of inflammation should be well-coordinated, as failure to resolve the inflammation leads to multiple chronic inflammatory diseases: arthritis [5], colitis [6], or asthma [7] associated with irreversible tissue damage and high odds of developing cardiovascular disease, cancer, osteoporosis, etc. [8–10].

Multiple genes work in a concerted manner to regulate molecular pathways that guide each phase of inflammation, including resolution. In addition to protein coding genes, the human genome encodes for non-protein coding RNAs which participate as transcriptional and post-transcriptional regulators of host functions. MicroRNAs (miRNA) are a class of endogenous gene regulatory non-coding RNAs that perform central functions in various cellular processes including cell differentiation, apoptosis, immune response, cell proliferation, etc. In this pursuit, miRNA have been identified as molecular switches to fine-tune both inflammation and the resolution process [11]. Thus, miRNAs, either as mimics or antagonists, hold therapeutic promise as drugs, in mitigating inflammation or augmenting resolution.

In this review, we summarize the sequence of events involved in the process of inflammation and resolution, and their control by specific miRNAs. Furthermore, we will provide insights on miRNA expression dynamics and regulomics (involving miRNA mimics/antagonist) can be leveraged in inducing the resolution of uncontrolled inflammation, which might otherwise result in chronic inflammation and tissue damage.

2. Inflammation Process For The Protection From Biological/Non-Biological Insult

The initiation of inflammation occurs after local non-immune or immune cells sense biological/non-biological antigens through highly conserved receptors and generate a conducive microenvironment for the activation and infiltration of other immune cells [1–4]. Amongst various classes of Pattern Recognition Receptors (PRRs), including C-type lectin receptors (CLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), and NOD-like receptors (NLRs), Toll-Like Receptors (TLRs) are both the most studied and highly conserved receptors [12, 13]. Typically, TLR signaling is mediated through myeloid differentiation factor-88 (MyD88) [14, 15] and involves nuclear transport of

transcription factors *viz*. activator protein-1 (AP-1) and NF-κB or interferon regulatory factor 3 (IRF3) in the nucleus for the production of pro-inflammatory molecules including cytokines/chemokines (interleukin-1 beta, interleukin-6, tumor necrosis factor alpha (TNF-α), etc.) and prostaglandins E2 (PGE2) [4, 14, 15]. Activated tissue resident cells secrete inflammatory mediators, which increase blood flow in the affected region to induce the redness (rubor) and increased heat (calor) characteristic of vasodilation in the inflammatory process. PRRs or Damage Associated Molecular Patterns (DAMPs) harboring macrophages and mastocytes release vasoactive amines (histamine and serotonin) as well as pro-inflammatory lipid mediators eicosanoids (*viz*. prostaglandin E2 and leukotriene B4) for the remodeling of local vasculature to increase the blood flow to the inflamed site [1–4, 16, 17]. Nitric oxide produced by the activated tissue resident macrophages further induces the permeability of blood vessels [18, 19], which results in the leakage of plasma proteins into the damaged tissue area (edema) and subsequent swelling (tumor) of the tissues [18–20]. Plasma proteins include complement, lysozyme, and antibodies to directly kill and facilitate opsonization of microbes, a perfect preparation for the imminent cellular phase [21]. When the inflammatory region is the wounded tissue, the exuded platelets, coagulants, plasmin and kinins induce clot formation around this area, thereby providing a structural scaffold in the form of a fibrin lattice to initiate wound repair events [22–25]. Some of the leaked tissue fluid containing bacteria is also reported to be funneled to the regional lymph nodes, wherein it prepares the host defense system to activate the adaptive immune response [26, 27]. Bradykinin released during this course also increases sensitivity to pain (hyperalgesia, dolor) in the affected region. Sometimes, loss of function (*functio laesa*) can be seen as a negative neurological reflex in response to pain [28].

Leukocytes, the cellular component of inflammation, play a pivotal role in clearing the origin of inflammation. Elicitation of adept innate and adaptive immune responses cannot be assured unless leukocyte extravasation occurs through blood vessels at the site of inflammation - the process known as diapedesis [29]. Activation of tissue resident macrophages induces secretion of cytokines (*viz*., IL-1 and TNF-α) and chemokines, which binds to proteoglycans located in the cell walls of inflamed tissue, passes through the injured/inflamed tissue and induces surface expression of P-selectin, E-selectin, Intercellular Adhesion Molecule 1 (ICAM1) and Vascular cell adhesion protein 1 (VCAM1) on endothelial cells [30]. Weak binding of carbohydrate ligands on the leukocyte cell membrane to these integrin molecules allows them to “roll” along the endothelial surface of the blood vessels - due to weak bond formation and breakage in a simultaneous manner. As a result, these leukocytes extravasate into the inflamed tissue to neutralize the antigenic stimuli and perform the following imperative functions: 1) phagocytic uptake of bacteria, viruses, and cellular debris, 2) release of enzymes to damage pathogenic invaders, and 3) secrete pro-inflammatory molecules to maintain the immune response until clearance of the pathogenic insult is achieved. Typically, granulocytes (PMN subtype; neutrophils) are known to induce acute inflammation, whilst monocytes and lymphocytes (T cells and B cells) are responsible for sustained inflammation. Activation of complement C3b, in conjunction with antibodies (produced by plasma cells) exuded into the inflamed tissue, augment phagocytosis and opsonization of microbial antigens by granulocytes and monocytes. These phagocytes also express opsonin receptors, Fc receptor (FcR) and complement receptor 1 (CR1), which

orchestrate activation of the complement system in order to clear the microbes from the host [18–20, 31].

Interestingly, DAMPs can also be triggered in the immune system in the absence of an acute infectious insult or activation of PAMPs. This situation is dubbed as 'non-infective sterile systemic chronic inflammation (SCI), which occurs more frequently with age. Typically, SCI promotes low-grade but persistent inflammation responsible for hypertension, hyperglycemia and dyslipidemia, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease (CVD), chronic kidney disease, depression, neurodegenerative and autoimmune diseases, osteoporosis and sarcopenia. Furthermore, the triggers of sterile inflammation have been classified as extracellular (originating from the extracellular matrix) and intracellular (including high-mobility group box 1 [HMGB1]), mitochondrial DNA and peptides, uric acid, and cellular chaperones (e.g., heat shock proteins)). A study involving murine renal IRI models provides the evidence that HMGB1 signaling via TLR4 is the key factor exacerbating the disease in these models. Also, more work is needed to understand the in-depth mechanism of sterile inflammation [32].

3. Chronic Inflammation Has The Potential To Damage Impacted Organs

Though inflammation has evolved as a protective response to neutralize foreign organisms/material, the safety and survival of the host also demands an efficiently operated, well-balanced regulatory system to induce the refurbishment of damaged tissue structures and function. Principally, PRR activation results in the activation of the following three signaling cascades: mitogen-activated protein kinase (MAPK), nuclear factor kappa-B (NF-κB), and Janus kinase (JAK)-signal transducer and activator of transcription (STAT). Therefore, the following four mechanisms are employed by the host to mitigate uncontrolled inflammation: 1) members of protein tyrosine phosphatase (PTP) family (SHP1/2 and CD45) negatively regulate tyrosine kinase (TK) signaling [33]. Further, MAPK kinase phosphatases (MKPs) of this family regulate the duration of TNF-α-mediated JNK activation [34]; 2) suppressors of cytokine signaling (SOCS), which function as ubiquitin ligases, are responsible for the negative feedback control of JAK–STAT signaling [35]; 3) ubiquitin ligase (A20) interferes with TLR and TNFR signaling and inhibits the NF-κB pathway [36]; and 4) anti-inflammatory mediators (IL-10) are induced by pro-inflammatory signaling pathways [37]. Häcker et al. reported that the gene expression equilibrium of TNF receptor (TNFR) associated factor (TRAF) −3 and −6, an upshot of TLR signaling, determines the expression of IL-10 [39]. Perturbation in any of the aforementioned mechanisms would result in chronic inflammation-mediated injuries to the host, wherein inflammation may persist for longer than the normal duration and may eventually cause tissue damage. Indeed, the progression of cardiovascular disease [40], lung diseases (COPD) [41], diabetes (T2D) [42], pancreatitis [43], intestinal inflammatory diseases (CD and UC) [44], liver diseases (alcoholic or nonalcoholic steatohepatitis, drug-induced liver injury, and ischemia/reperfusion) [45–47], kidney diseases, (glomerulonephritis, end-stage renal disease, or acute or chronic kidney disease) [49–50] have convincingly demonstrated organ-specific uncontrolled inflammatory events as central to these diseases. Table 1 lists the dysregulation of key inflammatory processes during the onset and progression of the aforementioned diseases.

4. Resolution Phase of Inflammation

The persistence of immunological, physiological and tissue architectural changes during the orchestration of acute inflammation can be harmful in the absence of satisfactory regulation and therefore demands timely recession after the neutralization of the pathogen/tissue injury threat [51, 52]. Thus, the successful resolution of inflammation requires: 1) gradual cessation of immune cell extravasation (*stop*), 2) counter-regulation of pro-inflammatory chemokines and cytokines (*sink*), 3) downplay of immune cell activation signaling, 4) induction of apoptosis of immune effector cells (both innate and adaptive) and their efferocytosis (of neutrophils) by reprogrammed M2 macrophages (*skew and kill*), 5) induction of immune suppressive cells to control pro-inflammatory cell activation and function, and 6) the induction of tissue healing processes (*heal*). Therefore, similar to the initiation phase of inflammation, resolution also necessitates a well-coordinated resonance of these pathways [51, 52]. Failure of one or more of these cardinal steps will likely result in human chronic inflammatory diseases [41–50].

Resolution of inflammation is very different from anti-inflammatory effects. For instance, glucocorticoids are given to inhibit the action of pro-inflammatory cytokines (IL-1α, IL-1β, TNF-α), keratinocyte growth factor, TGF-(β1, β2, and β3), platelet-derived growth factors (PDGF) and their receptors, tenascin-C, stromelysin-2, and macrophage metalloelastase at the wounded skin which impacts the expression of important genes involved in wound healing [53]. Intriguingly, a novel cyclooxygenase-2 (COX-2) inhibitor prescribed to avoid pain and inflammation induces thrombosis [54]. Also, clinical reports evince that TNF-α-neutralizing therapy should not be given to patients with known cardiac history [55]. This therapy dampens host potential to combat various pathogens and the host become susceptible to various opportunistic infections (listeriosis, pneumonia and aspergillosis) and activation of latent tuberculosis [56]. Therefore, anti-inflammatory agents can ameliorate the actions of specific pro-inflammatory mediators that are involved in tissue damage, whilst resolution activates the cellular processes that eventually coordinate not only to control the damage but also to trigger the damage repair and tissue healing processes.

5. Key Pathways Involved In Accomplishing Successful Infection Resolution

Recent scientific reports unraveled the upregulation, release and coordination of immune mediators that have the potential to shift acute inflammation towards resolution. These molecules include pro-resolving lipid mediators [lipoxins (e.g., LXA_4), resolvins (e.g., RvD1), protectins, and maresins] [57], proteins and peptides [e.g., annexin A1 (AnxA1), adrenocorticotropic hormone, chemerin peptides, and galectin-1] [58], gaseous mediators (e.g., H_2S and CO) [59], a purine (adenosine) [60], as well as neuromodulators (acetylcholine and other neuropeptides) released under the control of the vagus nerve [61]. In this section, we will discuss the generation of the aforementioned mediators during various infection pathways.

5A. Role of Prostaglandin Derived 15d-PGJ$_2$ in the Resolution of Inflammation

During inflammation, COX-2 activity produces PGD2 as a major molecule from a variety of immune subsets *viz.*, macrophages, DC, T cells, mast cells and platelets [62]. Dehydration of PGD2 yields sPGJ$_2$, Δ-PGJ$_2$ and 15-deoxy-Δ-PGJ$_2$ (15d-PGJ$_2$) [63]. Out of these metabolites, 15d-PGJ$_2$ has demonstrated high affinity towards peroxisome proliferator-activated receptor gamma (PPARγ) and therefore suppresses the induction of the NF-κB, AP-1, and STATs inflammatory cascades [64]. 15d-PGJ$_2$ also suppresses the inducible nitric oxide synthase, interleukin (IL)-1β, TNF-α and IL-12 in macrophages [65], microglial cells [66] and dendritic cells [67]. Importantly, 15d-PGJ$_2$ preferentially circumvents monocyte trafficking rather than PMN recruitment at the site of inflammation. Therefore, these molecules can control chronic inflammatory processes without affecting the onset phase of acute inflammation. Also, the apoptosis-inducing attribute of this molecule in granulocytes, macrophages, and myofibroblasts makes it imperative in preventing the exacerbation of tissue damage during the late phase of inflammation [68]. Importantly, 15d-PGJ$_2$ treatment is reported confer immune protection in the experimental models of ischemia reperfusion injury [69], inflammatory bowel disease [70], adjuvant-induced arthritis [71] and experimental autoimmune encephalomyelitis [72]. Furthermore, 15d-PGJ$_2$ has shown dose-dependent immune protection in different cell types (peripheral blood monocytes-macrophages, J774 macrophages or A549 cells) [73]. It is also reported that Heme Oxygenase-1 (HO-1) expression, a stress-inducible enzyme that enhances degradation of heme to liberate free iron, carbon monoxide, biliverdin and bilirubin in mammalian cells, regulates resolution of 15d-PGJ$_2$-mediated inflammation [74].

5B. Immune Cell-Derived Lipoxins and Resolvins Inhibit Leukocyte Recruitment, Efferocytosis and Apoptosis Induction by Macrophages

Recent progress in the field of lipidomics elucidated the presence of various eicosanoids in resolution exudates derived from mice. It has been shown that arachidonic acid [(AA; refers to all-*cis*-5,8,11,14-eicosatetraenoic acid, an omega-6 polyunsaturated fatty acid [PUFA])-derived eicosanoids can be released from the plasma membrane of activated immune cells expressing TNFR and TLR4 upon influx of Ca^{2+}. This process is catalyzed by the cytosolic Ca^{2+}-dependent enzyme Cytosolic Phospholipase A2 (cPLA2) [75, 76]. Conversely, cytosolic Ca^{2+}-independent PLA2 (iPLA2) and specialized pro-resolving mediators (SPMs) catalyze the recycling of AA back into the plasma membrane to restore cellular hemostasis [77, 78]. Importantly, transcellular conversion of AA via the lipoxygenase (LOX) superfamily of enzymes in multiple immune cells converts it into the lipoxin (LX) family of eicosanoid metabolites, which inhibit the following vital aspects of inflammation: 1) chemotaxis, 2) PMN rolling and transmigration through endothelial cells of blood vessels, and 3) PMN-mediated increase in vascular permeability to restore tissue homeostasis [79]. Successful resolution of allergic pleural edema via LX and their analogues and enhancing non-phlogistic phagocytosis of monocyte-derived macrophages to clear the apoptotic PMNs substantiated their potential therapeutic role in the resolution of inflammation [80]. Inhibitory signaling induced by LXA$_4$ and aspirin-triggered 15-epi-LXA$_4$, and their other stable analogues, is initiated after their binding to high affinity G-protein-coupled receptors (ALXR or FPRL1) [80].

Down-regulation of CD11b/CD18 in human neutrophils can control inflammation as it impairs endothelial–leukocyte interactions [81]. Interestingly, a TNF-α-induced murine dorsal air-pouch model of acute inflammation initially showed induction of leukotriene B_4, followed by PMN infiltration and PGE2 synthesis [82]. Later, a remarkable decrease in PMN infiltration was observed with the concomitant synthesis of 5-LOX-generated leukotriene B_4 to 15-LOX-elicited pro-resolving LXA_4 in the presence of PGE2. It was concluded that the presence of LXA_4 in this experimental inflammation setting suggests that it may serve as a signature of controlled rather than uncontrolled inflammation [82].

In addition to AA-derived fatty-acid substrates, the potent anti-inflammatory products derived from docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), omega-3 fatty-acid constituents of fish oils, have also been detected in the resolving phase of aspirin-treated TNF-α-induced inflammation. These products are known as resolvin (Resolvin D and E). The synthesis of RvD1 and RvD2 necessitates the catalysis of 15-lipoxygenase (15-LOX) and 5-lipoxygenase (5-LOX), which can take place in mononuclear cells (viz., neutrophils and macrophages) and between cells, such as leukocytes-endothelial cells and neutrophils-macrophages. EPA-derived RvE1 and RvE2 are catalyzed by aspirin-COX2 and 5-LOX via interaction of endothelial cells and leukocytes [83, 84]. Unlike RevDs, RevEs can be generated by an aspirin-independent pathway via cytochrome P450-driven oxygenation of EPA. RvE3 is generated from 18-hydroxyeicosapentaenoic intermediate through the 12/15-LOX pathway in eosinophils [85]. RvD1 acts through ALX/FPR2 and an orphan receptor GPR32 RvE1 on leukocytes, RvE1 mediate its function by binding to ChemR23 and LTB4 receptor (BLT1), while chemerin peptide C15 exert their action at ChemR23. Collectively, all these resolvins limit neutrophil activation and infiltration and specifically stimulate non-phlogistic macrophage phagocytosis at the site of inflammation [85]. Thus, multiple resolvins act via their respective receptors to control the diverse set of immune reactions leading to attenuation of inflammation.

Multiple reports have demonstrated a direct correlation of various inflammatory diseases and production of AnxA1, lipoxins, and resolvins in IBD, in the uncontrolled pathogenesis of atherosclerosis [86], periodontitis [87], chronic liver disease [88] and asthma [89]. In addition to gastrointestinal inflammation resolution, downregulation of LXA_4, its receptor FPR2, and 15-lipoxygenase was found to be associated with persistent airway inflammation (asthma) and wheezy infants as compared to control group [90]. Interestingly, LXs and their analogues turned out to be highly effective in the resolution of diseases in the following experimental models: immune-mediated glomerulonephritis [91], renal ischaemia-reperfusion injury [92], a variety of skin inflammatory-like diseases [93] and gastritis [94]. Importantly, the pro-resolving mediator RvE1 stimulates the production of LXA_4, which further bolstered the resolution events [95]). Moreover, LXA4 or Resolvin E1 (RvE1)-treated trinitrobenzenesulphonate (TNBS)-induced colitis models show attenuated leukocyte infiltration, reduced pro-inflammatory cytokines and IgG serum levels in different studies [96, 97]. Interestingly, it has also been reported that pro-resolving mediators including AnxA1 and LXA_4, induce the production of anti-inflammatory cytokines such as IL-10 [98].

5C. Perturbation of the NF-κB Pathway Induces Resolution

The NF-κB pathway plays a central role in inflammation by regulating the expression of pro-inflammatory cytokines/chemokines and anti-apoptotic genes that could protect the inflammatory leukocytes from programmed cell death. Therefore, the activation of endogenous pathways that could perturb the pro-inflammatory or anti-apoptotic gene networks of the NF-κB pathway would certainly have the potential to drive the host immune system towards the resolution of inflammation. Interestingly, 15d-PGJ_2 acting along with PPARγ activation is demonstrated to modify the DNA binding of NF-κB by alkylating the Cys179 of IKKβ (located in the kinase activation loop, and Cys62 and Cys38 residues located in the DNA binding subunits of NF-κB and RELA, respectively) [99]. As a result, NF-κB is unable to bind at the promoters of various pro-inflammatory cytokine genes. 15d-PGJ_2 also inhibits NF-κB-induced expression of BCL-XL (anti-apoptotic gene) in CD28 co-stimulated primary human CD4+ T cells *in vitro*, thereby arresting the effector function of T cells [100]. Similarly, 15d-PGJ2 directed inhibition of NF-κB plays a pivotal role by regulating the apoptosis of leukocytes and PMNs [101]. Häcker et al. has shown that TRAF3, a downstream signaling molecule of the TLR pathway, plays an important role in controlling the NF-kB-mediated inflammatory cascade by inducing IL-10. Overproduction of pro-inflammatory cytokines IL-12 and IL-6 in myeloid cells from $Traf3^{-/-}$ mice further substantiated this observation [39]. Overall, in conjunction with anti-inflammatory cytokines (IL-10, IL-1RA and TGF-β), lipid mediators facilitate timely activation of the resolution phase.

6. microRNA Biogenesis Pathways and Regulation by Inflammation

Since their discovery by Victor Ambros and colleagues in *Caenorhabditis elegans* as domineering gene regulators [102, 103], ~2500 miRNAs in humans have been cataloged with various degrees of inter-species conservation [104]. Interestingly, unlike transcription factors (TF), miRNAs are readily available effector molecules as they do not require translation, post-translation modifications, or translocation back into the nucleus to begin their effector functions. Burgeoning reports suggested that miRNAs play imperative roles in controlling key regulators of acute and chronic inflammation. Lately, the regulatory role of miRNAs has been demonstrated in controlling the development and functions of various lineages of immune cells [104–106]. Interestingly, expression dynamics of miRNAs have shown their potential to regulate host immune response outcomes - both in positive and negative manners [107, 108]. miRNAs can control immune reactions either by inhibiting pro-inflammatory molecules (negative feedback) or by reinforcing the inflammatory environment by repressing the expression of inhibitors (feed forward) [109, 110]. The effects of miR-155, miR-146a and miR-223 have been widely studied and shown to be implicated in a multitude of innate immune activities [109, 111, 112]. However, these miRNAs only represent a fraction of human-encoded miRNAs. To gain a holistic understanding of miRNA regulated gene networks, further studies on cell-specific, inflammation- or resolution phase-enriched miRNAs will provide finer details of their intricate yet integral functions. The following are the two known processes for miRNA biogenesis in the cell.

(i) The Canonical miRNA Biogenesis Pathway:

This pathway involves RNA polymerase II-driven transcription of a primary miRNA transcript (pri-miRNA), which is then processed by the endoribonucleases Drosha/DGCR8 in the nucleus - termed as precursor miRNA (pre-miRNA) - and exported to the cytoplasm *via* the Exportin 5/RanGTP-dependent pathway. However, intron-derived miRNAs (mirtrons) use Exportin 1 instead of Exportin 5 for their nucleus-to-cytoplasm transport. Pre-miRNAs are then cleaved by Dicer (another endoribonuclease) at their looped end in the cytoplasm. The resultant short (20–25 bp), double-stranded RNA is the product of this cleavage - containing miRNA and its complementary sequence. Thereafter, the double stranded RNA duplex is unwound by Argonaute (AGO) and the mature miRNA (either 5p or 3p strand of the miRNA duplex) is loaded onto the miRNA-induced silencing complex (miRISC) [112].

(ii) Non-Dicer Dependent miRNA Biogenesis Pathway:

This alternative pathway of miRNA biogenesis solely depends on Ago2 to perform the final processing of the miRNA. Importantly, the secondary structure of the pre-miRNA (with distinct loop and hairpin structures) determines whether Dicer or Ago2 will act on the miRNA precursor. Multiple miRNAs have so far been reported to be processed by this pathway. miR-451 is the most well-characterized miRNA in this context. The precursor of miR-451 possesses a very small and distinctive loop structure [113].

miRNAs generated via either biogenesis process are loaded onto the RISC and guide the ribonucleoprotein complex to cognate mRNA sequences via Watson-Crick base-pairing rules and induce either translational repression and/or transcript degradation via mRNA deadenylation and decapping [114]. Increasing scientific reports affirm that the production of various inflammatory proteins during the process of acute inflammation either directly or indirectly impact the biogenesis of miRNAs and their target recognition. For instance, miR-21 maintains the contractile phenotype of human vascular smooth muscle cells by targeting PDCD4 (programmed cell death 4). It turned out that Transforming Growth Factor beta (TGF-β) and Bone Morphogenetic Proteins (BMP) signaling increases the processing of pre-miR-21 by assisting the crosstalk between SMAD signal transducers and RNA helicase p68 (also known as DDX5), a component of the DROSHA microprocessor complex [115].

Furthermore, Adenosine deaminase acting on double-stranded RNA 1 (ADAR1) is reported to impair pri-miRNA processing events. This enzyme catalyzes A-to-I edits in noncoding regions, particularly within the SINE family of retrotransposons that form long double-stranded RNAs, thus disabling their capacity to trigger the activators of innate immunity and resultant autoimmunity. The deficiency of ADAR1 results in development of a condition of sterile immunity – activation of innate immune cells via double-stranded RNA intermediates of various vital reactions for the cell. Yang et al., has demonstrated that ADAR1 has intrinsic capability to edit multiple pri-miRNAs including pri-miR-142, pri-miR-181a, pri-miR-200, etc. Amongst these, miR-142 and miR-181a have clearly been shown to be involved in T cell function [116].

7. microRNAs Regulate Innate And Adaptive Immune Signaling

In light of the above section, we can clearly state that miRNAs can potentially influence immune responses. Multiple miRNAs have been found to be important for the development, differentiation, survival, and function of both innate and adaptive immune cells. Various studies have revealed the expression modulation of miR-146a, miR-125b, miR-155, miR-9, etc. upon TLR activation [117–120]. Similarly, miR-155 expression dynamics were deciphered in Th1 and Th2 differentiation events. Rodriguez et al., reported Th1 to Th2 shift in CD4+ T cells complemented with the production of cytokines like IL-4, IL-5 and IL-10 [121]. In the absence of miR-155, a reduced proportion of germinal center B cells and extra-follicular B cells which failed to produce high affinity IgG1 antibodies were observed. Other studies, in this pursuit, have reported the role of miR-155 in the generation of plasma cells by directly repressing its target gene PU.1 [122]. The focus of this review is resolution phase regulation by miRNAs; therefore, we will not delve into miRNA-mediated control of inflammatory pathways. Nonetheless, we have catalogued multiple miRNAs involved in innate and adaptive immune signaling (Table 2). For a detailed mechanistic regulation of inflammation pathways by miRNAs, please refer to excellent review articles [106, 107].

8. microRNAs Regulate Resolution And Wound Healing

Burgeoning evidences have now demonstrated a critical role of miRNAs in resolution of the infection. Sashwati et al., have shown the direct involvement of miRNAs in the resolution of ischemic wound repair via regulation of the cellular redox environment in human microvascular endothelial cells (HMECs) [148]. Changes in miRNA profiles during the onset of T2D and insulin resistance were shown to interfere with wound healing [149]. Recchiuti et al., showed that the pro-resolving mediator RvD1 induces time-dependent expression of various miRNAs in exudates both *in vivo* and *in vitro* [150]. These miRNAs have been reported to target genes that have key roles in pro-inflammatory responses. We will discuss how miRNA expressional dynamics will impact the regulation of inflammation, resolution and tissue healing processes. Figure 1 illustrates how various miRNAs can shape initiation and resolution of inflammation by directly targeting genes involved in cytokine signaling, innate immune functions and lipid pathways.

8A. miRNA Regulation of the Resolution Phase

(i) miR-155 Knockout Induces The Resolution of Inflammatory Diseases—The miR-155 gene is located on chromosome 21 in the B-cell integration cluster (BIC) [151]. LPS or type I interferons (IFN) induce the expression of miR-155 both in monocytes and macrophages derived from humans and mice, thereby suggesting its pivotal role in both bacterial and viral infection. Interestingly, miR-155 is highly expressed in activated B and T cells and impacts expression of various cytokine genes [139,146]. Activation of MyD88, the TRIF pathways via LPS, or poly I:C stimulation can all induce the expression of miR-155. Interestingly, in LPS-stimulated macrophages, miR-155 binding with 3’UTR of the TNF-α transcript releases it from self-repression, thereby facilitating its translation [117]. In contrast, miR-155 expression is inhibited by anti-inflammatory cytokine IL-10 [152]. Treatment with IL-10 enhances the expression of the miR-155 target gene, Src

homology2 (SH2) domain-containing inositol 5′-phosphatase 1 (SHIP1), which in turn negatively regulates TLR-induced responses [153].

miR-155 KO mice have been demonstrated to show a defective immune response against *Salmonella typhimurium* due to defective B- and T- cell action. Moreover, DCs were unable to present the antigen in this study due to altered Th1 responses [121]. In a separate study, miR-155 KO mice exhibit high levels of activation-induced cytidine diamine (AID), which which has high mutagenic potential during class switching and somatic hypermutation in B cells [154]. Typically, B-cells obtained from WT mice undergoing class switching express high but regulated levels of AID; however, mutation in the 3'UTR binding site of miR-155 has been shown to increase proportions of *Myx-Igh* translocations, thereby leading to disrupted affinity maturation of B cells [154].

Anti-inflammatory dietary compounds including resveratrol [155], curcumin [156], apigenin [157], and quercetin [158] are reported to facilitate the downregulation of miR-155. Similarly, polyunsaturated fatty acids, docosahexaenoic acid, and arachidonic acid significantly reduce the expression of miR-155 in LPS-stimulated murine macrophages [159]. Overall, these findings clearly demonstrate that restoration of miR-155 expression can both augment the resolution phase and concomitantly suppress inflammatory pathways.

(ii) miR-146 Functions as a miR-155 Antagonist in The Resolution Phase

—The miR-146 family consists of two isoforms viz., miR-146a and miR-146b located on chromosome 5 and chromosome 10, respectively. Both isoforms share an exact seed sequence, 2–8 nts from the 5′ end of mature miRNA, suggesting that they target similar transcripts. miR-146a and miR-146b have been elucidated in negative regulation of inflammatory diseases and tumors (e.g. lymphoma) by targeting key molecules involved in the NF-κB pathway [160]. Furthermore, various studies have divulged the development of B cell lymphoma and other myeloid malignancies in aging miR-146a/b knockout (KO) mouse models [161, 162]. The B-cell lymphomas observed in miR-146a- and −146b–KO mice were different in terms of histological changes and malignancy. For example, the malignant rate of B cell lymphoma in miR-146b KO mice was lower than in miR-146a KO mice. Both of these miRNAs target TRAF6 and interleukin-1 receptor–associated kinase 1 (IRAK1), which are endogenous inhibitors of NF-κB activation [162]. Furthermore, cancer cells require constitutively active nuclear factor-κB (NF-κB) to maintain survival, proliferation, and metastatic potential. Therefore, the NF-κB signaling inhibition potential of miR-146 has potential therapeutic value in cancer resolution. In this pursuit, miR-146b overexpression has been shown to prevent the development breast cancer, glioma, gallbladder cancer, and large B-cell lymphoma [162–166].

Interestingly, miR-146 plays an imperative role in counteracting miR-155-induced targets during inflammation via targeting NF-κB activity. To counterbalance the pro-inflammatory effect of miR155, expression of miR-146 accumulates concomitantly and targets IRAK1 and TRAF6 to suppress NF-κB activation. Luly et al., has shown that the inhibition of miR-146a in lipopolysaccharide (LPS)-stimulated macrophages obtained from cystic fibrosis patients results in increased IL-6 production, thereby substantiating the role of miR-146 in inflammation resolution [167]. In congruence, Cheng et al, highlighted the role of miR-146a

and miR-146b in restraining the extent and duration of endothelial cell activation in response to pro-inflammatory cytokine stimulation and recruitment of leukocytes in response to IL-1β treatment. The group unequivocally showed that miR-146a over-expression controls the expression of VCAM-1 and SELE (endothelial activation markers for leukocyte recruitment), and facilitates the reduction of THP-1 monocytes that would otherwise remain adhered to IL-1β-treated endothelial cells [168]. Interestingly, Chatzikyriakidou et al., demonstrated a clear association between a polymorphism in the 3′UTR of miR-146a target IRAK1 with susceptibility to Rheumatoid Arthritis (RA) [169]. Similarly, Tang et al., elucidated that under-expression of miR-146a and over-activation of the type I IFN pathway could contribute to the pathogenesis of SLE [170]. These studies clearly highlight the significance of miRNA regulatory networks that counterbalance reciprocal functions. In this regard, miR-155 and miR-146 mimic pro-inflammatory (IL-1, IL-6 and IL-8) and anti-inflammatory (IL-10 and IL-1RA) cytokines that antagonize each other's function in a pleiotropic manner. In addition, both can have autocrine and paracrine effects thus reflecting their widespread impact. Thus, miRNAs and effector immune mediators work in concert to reinforce their purpose and perturbation in their functional axis can have a detrimental impact on timely inflammation resolution.

(iii) miR-21 Controls Inflammation Through IL-10 Induction—Recent reports have identified miR-21 as an anti-inflammatory miRNA which curbs excessive inflammatory responses and initiates the resolution phase. miR-21 is shown to regulate the expression of IL-10 (a potent anti-inflammatory cytokine) in LPS-induced macrophages by targeting PDCD4, a negative regulator of IL-10 [171, 172]. A study by Lu et al., has elucidated the role of this miRNA in controlling the production of pro-inflammatory IL-12 in dendritic cells [173].

Similar to miR-146, upregulation of miR-21 expression occurs upon challenge with LPS or the Gram-negative bacterium *V. anguillarum*, which subsequently suppresses the expression of LPS-induced pro-inflammatory cytokines by targeting IL-1 receptor-associated kinase 4 (IRAK4). Therefore, the expression of both miR-146 and miR-21 could be a plausible counter-regulatory mechanism to control excessive inflammatory damage by NF-κB signaling [175].

Multiple studies have shown induction of miR-21 expression after treatment of monocytes with: 1) all-trans retinoic acid (to generate neutrophils) [172], 2) GM-CSF/IL-4 (to generate immature DCs) [176], and 3) LPS-mediated B-cell activation [177]. Upregulation of miR-21 in epithelial cells and in mesenchymal cells plays a crucial role in the initiation of cell migration and during wound healing, respectively [178]. Adequate expression of this miRNA has been considered as one of the decisive factors during tissue remodeling after pulmonary and cardiac injury [180].

(iv) miR-208, miR-219, miR-19a-3p and miR-125b-5p Regulate Leukotriene Biogenesis in Resolution—As described earlier, leukotrienes are central in the execution of inflammation resolution. PUFA-generated RvD1 is shown to up-regulate miR-208a and miR-219 in exudates isolated from ALX/FPR2 transgenic mice (a self-limited peritonitis model) [150]. In this study, RvD1 (100 mg/mouse) treatment was associated with

the upregulation of miR-208a and miR-219 in exudates isolated from ALX/FPR2 transgenic mice compared with control littermates. RvD1-treated mice also showed 50% reduction in PMN infiltration in the murine dorsal air-pouch model. In this study, the overexpression of miR-208a in human macrophages was associated with the up-regulation of IL-10 [150]. miR-219 overexpression in macrophages led to significant reduction in CD14, TNF receptor II, phospholipase C2, arachidonate 5-LOX and leukotrienes. Interestingly, leukotriene-generating enzyme 5-LO was shown to be regulated by miR-19a-3p and miR-125b-5p, thereby suggesting tight regulation of the resolution process by a subset of co-expressed miRNAs [150].

(iv) miR-142 Exerts Pleiotropic Inhibition of Inflammatory Pathways—The *mir142* gene is a highly conserved mammalian miRNA located on chromosome 17. The pre-miR-142 encodes for two mature isoforms: miR-142-3p and miR-142-5p, each with distinct target subsets. These miRNAs are broadly expressed in hematopoietic stem cell-derived lineages and play a central role in the differentiation of megakaryocytes, eosinophils, neutrophils, mast cells, dendritic cells, monocytes/macrophages, erythrocytes, T/B cells, natural killer (NK) cells and innate lymphoid cells (ILCs) [181–183]. In addition, miR-142-3p and -5p regulate numerous cellular and effector functions of immune cells including cytoskeletal rearrangement, innate and adaptive immune responses, cell polarization, apoptosis, inflammatory signaling cascades, etc. [181–184]. Studies from our lab have unequivocally demonstrated multiple functional aspects of miR-142-3p in myeloid cell functions. Both miR-142-3p and -5p are downregulated during the differentiation of monocyte-derived macrophages and dendritic cells. Interestingly, this precedes the functional acquisition of differentiated cells as reflected by remarkable induction of surface markers [182, 183]. Enforced expression of miR-142-3p attenuated phagocytosis, antigen uptake and processing, and innate immune responses, primarily by targeting protein kinase C alpha (PRKCA) transcripts in myeloid cells [182, 184, 185]. Challenge with multiple inflammatory stimuli (e.g., microbes or IgG coated beads) causes miR-142-3p suppression with concomitant upregulation of inflammatory pathways in the initial phase of inflammation. We have recently observed that downregulation of transcription factor PU.1, a TF that regulates miR-142 expression, upon bacterial challenge and simultaneous induction of pro-inflammatory miR-155, which directly targets PU.1, together inhibit miR-142-3p expression [*Valverde et al., Unpublished results*]. Thus, it is possible that miR-155-mediated suppression of miR-142 is required to elicit a potent immune response and the gradual induction of miR-142-3p reinforces anti-inflammatory miR-146 to counterbalance the pro-inflammatory activity of miR-155.

An immuno-protective function of miR-142 has been demonstrated in maintaining regulatory immune cells. For instance, H3 lysine-4 tri-methylation (H3K4me3) at the *Mir142* locus is mediated by super enhancer bound by the forkhead box P3 (FOXP3), a Treg lineage–determining TF. Higher expression of miR-142-5p in Tregs downregulates its cognate mRNA, phosphodiesterase-3b (PDE3B), which controls cellular cAMP/cGMP levels required for maintaining Treg function [186]. miR-142$^{-/-}$ CD4+ T cells had higher AMP/GMP levels and produced higher levels of cytokines (IL-2, lL-4, IL-17, IFN-γ) that facilitated effector T cells functions. Interestingly, Tregs from miR-142 KO mice

failed to suppress proliferation of effector T cells - strongly supporting a central role of miR-142 in shaping immune-suppressive pathways. Myeloid-derived suppressive cells (MDSC), similar to Tregs, perform immunosuppressive functions by attenuating effector T cell function and proliferation. Enforced expression of miR-142 in bone marrow cells predominantly impaired CD11b+Gr-1lo-neg cell subset generations composed of mature macrophages [187]. IL-6-mediated induction of MDSC is mediated by higher LAP* levels which promotes macrophage differentiation. By directly binding to the UTR of gp130 and C/EBPβ LAP*, miR-142-3p dampens signaling cascades required for macrophage differentiation and promotes granulocytic cells. This function of miR-142-3p, in conjunction with adoptive transfer of tumor-specific cytotoxic T lymphocyte (CTLs), blocked tumor-associated macrophage (TAM) differentiation and impaired tumor growth *in vivo*. These data demonstrate a broad function of miR-142 in attenuating tumor inflammation and highlight its potential as a therapeutic target.

Global transcriptome analysis of miR-142-3p-overexpressing dendritic cells showed a wide range of pathways regulated by miRNA including cell adhesion, cell movement, cytoskeletal homeostasis, immune pathways, etc. [188]. Consistent with this, miR-142-3p-transfected cells exhibit loss of cell polarity and disrupted actin polymerization status. Surface electron microscopy and confocal microscopy further shows smaller cell size of miR-142-3p overexpressing cells. Chapnik et al., identified various actin pathway-related gene targets in *Mir142*$^{-/-}$ mice, further supporting its role in cytoskeletal dynamics; miR-142-deficient mice also failed to execute actin-dependent proplatelet formation [181]. Chemotaxis, phagocytosis, cytokine production and antigen presentation are key aspects of leukocytes, all of which rely on robust cytoskeletal function. Dysregulation of miR-142 can severely perturb a wide spectrum of cell-intrinsic leukocyte functions. Not surprisingly, altered expression of miR-142-3p/5p is commonly reported in various immune-mediated diseases including multiple sclerosis, systemic lupus erythematosus, periodontitis, Sjögren's syndrome, etc. [189–192]. Exploiting the diagnostic and therapeutic potential of immune-suppressive miR-142-3p/5p may provide new treatment modalities for a wide spectrum of immune disorders.

8B. Role of miRNAs in Wound Healing: Lessons from Skin Model

Multiple groups strived to work on the skin wound healing process in order to divulge the sequence of events involved. Herein, we are presenting various steps in wound healing and their miRNA-mediated regulation. Broadly, skin wound healing involves three overlapping phases: inflammation, proliferation/migration, and maturation (Figure 2). During the inflammatory phase, neutrophils transmigrate from blood vessels at the wound margin along with a fibrin clot and engulf microbes via NADPH oxidase pathway driven respiratory burst [193]. Neutrophils produce fibrillar networks at the wound margin to avoid the undesirable spread of antimicrobial peptides/enzymes to prevent the spread of infection [194]. Subsequently, the proliferation phase ensues which attracts macrophages to the wound site. Macrophages at the wound site perform: 1) efferocytosis of apoptotic neutrophil population, and 2) secrete biologically active substances which stimulate epithelial cells and wound-infiltrated fibroblasts [195] to cover the wound surface (Figure 2). The phenomenon of efferocytosis – an important component of the resolution phase- is regulated by miR-21

by inducing M1 to M2 macrophage phenotype switch [174]. Both professional and non-professional phagocytes are involved in elimination of apoptotic neutrophils, which are a predominant population of circulating white blood cells (WBCs) in humans and function as critical players in host defense against bacterial and fungal infections. Spleen, liver, and bone marrow are the prime sites for neutrophil efferocytosis events. Nucleotides, lysophosphatidylcholine, and sphingosine-1-phosphate are a few important chemoattractants that signal the location of apoptosis-undergoing cells to phagocytes (M2 macropahges). Furthermore, apoptotic cells also express resolvin E1 (RvE1), protectin D1 (Ref. 101), lactoferrin and annexin A1, to restrict further recruitment of granulocytes and thus, favor the preponderance of PMNs- a necessary factor for resolution and optimal wound healing. Interestingly, these apoptotic cells lose expression of 'don't-eat-me' cell-surface molecules viz CD31 and CD47 and concomitantly upregulate expression of various pro-phagocytic signals e.g., phospholipids, nucleotides and phosphatidylserine. The crosstalk between tissue-resident M2 macrophages and dying PMNs harboring pro-phagocytic signals ensures the successful removal of apoptotic cells before they can perpetuate another cycle of inflammation by releasing histotoxic mediators upon membrane rupture. Engulfment of PMNs undergoing apoptosis triggers the immune-regulatory or pro-resolution phenotype *viz.*, PDL1 and ICOS ligand expression, secretion of anti-inflammatory cytokines IL-10 and TGFβ, production of PCNA-associated factor, production of PGE2 and cAMP, or inhibition of the secretion of pro-inflammatory cytokines such as TNF, GM-CSF, IL-1β, IL-12 and IL-18 to limit the potential collateral tissue damage [3, 51–53]. Dermal fibroblasts transdifferentiate into myofibroblasts which are involved in wound contraction, secretion of extracellular matrix (ECM) including collagens, proteoglycans, and adhesive glycoproteins for the formation of granulation tissue, and induce endothelial cells to form blood vessels within the granulation tissue [196].

The decisive role of miRNA expression dynamics has been independently reported by various groups in improving the efficiency and quality of skin wound healing. Yang et al, has demonstrated that downregulation of miR-155 via antisense oligodeoxynucleotides (AS-ODN) at wound sites reduces fibrosis [197]. In addition to this, another group has shown that over-expression of miR-21 at the wound sites using a lentivirus vector facilitated the murine skin wound healing process [198]. Furthermore, expression of miR-146a and miR-106b during skin wound healing has been shown to prevent transepidermal water loss at biofilm-infected chronic skin wound sites. Inhibition of miR-210 via administration of lipid nanoparticles containing encapsulated miR-210 results in enhanced re-epithelialization. Interestingly, inhibition of miRNA function via the antisense ODNs miR-15b AS ODN, miR26a AS ODN, light-inducible anti-miR-92a, miR-200b AS ODN, and miR-132 mimic have shown therapeutic implications during skin repair in diabetic wounds. Also, miR-142 plays a critical role in clearing *S. aureus* infected-skin wound sites via neutrophils [199]. Table 3 elucidates the roles of various miRNA in regulating important events in the skin-wound healing process. Together, these studies demonstrate a requirement of miRNAs in the skin wound healing model and therapeutic targeting of miRNAs may restore or augment the normal repair/regeneration process.

9. Diagnostic and Therapeutic Use of miRNAs in Disease Resolution

Induction of resolution events is now considered a holy grail of treatment of acute and chronic inflammation. Instead of inducing individual miRNAs or treating the host with multiple miRNAs using complicated delivery vehicles, Recchiuti et al. treated the self-limited murine peritonitis model with RvD1 (300 ng/mouse or 15 μg kg^{-1}). Interestingly, they observed significant modulation of expression of multiple miRNAs including miR-21, miR-146b, miR-208a, miR-203, miR-142, miR-302d, and miR-219, in resolving exudates of this murine model. Their findings corroborate previous studies showing temporal expression changes in these miRNAs. Interestingly, miR-21 and miR-203 were upregulated only after 12 h post-RvD treatment [150]. It was proposed that an initial subset of miRNAs might be involved in the induction of resolution, whilst a later group of miRNAs may participate in the maintenance or final events associated with inflammation resolution. A remarkable reduction (25–50%) in zymosan-elicited neutrophil infiltration into the peritoneum was observed, suggesting a pro-resolving function of RvD1. In addition, this group further treated human macrophages overexpressing recombinant RvD1 receptors ALX/FPR2 or GPR32 with RvD1 (at concentrations as low as 10 nM) *in vitro* and observed similar changes in miRNA profiles, strongly supporting their *in vivo* findings. RvD1 treatment attenuates nuclear translocation of NF-κB and SMAD and reduces phosphorylation of IκB, an endogenous inhibitor of NF-κB. Recchiuti et al., found that RvD1-dependent miRNA changes were solely based on the expression of its receptor and dose; therefore, the group also expressed the above miRNAs (appeared in the resolution exudates) via expression vectors and found significant downregulation of their gene targets. For example, human macrophages overexpressing miR-146b showed downregulation of S100A12, LPS binding protein (LBP), C-reactive protein, complement component 8 α polypeptide (C8a), Toll-like receptor (TLR) 9 and 10, and peptidoglycan recognition protein (PGLYRP) 1 and 2. miR-208a-overexpressing human macrophages showed reduced expression of CD14, CD40 ligand (CD40L), prostacyclin I_2 receptor (PTGIR), thromboxane A_2 receptor (TBXA2R), and programmed cell death 4 (PDCD4). Also, miR-146b overexpression led to significant down-regulation of IL-8, IL-10, IL-12 receptor β2, chemokine CC motif receptor 3 (CCR3), interferon (IFN) α1 and IFNβ1, and members of the IL-1 family. Expression of miR-219 resulted in significant downregulation of CD14, TNF receptor II, phospholipase Cγ2, and arachidonate 5-lipoxygenase [150]. Therefore, miRNA treatment has demonstrated a wide gamut of regulatory functions *in vivo* compared to RvD alone.

Resolvin D1 has also proven effective in the resolution of the long-term lung inflammation-associated with *P. aeruginosa*. RvD1 treatment considerably reduced the *P. aeruginosa* load, leukocyte infiltration, lung tissue damage and inflammatory signaling by affecting the gene expression of TLR (and their downstream genes) and miR-21 and −155 [200]. Research in the area of therapeutic targeting of miRNA to potentiate disease resolution is still in its infancy and demands extensive studies to understand the role of RvD-induced miRNAs in treating various other chronic inflammatory diseases associated with different organs based on their endogenous RvD receptors. *In vivo* delivery of both resolvins coupled with miRNA over-expression vectors could be a promising stratagem to induce the sequence of events involved in resolution. Furthermore, expression of the aforementioned miRNAs in the tissue

exudates can be explored for diagnosis of the resolution phase, a reasonable strategy to be embarked upon in the impending future.

10. Conclusions

In summary, resolution of inflammation is a highly regulated sequence of events that eventually restores tissue homeostasis and stymies the development of chronic inflammatory disease. Numerous studies have extensively delineated the underlying role of miRNAs in regulating inflammation and resolution events to maintain tissue homeostasis. Despite compelling evidence, exploiting the knowledge of expressional dynamics of selected miRNA to achieve desired inflammation resolution during chronic inflammatory diseases remains a challenge. Over-expression of miR-21, miR-142, miR-146 and miR-208, and concomitant down-regulation of miR-155, may provide convincing evidences to exacerbate the pro-resolution molecular circuitry in acute/chronic inflammatory disease. Additionally, miRNAs can also be used in conjunction with lipid mediators of resolution. Synergistic targeting of two distinct yet mutually inclusive pathways may drive resolution in a robust manner. The crux of inflammation and resolution is wound healing; therefore, further identification and elucidation of miRNA-mediated precise regulation of the skin wound healing process will advance our understanding of the pathway. It is possible that information from inflammation resolution can be translated to treat cancers, despite an immunosuppressive microenvironment, and may involve dysregulation of similar repertoire of miRNAs. In the last decade, miRnome analysis in various immune-mediated diseases and cancers have identified a subset of miRNAs with potential diagnostic and prognostic functions. However, translating this knowledge remains a daunting task. *In vivo* targeted delivery of miRNAs, their long-term expression, and safety issues remain as major limitations. Selecting appropriate and effective delivery strategies for multiple miRNA/antagomirs will allow simultaneous modulation of multiple host genes (under direct influence of miRNAs) to mitigate inflammatory diseases and prevent tissue damage. Researchers anticipate that development and standardization of miRNA-based strategies will curtail the dreaded effects of multiple chronic inflammatory conditions, which so far remain incurable.

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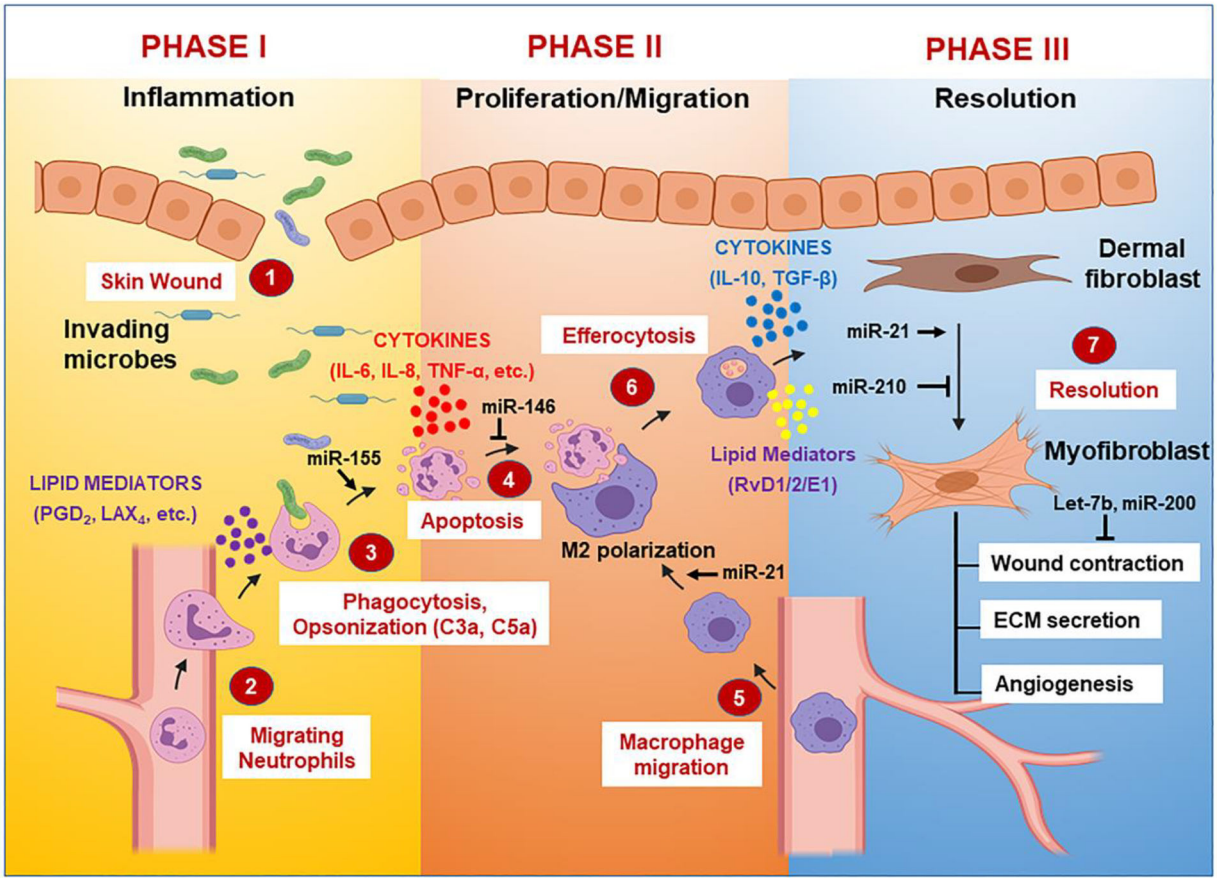

Figure 1. MiRNA-mediated regulation of inflammation and resolution.

The key events involved in the inflammation and resolution are directly regulated by various miRNA expression.

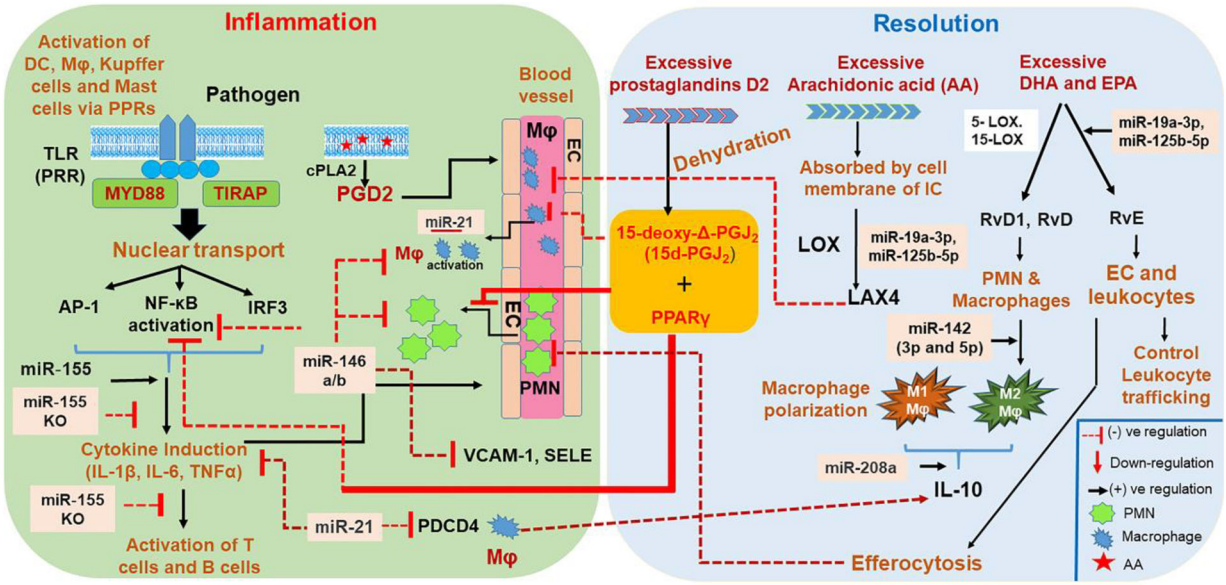

Figure 2. Sequence of events in resolution of inflammation.

Schematic depicting the three phases involved in skin wound healing following injury/ trauma. The coordinated and synergistic temporal events during these phases are modulated by various cytokines, lipid mediators and spatiotemporal miRNA expression.

Table 1:

Diseases associated with uncontrolled inflammation.

Name of the organ	Name of the disease	Dysregulated immune signaling	Reference
Cardiovascular disease	atherosclerosis	Intracellular components TLR-mediated NF-κB signaling via necrotic cells	[40]
Pancreas	Type 2 diabetes	High levels of IL-1β, IL-6, TNF-α, CRP, fibrinogen, serum amyloid A, plasminogen activator inhibitor, and haptoglobin, sialic acid, IL-1 receptor antagonist (IL-1RA), activation of NF-κB, MAPK, and JAK-STAT pathways	[42]
Pancreas	Pancreatitis	Activation of macrophages, neutrophils, and granulocytes, inflammatory cytokines mediated pancreatic stellate cells (PSCs) activation	[43]
Kidney	glomerulonephritis, end-stage renal disease, or acute or chronic kidney disease (CKD	Activation of transcription factors (NF-κB or MAPK), DAMPs, and PAMPs, and Nod-like receptors (NLRs).	[49–50]
Liver	alcoholic or nonalcoholic steatohepatitis, drug-induced liver injury, and ischemia/ reperfusion	DAMPs (during SI) and PAMPs activation and formation of inflammasome, high levels of of IL-1β and other pro-inflammatory cytokines, activation of Kupffer cell leading to hepatocyte damage, and/or cholestasis.	[45–47]
Lung	COPD, asthama	Asthama :Activation and uncontrolled infiltration of macrophage, neutrophil, and T lymphocyte into airways COPD: production of cytokines (TNF-α, IL-6 and IL-8) chemokines, oxygen radicals, proteases.	[41]
Intestine	Ulcerative colitis (UC) and Crohn disease (CD)	CD: IFN-γ/IL-17 and IL-12/IL-23 UC: IL-13	[44]

Table 2:

miRNAs regulates various imperative events in inflammation by targeting critical genes involved in the pathway.

miRNA	Targets	Process	References
TLR pathway			
miR-9	NF-κB1/p50	Transcription by NF-κB is decreased	[123]
miR-16	TNF-α	Decrease levels of inflammatory	[124]
miR-17–5p, 20a, 106a	Transcription factor CBF	Inhibition of monocyte maturation	[125]
miR-21	PDCD4, IL12p35	Derepression of IL-10	[126]
miR-27b	PPARγ		[127]
miR-105	TLR2		[128]
miR-106	IL-10	Cooperates with RNA binding protein	[129]
miR-125b	TNF-α	to decrease IL-10	[130]
miR-145	MAL	Impedes TLR signaling	[131]
miR-146a	TRAF6, IRAK1, IRAK2	Negative feedback regulator in TLR signaling	[132]
miR-155	AID, MyD88, TAB2, IKKε, SHIP1, SOCS1, C/.EBPBβ	Proinflammatory in TLR signaling	[133]
miR-199	IKKβ	TLR4/NF-κB p65/NGAL pathways	[134]
miR-221	TNF-α		[135]
miR-223	TLR3, TLR4, IKKα	Granulopoiesis and monocyte activation	[136]
Let-7i and let7e	TLR4	Downregulate inflammatory signaling	[137]
T cell development and function			
miR-181a	SHP2	T cells: strength of the transduced T-cell receptor signal.	[138]
miR-155	SOCS1	miR-155-deficient mice suffer impaired survival of Treg, T regs/Th17 ratio	[139]
miR-146a	STAT1	miR-146a-deficient Treg (FoxP3) cannot inhibit hyperactive immune system. Upregulated in RA	[140]
miR-17~92 cluster	pten	immunoproliferative disorder and autoimmune disease	[141]
miR-326	Ets-1 transcription factor	autoimmune inflammation	[142]
B cells development and function			
miR-181a	Lin28/Mcl-1	guided B-cell development	[143]
miR-150	c-Myb and Foxp1	B-cell development	[144]
miR-34a	c-Myb and Foxp1	B cell development	[145]
miR-155	Pu.1, SHIP1 and AID	regulate antibody secretion and class-switch recombination	[146]
miR-181b		reduce the class-switch recombination rates	[147]

Table 3:

miRNA expression patterns during skin wound healing and their regulation of various aspects of the process.

miRNA	Process	References
miR-155	Down regulation via AS ODNs can improve efficiency and quality of skin wound healing by reducing inflammation	[190] [191]
miR-21	(a) Upregulated in epithelial cells at the initiation of beginning of cell migration at wound site. (b) Down-regulation delayed wound healing from 1–14 days after injury. (c) Over-expression via lentivirus facilitated the improved healing in rat model targeting Pten gene	[178],[192]
miR-146 a miR-106b	(a) Prevent the skin infection during wound healing	[193]
miR-200c	(a) Overexpression delayed re-epithelialization in human skin model	[194]
miR-210	(a) Downregulation embargo skin re-epithelialization	[195]
miR-15b, miR26a, miR-92a, miR-200b,	(a) Down regulation Improved skin healing in diabetes patients	[196]
miR-132, miR27b	(a) Downregulation improved skin wound healing in diabetes patients	[197][198]
miR29b and miR-1908	(a) Overexpression inhibit scarring	[199] [200]
miR-132	(a) enhance the transition from inflammation to proliferation during wound healing	[201]
miR-142	(a) neutrophils to clear S. aureus infected-skin wound sites	[202]
Let-7b	(a) overexpression exhibit a delay in re-epithelialization at wound site	[203]
miR-198	(a) inhibits keratinocytes migration and proliferation	[211], [212]
miR-23b	(a) cutaneous wound healing via inhibition of inflammatory reactions	[213]
miR-483-3p	(a) controls proliferation in wounded epithelial cells	[214]