Noncoding RNAs and chronic inflammation: Micro-managing the fire within

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Inflammatory responses are essential for the clearance of pathogens and the repair of injured tissues; however, if these responses are not properly controlled chronic inflammation can occur. Chronic inflammation is now recognized as a contributing factor to many age-associated diseases including metabolic disorders, arthritis, neurodegeneration, and cardiovascular disease. Due to the connection between chronic inflammation and these diseases, it is essential to understand underlying mechanisms behind this process. In this review, factors that contribute to chronic inflammation are discussed. Further, we emphasize the emerging roles of microRNAs (miRNAs) and other noncoding RNAs (ncRNA) in regulating chronic inflammatory states, making them important future diagnostic markers and therapeutic targets. Copyright Line: © 2015 The Authors

Introduction

The mammalian inflammatory response is a double-edged sword. Although immune responses are necessary for efficient pathogen clearance, symbiosis with commensal microbes, wound repair and overall tissue homeostasis, these responses can become dysregulated and initiate a chronic reaction that lacks resolution [1]. This condition, referred to as chronic low-grade inflammation, can fester for long periods of time and adversely contribute to, or possibly even cause, many diseases associated with the aging including obesity [2], type 1 diabetes (T1D) [2], rheumatoid arthritis (RA) [3], systemic lupus erythematosus (SLE) [4], neurodegeneration [5], and cardiovascular diseases (CVD) [6]. In many of these cases chronic inflammatory symptoms, such as elevations in inflammatory cytokines and autoantibodies in the serum, can serve as a prognostic indicator of later disease manifestation and overall morbidity and mortality [7].

As the world’s elderly population continues to grow at an alarming rate, there is tremendous need to predict which individuals are at the highest risk for developing many of the disorders mentioned above. However, because chronic inflammation does not typically cause obvious clinical symptoms, and screening for inflammatory markers is not a test performed during routine medical exams, the potentially predictive power of one’s chronic inflammatory state is not currently being harnessed. This is in part due to the fact that elevated inflammatory factors in the serum are not markers specific to chronic inflammation, and thus their diagnostic value is currently limited. Further, until a better understanding of the mechanisms underlying this deleterious condition is obtained, therapeutic inhibition of chronic inflammation will remain challenging.

In this article, we review our current understanding of the known causes of chronic low-grade inflammation with a focus on factors distinct from chronic infection. We will also focus on cells of the immune system, although we recognize that non-immune cells also contribute to this state. We also discuss recent evidence that mammalian microRNAs and long noncoding RNAs (IncRNAs) have evolved to regulate chronic inflammation.

Keywords:
- aging; autoimmunity; chronic inflammation; miRNAs; noncoding RNA

DOI 10.1002/bies.201500054

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Abbreviations:
- AD, Alzheimer’s disease; CVD, cardiovascular diseases; IBD, inflammatory bowel disease; IncRNA, long noncoding RNA; ncRNA, noncoding RNA; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; TLR, Toll-like receptor.

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inflammatory states including those that occur during the aging process, and describe how they provide both diagnostic and therapeutic opportunities moving forward.

Causes of chronic inflammation

During chronic inflammation the resolution phase of the inflammatory response does not occur. This can be a result of either a persisting stimulus and/or the perturbation of molecular mechanisms involved in the resolution of inflammation. Thus, normal “healthy” immune responses can progress to chronic inflammatory states in instances where either of these events takes place.

Immune responses involve a resolution phase where the inflammatory response is shut down once the stimulus, such as a pathogen, is cleared. Mechanisms of resolution have been an intense area of study in recent years, and many important steps in this process have been discovered. Specialized cell types, such as T regulatory cells (Tregs), carry out critical immune repressive functions that are essential in preventing autoimmunity [8]. At the molecular level, the cytokine IL-10 [9, 10], the signaling molecule A20 [11], the signaling receptor PD1 [12], the signaling molecule CTLA4 [13], and the secreted factor ILIRA [14] are all examples of molecules that have evolved to balance and ultimately shut down immune cell activation. In some cases, these pathways are already being exploited therapeutically for such applications as cancer therapy. For instance, antibody disruption of the PD1 pathway, which enhances the immune response against tumors, is proving to be an effective therapy for melanoma [15]. Further, as we will describe below, specific miRNAs such as miR-146a have also evolved to keep immune responses in check.

Initial causes of some forms of chronic inflammatory states are also incompletely understood, yet their identification and prevention is key to avoiding the disease process. Recently, several distinct contributing factors have been described (Fig. 1) and include the following: (i) chronic inflammation can be primarily initiated by immune responses to self-tissues. The recognition of self-antigens by the immune system can result in diseases such as RA [16], SLE [17], multiple sclerosis (MS) [18], and T1D [19], and this self-recognition may or may not have a microbial component; (ii) in other instances, the immune response appears to be a secondary event that emerges in response to damage associated molecular patterns (DAMPs) that are produced following a breakdown in tissue homeostasis where the ensuing immune response driven by DAMPs alters tissue function [20]. Examples of diseases associated with DAMPs include obesity – where nutrient excess and hypertrophic adipocytes are the primary drivers [21], CVD – where lipoprotein buildup initially seeds the pathology [22], and certain neurodegenerative disorders such as Alzheimer’s disease (AD) – mediated by protein aggregation [5]; (iii) contributions by the microbiota are also documented in some types of chronic inflammation, as their metabolites can influence both gut and peripheral tissues [23]. Obesity has been associated with alterations to the gut microbiota composition [24]; (iv) finally, the aging process itself leads to changes in immune system phenotypes and correlates with increasing inflammatory status as we grow older [25]. In this section, we will expand on each of these aspects of chronic inflammation.

Self-antigens produce autoimmune responses

A common cause of inflammatory conditions involves the inappropriate immune response to self-tissues, as is the case for RA [16], SLE [17], MS [18], and T1D [19]. For instance, in RA auto-reactive leukocytes attack joint tissues through a variety of mechanisms including production of autoantibodies, reactive oxygen, and nitrogen species as well as secretion of pro-inflammatory cytokines that recruit additional immune cells to the site of tissue damage [16]. Although this phenotype is fairly well characterized, and thought to arise from an inappropriate initial response by the immune system, the underlying triggers of diseases such as RA are still being deciphered. Studies have found a link between a person’s genetics, such as MHC type, and disease risk and this is consistent with antigen presentation playing a critical role in the triggering of disease [26, 27]. Additionally, self-antigen responses might also ensue as a result of cleaning up dead or dying cells that may trigger responses against antigens from the tissue where these cells were derived [28].

Additional contributions may also be made by microbial pathogens that produce antigens that are similar to host proteins [29]. This type of molecular mimicry is an attractive hypothesis; however, the identity of pathogens that trigger these responses in different autoimmune settings remains largely elusive. One example of an infectious agent that triggers chronic arthritis is Borrelia burgdorferi [30]. Although most people return to health after clearing the infection, about 10% of infected individuals develop chronic arthritis in their joints even after the infection is cleared [31]. Whether this is working through molecular mimicry or a persistent, hard to detect microbial reservoir is unclear and future work is needed to better define this process.

Another interesting theory is that human endogenous retroviruses may also play a role in driving disease onset. Human endogenous retrovirus-K has been implicated in the development of RA [32]. It is thought that this retrovirus impacts the development of RA through molecular mimicry of self-antigens. Additionally, human endogenous retrovirus type W envelope expression has been associated with MS [33]. Along with these examples, there have been several implications for human endogenous retroviruses in the development of inflammatory diseases [34].

DAMPs are initiators of chronic inflammatory states

In other instances, sustained inflammatory responses can be driven by DAMPs produced as a result of tissue damage or stress, or other events that disrupt tissue homeostasis. Examples include lipoproteins in the vasculature that drive atherosclerosis [35], and protein aggregates in the CNS that are associated with AD [36]. In such cases, DAMPs are produced and are recognized by Toll-like receptors (TLRs) or Nod-like...
receptors (NLRs) on innate immune cells [37]. In these instances, the innate immune system plays a secondary role as it responds to the inappropriate buildup or localization of certain molecules that signal disruptions to tissue homeostasis.

In the case of metabolic syndromes, such as obesity and diabetes, nutrient excess drives adipocyte hypertrophy, production of adipokines as well as inflammatory cytokines leading to eventual necrosis [38]. As adipocytes begin to die, their contents are taken up by tissues macrophages that are activated by products such as secreted cytokines and fatty acids that are detected by macrophage TLRs [39]. This response can change the nature of the tissue macrophage from an M2 to an M1 subtype, which subsequently initiates low-grade inflammation within adipose tissues. This includes the recruitment of a variety of immune cell mediators that reinforce the inflammatory state and promote insulin resistance, an early step in the development of type 2 diabetes (T2D). This is a good example of how a stressed tissue can induce an inflammatory response that is self-sustaining.

**The microbiota and their products impact chronic inflammatory states**

It is now widely recognized that the human microbiome, most of which resides in the intestinal tract, has an enormous
impact on our health. Thus, it is not surprising that commensal bacteria have been linked to a variety of chronic inflammatory conditions including inflammatory bowel disease (IBD), TID, obesity, and neuroinflammatory diseases such as MS [40]. In each case, the microbiome of diseased individuals differs from that of healthy controls. Further, animal models have shown that the microbiota can cause or inhibit disease, based on its composition. This influence is mediated, at least in part, through the production and delivery of TLR ligands and other metabolites to either intestinal or extra-intestinal tissues that alter tissue homeostasis [41].

Many factors can influence the microbiota including diet, exposure to animals and agriculture, stress, and geographical location, indicating that lifestyle choices play an important role in microbiota composition [42]. However, while the importance of the microbiota in human health, including chronic inflammation, has become clear in recent years, the contribution of different microbial members to disease phenotypes is still under intense study as it is a complex mixture of distinct species.

The immune system changes with aging
Like other systems in our body, our immune system undergoes a variety of alterations as we grow older. Our thymus produces fewer naïve T lymphocytes [43], restricting one’s ability to adequately respond to novel antigens and form memory against new pathogens or in response to vaccination. There is also an elevated amount of serum autoantibodies against self-tissues [44] and memory phenotype T cells can produce higher levels of inflammatory cytokines as they respond to persistent/chronic viral infections [45]. Hematopoietic output of innate immune myeloid cells becomes more prevalent [46], and senescent macrophages secrete higher amounts of inflammatory cytokines and produce ROS spontaneously [47]. Thus, the aging process creates an immune system that is less specific and more deregulated leading to a higher prevalence of autoimmunity in older versus younger individuals. It is also not surprising that a majority of diseases that emerge in the elderly are correlated with high levels of chronic inflammatory markers during middle age. As the world’s aging population continues to grow larger, the need to prevent or treat disease in the elderly has become vital.

MicroRNAs, immune responses, and the regulation of cellular physiology
MicroRNAs are small, single-stranded ncRNAs that were first discovered in C. elegans [55] approximately one decade before they were appreciated in mammalian cells [56, 57]. Since then, research involving miRNAs has exploded over the past 10–15 years, and much has been learned regarding their biogenesis, expression patterns and functions at the molecular, cellular and organismal levels. miRNAs clearly function to repress gene expression and influence virtually all organ systems in vertebrates [58]. Much of this has been extensively reviewed elsewhere [59]. However, there are certain fundamental attributes of miRNAs that make them ideally suited to regulate chronic inflammatory conditions.

Through their ability to modulate gene expression networks by adjusting the levels of dosage sensitive target genes, miRNAs are able to shift thresholds that dictate whether a cellular response will occur or not, how strong it will be, and if it will be resolved (Fig. 2) [60]. For instance, miR-146a is induced in response to TLR signaling and forms a negative feedback loop that inhibits Traf6 and Irak1, two critical upstream TLR-signaling mediators that promote macrophage activation (Fig. 2A). While miR-146a is a repressor of immune cell signaling [61], miR-155 and miR-181a are activators of inflammation. miR-155 is induced in activated myeloid cells and represses both Socs1 and Shpi1 to enhance cytokine production by dendritic cells and macrophages (Fig. 2B) [62]. miR-155 has also been shown to enable CD8+ T cells to respond to limiting doses of γ-chain cytokines, which enables robust immune responses in lymphoreplete hosts [63]. T cell receptor (TCR) signaling strength is regulated by miR-181a, which modulates expression of several phosphatases.
that inhibit TCR-induced signaling pathways resulting in activation of T cell genes (Fig. 2C) [64]. Thus, miRNAs can both enhance or hinder signaling pathways that control innate and adaptive immune responses that underlie inflammation.

Further, miRNAs have also been shown to confer robustness to cellular states. In these scenarios, specific miRNAs play important roles in determining the extent to which differentiation occurs. For example, the miR-17~92 cluster of miRNAs repress Pten and Phlp2, inhibitors of Icos signaling in activated T cells, resulting in the skewing of cells into T follicular helper cells (Tfh cells) (Fig. 2D) [65]. In the absence of the miR-17~92 cluster, these proteins are at higher levels and reduce the amount of Tfh cells produced during inflammatory responses. Another example is miR-155, a miRNA that is necessary for both T cell homeostasis and optimal differentiation of multiple T cell types including Th1 [66, 67], Tfh [68], Th2 [69], and Th1 cells [70]. In these cases, miR-155 appears to be working through repression of multiple targets including Jarid2, Socs1, Ship1, Ets1, Peli1, Fosl2 (and possibly others). However, additional work is needed to determine if unique target/s are used by miR-155 depending on the Th cell type produced. Because T cells are central regulators of inflammatory responses, their modulation by miRNAs is of significant relevance to chronic inflammatory states, as described below.

Additionally, several miRNAs have been implicated in regulating macrophage lineage skewing during inflammatory responses. Macrophages can be skewed toward either pro-inflammatory subtypes (M1), or toward more reparative and less inflammatory subtypes (M2). miR-125 has been shown to repress M1 skewing while promoting the M2 fate [71, 72]. miR-223 has also been implicated in macrophage skewing where miR-223 promotes macrophage polarization toward the M2 subtype [73]. Additionally, miR-223 has been implicated in control of granulocyte activation, and miR-223/- mice display overactive immune responses and develop inflammatory lung pathology [74].

Further highlighting the importance of miRNAs in human systems, greater numbers of miRNAs have emerged throughout evolution, in addition to increased target diversity [75]. This suggests that miRNAs are among the regulatory mechanisms that enable increased human complexity despite a genome size that is similar to less complex organisms. This appears to include critical roles in establishing proper inflammatory set points and facilitating optimal responses and resolution by our immune system. In the next section, we will assess our current understanding of how miRNAs influence distinct types of chronic inflammatory conditions.

### Functional roles for miRNAs during chronic inflammation

#### MicroRNAs regulate antigen specific responses

There has been a substantial amount of work to date assessing how miRNAs control different types of acute inflammatory responses following infection, immunization, tumor challenge, and induction of several antigen-dependent autoimmune conditions that are all rooted in inflammation [76]. In each case, specific miRNAs have been shown to play pivotal roles during disease onset, peak magnitude, and rate of resolution by influencing the immune cell populations that mediate these steps (Table 1). Examples include a pro-

<table>
<thead>
<tr>
<th>Species</th>
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inflammatory role for miR-155 in T cells during antigen-induced experimental autoimmune encephalomyelitis (EAE) in mice [70], in B and T cells during collagen-induced arthritis in mice [77], in licensing CD8+ T cell responses against viruses and tumors [78], and in B cells during murine lupus [79].

miR-17~92 has been shown to enhance antibody responses against viral infections through its promotion of Th cell differentiation [65, 80], to promote Th1 cell responses against solid tumors [81], and to provoke asthma through its augmentation of Th2 cell development [82]. miR-146a has been shown to play a critical role in preventing the onset of arthritis following infection by Borrelia burgdorferi by influencing macrophage responses [83]. Importantly, this body of work strongly implicates miRNAs in the human iterations of these disorders where their altered expression is often observed. It is also relevant to note that while many of these studies are based upon induced disease states in mice, several of these disorders have been linked to pre-conditions of low-grade inflammation characterized by elevated titers of self-reactive antibodies and/or pro-inflammatory cytokines.

Although studies continue to unravel roles for different miRNAs in autoimmune disease states mediated by auto-antigens, far fewer studies have determined the role of miRNAs during chronic low-grade inflammation triggered by DAMPs, aging and the microbiota, and the diseases that emerge as a result of these triggers. We next turn to these emerging areas.

**Figure 2.** Mechanisms of miRNA function in the immune system. miRNAs can have various functions within the immune system and can act in different manners. **A:** For example, miR-146a acts as an anti-inflammatory miRNA via feedback inhibition of an inflammatory pathway. **B:** miR-155, on the other hand, is a pro-inflammatory miRNA that acts in a feed-forward manner bolstering the immune response. **C:** miR-181a is also a pro-inflammatory miRNA that acts by inhibiting phosphatases that block the activation of T cell genes thus activating T cells. **D:** Finally, the miR-17~92 cluster is involved in promoting the differentiation of a subset of inflammatory T cells called T follicular helpers cells (Tfh).

**MicroRNAs are involved in inflammaging**

As described above, the aging process itself is associated with inflammatory phenotypes. Early studies in *C. elegans* have functionally linked miRNAs to lifespan, perhaps offering a first clue that miRNAs are involved in different aspects of the aging process. For instance, lin-4 loss-of-function mutants
have shortened lifespans while lin-14 loss-of-function mutants have increased lifespans [84]. Additionally, mouse studies have shown that certain miRNAs alter expression patterns with aging. For example, in the mouse brain miR-22 and miR-101a are up-regulated in aged mice [85]. These studies reveal that miRNAs can both affect the aging process as well as be affected by it.

Recently, the roles of miRNAs in age-dependent inflammatory phenotypes have started to be explored. In particular, it has been discovered that mice lacking miR-146a develop an age-dependent, chronic inflammatory disease that is spontaneous, life-shortening, associated with inflammatory cytokines and autoantibodies, and that involves a variety of hematopoietic abnormalities and/or malignancies typically associated with the aging process [68]. Further, the condition has been shown to involve activated lymphocytes and be largely dependent upon NF-kB [86].

Our group and others have recently explored this miR-146a deficiency phenotype further and found that it involves the spontaneous development of T follicular helper cells that play a pivotal role in facilitating germinal center (GC) B cell development, production of high affinity, class-switched antibodies, and formation of B cell memory [68]. Consistent with this, both Thf and GC B cells begin to spontaneously arise in younger miR-146a-/- animals, and this precedes most other phenotypes in this model. Upon reaching middle age, these animals begin to produce anti-dsDNA autoantibodies as a consequence of their deregulated GC response, and begin to display inflammation in a variety of different peripheral tissues. Of relevance, this phenotype was largely dependent on T cell expression of miR-155 indicating that these two miRNAs counter-regulate chronic inflammation. Although more work remains, it is plausible that these autoantibodies contribute to tissue stress and ultimately the onset of disease upon reaching old age (Fig. 3).

**MicroRNAs are involved in other chronic inflammatory contexts**

A role for miRNAs in controlling commensal bacteria populations and their production of metabolites that influence inflammatory conditions is beginning to emerge [87]. This has important implications both within the gut and in peripheral tissues. miRNA specific knockout mice have been shown to have altered gut microbiota. For example, miR-155-/- mice have increases in pathobionts within the gastrointestinal tract due to defective humoral immunity [88]. This suggests that the function of miRNA within host immune cells can help shape the composition and control of commensal microbes. However, it remains unclear if miRNAs shape populations that influence chronic inflammatory disease states.

Although specific miRNAs have been shown to regulate metabolic syndromes, there is little functional evidence thus far linking miRNAs, inflammation, and obesity/diabetes. However, based upon our understanding of miRNA functions in other contexts, it is highly likely that miRNAs regulate low-grade inflammatory conditions that influence weight gain and insulin resistance. Further, clinical evidence is beginning to emerge. For instance, there have been reports linking altered miR-146a expression and T2D [89].

**MicroRNAs are emerging biomarkers and therapeutic targets in chronic inflammation**

As miRNAs have been functionally connected to the development of chronic inflammation, it follows that alterations to miRNA levels could be a reasonable way to detect the presence of chronic inflammatory states in patients. miRNAs are currently being used as diagnostics for at least some types of diseases, including some forms of chronic inflammation such as colitis and IBD [90, 91]. With some diseases, miRNAs can even be used for both diagnosis and prognosis [92]. The appeal of using miRNAs as diagnostic markers comes from the high sensitivity that miRNA biomarkers possess as well as the ability to use miRNA profiles to stratify distinct downstream disease outcomes. The hope is that miRNAs associated with chronic inflammation can be used to diagnose chronic inflammation before clinical manifestations appear. This
would allow for preventative treatment of diseases that stem from chronic, low-grade inflammatory states.

Recently, the identification of miRNAs in blood serum as well as other biological fluids has opened the door for diagnosis of various diseases using these samples obtained through non-invasive methods. Serum miRNAs can either exist cell-free in association with the RISC complex or within small lipid vesicles such as exosomes [93]. Recently, there has been significant interest in utilizing these extracellular miRNAs as biomarkers because of their specificity and sensitivity of detection. Specific secreted miRNAs in the serum can be used to diagnose chronic inflammatory diseases such as IBD [94] where each disease has a unique profile of secreted miRNAs. This could also be an approach to diagnosing other forms of chronic inflammatory states, such as those described above.

The presence of extracellular miRNAs raises questions regarding the biological role of these secreted miRNAs. One current theory of the role of extracellular miRNAs, especially those within exosomes, is that they constitute a novel form of intercellular communication [95, 96]. This idea is supported by several reports providing evidence that secreted miRNAs are functionally passed between various cell types including immune cells [97–99]. It is possible that these extracellular miRNAs could play a role in the development, advancement, or inhibition of chronic inflammatory states. However, further investigation is needed to determine the role of extracellular miRNAs during chronic inflammation and diseases derived from this condition.

miRNAs have also begun to emerge as therapeutic targets. Currently, several anti-miRNA therapeutics are in clinical trials: most notably antisense inhibitors of miR-122 are being used to combat HCV infections [100, 101]. The therapeutic targeting of miRNAs is discussed in further detail in Li and Rana’s 2014 review [102]. Based on the success of these approaches, it is our view that miRNAs that regulate chronic inflammation, such as miR-155 or miR-146a, could also be targeted therapeutically with optimal doses of anti-miRs or miRNA mimics. Ideally, chronic inflammatory disease could be diagnosed early using miRNA detection in blood serum samples, and then possibly treated with specific cocktails targeting the particular miRNAs that are dysregulated. However, there are some barriers to utilizing miRNAs as therapies. One of the biggest hurdles is targeting the miRNA therapeutics to the cells of interest. Exosomes and other lipid carriers have received a lot of attention lately as possible ways by which miRNAs and other therapies may be delivered to specific cell types [102]. However, there is still additional understanding that is required before these approaches can be effectively used in the clinic to provide specificity and sufficient dosing.

**Conclusions and outlook**

The association of chronic inflammation with a variety of diseases emphasizes the importance of gaining a deeper understanding of the underlying mechanisms behind this phenomenon. In this review, we have highlighted factors that contribute to chronic inflammation emphasizing the newly identified roles of miRNAs and other ncRNAs. As we move forward, it will be essential to consider contributions by both coding and noncoding factors in order to formulate an optimal approach for diagnosing, treating, and/or preventing diseases associated with chronic inflammation.

Despite the potential that ncRNAs pose as therapeutic reagents or targets, there are significant barriers that must be overcome in order to achieve therapeutic efficacy. Cell-specific delivery of reagents to manipulate ncRNAs remains a significant challenge. Although progress has been made on cell targeting therapies utilizing lipid vesicles and nonlipid carriers containing antisense miRNAs or miRNA mimics, this remains a substantial challenge facing the field of ncRNA therapy. Additionally, delivery of effective doses of ncRNAs or their inhibitors is also a major hurdle for therapy. For diseases brought on by chronic inflammation, it may also be difficult to determine when to begin treatment, although the use of ncRNA biomarkers in patients’ biofluids should hold to indicate when treatment should begin. Despite these barriers, the manipulation of ncRNAs represents a potential way to treat chronic inflammatory diseases, and hopefully surmounting these barriers will lead to more efficacious uses of ncRNAs as therapeutics.

The authors have declared no conflicts of interest.

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