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REVIEW

The role of microRNA in rheumatoid arthritis and other autoimmune diseases

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Abstract MicroRNAs (miRNAs) represent a class of non-coding RNA molecules playing pivotal roles in cellular and developmental processes. miRNAs modulate the expression of multiple target genes at the post-transcriptional level and are predicted to affect up to one-third of all human protein-encoding genes. Recently, miRNA involvement in the adaptive and innate immune systems has been recognized. Rheumatoid arthritis serves an example of a chronic inflammatory disorder in which miRNAs modulate the inflammatory process in the joints, with the potential to serve as biomarkers for both the inflammatory process and the potential for therapeutic response. This review discusses the investigations that led to miRNA discovery, miRNA biogenesis and mode of action, and the diverse roles of miRNAs in modulating the immune and inflammatory responses. We conclude with a discussion of the implications of miRNA biology in rheumatoid arthritis and other autoimmune disorders.

Contents

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Introduction

MicroRNAs (miRNAs) constitute a recently discovered family of small RNAs, 21–25-nucleotides (nt) in length, that play critical roles in the lives of cells [1]. Since the identification of the miRNA *lin-4* as a regulator of developmental timing in the nematode *Caenorhabditis elegans* (*C. elegans*) [2], it has become evident that these short non-coding RNAs act post-transcriptionally to regulate eukaryotic gene expression [3]. miRNAs negatively influence mRNA expression by repressing translation or directly leading to cleavage of mRNA sequences. miRNAs are thought to regulate about 30% of the protein-coding genes of the human genome, and individual miRNAs typically target several transcripts rather just one specific gene [4]. Over the last decade, more than 9539 miRNAs have been recognized (http://microrna.sanger.ac.uk/sequences/), including more than 650 expressed in humans. Our understanding of the role of miRNA has expanded to include its involvement in a wide array of biological processes, including cell development, proliferation, differentiation, metabolism and apoptosis [5].

Accumulating data suggest that miRNA control is an important feature of the mammalian immune system. Genetic ablation of the miRNA machinery, as well as loss of deregulation of certain individual miRNAs, severely compromises immune development and regulation, implicating miRNA in the pathophysiology of both immunity and autoimmunity [6–8]. Among the most common of the autoimmune diseases is rheumatoid arthritis (RA), a systemic illness characterized by diffuse joint inflammation and destruction. Recent studies suggest that miRNA dysregulation may contribute to RA etiopathogenesis. Better understanding of miRNA mechanisms might therefore shed light, not only on the pathogenesis of RA, but also on potential approaches for managing or even suppressing disease.

In this review, we summarize the history of miRNA discovery and biogenesis, with an emphasis on its role in the pathogenesis of inflammatory and autoimmune disorders. We then consider evolving knowledge on the role of miRNA in clinical medicine, as a potential prognostic biomarker in RA and other autoimmune conditions.

The basic biology of miRNA

miRNA discovery

The occurrence of double-stranded RNAs (dsRNAs) in biological systems was first recognized in the early 1960 s, in the context of viral infections [9,10]. At that time, the central dogma of molecular biology affirmed the concept that double-stranded DNA (dsDNA) and single-stranded RNA (ssRNA) were utilized for long and short-term information storage, respectively, reserving a role for dsRNA exclusively in the replication of RNA viruses.

Three decades later, the novel concept that dsRNAs regulate fundamental biological processes emerged from studies of the regulation of heterochronic genes in *C. elegans*. In *C. elegans*, cell lineages show distinct characteristics during 4 different larval stages (L1–L4), with developmental programs rigidly controlled by temporally regulated gene cascades [11]. *lin*-4 and *lin*-14 are heterochronic genes essential for the normal temporal control of developmental events in the *C. elegans* postembryonic cell lineage. Mutations in *lin*-4 and *lin*-14 affect the timing of events in diverse cell lineages, resulting in either precocious or retarded development [12,13]. Mutations in *lin*-4 cause L1-specific cell-division patterns to reiterate at later developmental stages [12], whereas the opposite developmental phenotype – omission of the L1 cell fates and premature development into the L2 stage – is observed with deficiency of *lin-14* [13] and its nuclearly expressed protein, LIN-14 [14]. *lin-4* was early identified as a negative regulator of *lin-14*, though the mechanism of *lin-4* action on *lin-14* was not initially known [11,15]. Insights into *lin-4* activity came with the recognition, in 1993, that *lin-4* encodes 22- and 61-nucleotide non-coding RNAs that are complementary to a sequence element repeated 7 times in the 3′-untranslated region (UTR) of *lin-14*, suggesting that these small *lin-4* RNAs might regulate *lin-14* translation by an antisense RNA-RNA interaction [2,16]. The complementary sequences fall in a region of the *lin-14* 3′ UTR already proposed to mediate repression by *lin-4* [17]. The resultant negative regulation of *lin*-14 substantially reduces the amount of LIN-14 protein expressed [2,17]. These discoveries supported a novel role for the small *lin-4* RNAs: the induction of translational repression as part of the regulatory pathway responsible for the nematodal transition from larval stage L1 to stage L2 [2,16].

The paradigm of small, non-coding RNA molecules regulating gene expression received additional support when *let*-7, another heterochronic gene of C. *elegans*, was discovered to encode a 21-nt regulatory RNA. Similar to *lin-4*, *let-7* RNA performs its function by pairing to sites within the 3′ UTR of target mRNAs (in this case *lin-41* and *hbl-1* (*lin-57*)), inhibiting their translation and triggering transition to the next developmental stage [18–20]. Homologs of *let-7* were soon identified in the human and fly genomes, and *let-*