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ReviewArticle

MicroRNAs in health and disease; a review of its multifaceted roles

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ABSTRACT

A new class of noncoding small RNAs, called microRNAs (miRNAs), has emerged as important regulators in biological processes. The important role of miRNAs in inflammation and immune response is highlighted by studies in which deregulation of miRNAs was demonstrated to accompany diseases associated with excessive inflammation. It is now known that miRNAs are involved in a broad range of developmental and physiological processes and their deregulation appears to play a fundamental role in the onset, progression, and dissemination of many cancers as well as in many other human diseases. This review article encompasses the roles of miRNAs that have been characterized in innate and adaptive immune responses. It also evaluates the roles of miRNAs as modulators of protein output from hundreds of target genes; they may impact physiological processes by regulating the concentrations of just a few key cellular proteins.

Key words: miRNA, protein, inflammation, immune, transcription

INTRODUCTION

In the past twelve thirteen years, a new class of small noncoding RNAs, called microRNAs (miRNAs), has emerged as crucial regulators in the development of immune and inflammatory responses.[1] The significance of miRNAs in the modulation of normal and pathological immune function has been shown in several studies in which deregulation of miRNAs was demonstrated to be associated with diseases with excessive or uncontrolled inflammation[2-3]Like protein-coding genes, miRNAs are generally transcribed by type II RNA polymerase enzyme. This feature relates miRNA expression to positive and negative regulation at the transcriptional level, similar to protein-coding genes. Perhaps less well appreciated is the regulation of miRNA biogenesis at the posttranscriptional level[4]. Thus miRNAs contribute in almost every cellular event such as development, differentiation, proliferation and apoptosis.

microRNA and organization of the genome:

A certain degree of redundancy exists among miRNAs. In humans approximately 50 % of the known human miRNAs are found in clusters and they are transcribed as polycistronic primary transcripts. There are usually two or three genes per cluster and the largest cluster, at 13q31, is composed of seven. This genomic organization confers simultaneous expression of similar miRNAs, possibly leading to synergistic effects their ultimate function[5]. Moreover, a significant portion of miRNAs are located in the intronic region of protein-coding and/or -noncoding transcription units, whereasa minor subset of miRNAs are mapped to repetitive sequences such as long interspersed nuclear elements[6]. There are four groups of miRNA genes according to their genomic location: intronic miRNA in noncoding transcription units;exonic miRNA in noncoding transcription units; intronic miRNA in protein-coding transcript units or exonic miRNAs in protein-coding transcripts.

Patho-physiological roles of microRNAs:

MicroRNAs may contribute in many biological processes in health and disease. Some miRNAs are naturally present, representative examples of the wide scope of miRNA regulation are found in the miRNA let-7, a miRNA critical for developmental time regulation; a developmentally regulated miRNA, that controls cell proliferation via

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regulation of apoptosis miRNAs that control ES cell differentiation by stabilizing the self- renewing versus differentiated cell fates; and stem cell division. Specifically, the let-7miRNA is essential for normal development and has a temporally regulated expression pattern[7-9]. The misexpression of let-7 has been linked to several types of human cancer. Other examples are miR-196, which is involved in hind limb development, and the brain-specific miR-134, which is necessary for synaptic development and plasticity. Skin differentiation is promoted by miR-203, which represses p63 in stratified epithelial tissues, while precise levels of miR-1 are critical in cardio genesis. Several studies implicated miRNAs with several different diseases besides cancer[10]. MiRNAs are not only required for the development of early embryonic stem cell survival and differentiation, but also plays an important role in maintaining the survival of mature neurons and their function. In neurological diseases, the loss of miR-20a/b-1 cluster has been implicated in the neurodegenerative disorder like the Alzheimer's disease and the loss of miR-133b may contribute to the decrease in dopaminergic neurons seen in Parkinson's disease[11,12]. In the heart disease the expression of miR-21 in cardiac fibroblasts contributes to interstitial fibrosis and cardiac hypertrophy, while miR-1 and miR-133 in cardiomyocytes protects against the hypertrophy[13].

Delivery of microRNAs:

In a new study, Artzi and Conde [14]exploited the ability of dendrimer to form a self- assembled structure with the microRNAs of interest. First, they wound three strands of microRNA together in a triple helix, creating a molecule that is much more stable than a single or double RNA strand. These triplexes then bind to dendrimer molecules, some of which form nanoparticles, and when dextran is added the injectable formulation gels on top of the solid tumor. Once placed on the tumor, the gel slowly releases microRNA-dendrimer particles, which are absorbed into the tumor cells. After the particles enter the cells, enzymes chop each triple helix into three separate microRNA strands. MicroRNA alters gene expression by disrupting messenger RNA molecules, which carry DNA's instructions to cells' protein-building machinery. The human genome is believed to encode more than 1,000 microRNAs, and many of these can cause disease when not functioning correctly.

In this novel study, the researchers delivered two targeted microRNA sequences, plus a third strand whose only function is to keep the helix stable. One of the strands mimics the actions of a naturally occurring microRNA called miR-205, which is frequently silenced in cancer cells. The other blocks a microRNA called miR-221, which is often overactive in cancer cells[15].

The researchers tested this unique microRNA delivery platform in mice implanted with triple-negative breast tumors, which lack the three most common breast cancer markers: estrogen receptor, progesterone receptor, and Her2. Such tumors are usually very difficult to treat with conventional drug therapy[16]

MicroRNA and inhibition of translation?

Mammalian miRNAs pair to the 3' UTR of their target mRNA[17]. It is thought that perfect or near-perfect matching of the 5' end of an miRNA the"seed" region to the target site within the 3' UTR was the sole requirement for miRNA's function.

And this leads to translational inhibition.An alternate pathway of miRNA : target binding exists, which appears to rely on matching of a different stretch of sequence within the miRNA to a 3' UTR. This second pathway is thought to lead not to translational inhibition but rather to mRNA destabilization through adenosine/uridine rich elements (ARE)-mediated decay. These noncanonical types of miRNA : target interactions have not extensively been studied.

Epigenetics and microRNA and role of epigenetic modulating drugs:

Epigenetic changes such as DNA methylation and histone modification are associated with chromatin remodeling and regulation of gene expression in mammalian development and human diseases, including cancer. The first evidence for the epigenetic regulation of miRNAs in cancer was obtained by using chromatin modifying drugs to reactivate miRNAs at the transcriptional level[18]. Emerging evidence shows that more than one hundred miRNAs are regulated by epigenetic mechanisms, and about one-half of them are modulated by DNA methylation[19].

Because CpG methylation can be analyzed by a variety of techniques with relatively high sensitivity, it is possible to identify miRNAs deregulated by aberrant DNA methylation in primary samples that might be limited in number and of poor quality. However, DNA methylation does not always take place alone, but often occurs in the presence of other epigenetic modifications, such as histone modification, which constitutes the second major epigenetic regulatory system of miRNAs. While DNA methylation leads to miRNA silencing, histone modification, especially histone methylation, can either trigger or suppress miRNA expression, depending on the target amino acid residues and the extent of methylation. Given that miRNA expression is tissue-specific and depends on cellular context, histone modification might regulate distinct subpopulations of miRNAs in different types of cancers[20-22]. In addition, the analysis of chromatin modification status should be performed preferably on pure cell populations. Accordingly, identifying the specific miRNAs, which are regulated by aberrant histone modification in clinical tissue samples, remains challenging. The frequent dysregulation of miRNAs and their interplay with epigenetic regulators in cancer make them attractive biomarkers and prospective therapeutic targets in clinical applications[23]. The therapeutic application of miRNAs in cancer involves two strategies: 1) inhibition of oncogenic miRNAs by using miRNA antagonists, such as anti-miRs or antagomiRs; or 2) introduction of tumor suppressor miRNAs through either synthetic miRNA mimics or by stable and vector-based transfection of genes coding for miRNAs. Moreover, a deeper understanding of these epigenetically regulated miRNAs might lead to a novel therapeutic strategy based on using of epigenetic drugs to control the expression of both onco-miRNAs and tumor-suppressor-miRNAs for prevention or treatment of human cancers[24]. Epigenetic control also contributes to miRNA gene regulation through the methylation of CpG islands at the promoter of miRNA genes that silences their transcription. miRNA promoters are also regulated by histone modifications during development and disease[25].

The abnormalities of epigenetic in cancer, unlike genetic lesions, can be reversed by epigenetic-regulated drugs, which provide an opportunity for epigenetic therapy. The goal of epigenetic therapy would be to target the chromatin in rapidly dividing tumor cells in order to bring them to a more 'normal state', while only mildly disturbing the epigenome of healthy cells[26]. Five kinds of epigenetic drugs are known, including DNMT inhibitors, HDAC inhibitors, histone acetyltransferase (HAT) inhibitors, histone methyltransferase (HMT) inhibitors and histone demethylase (HDT) inhibitors. Most of the research efforts focused on the first two agent types. For example, two DNMT inhibitors, 5-azacytidine (5-AzaC) and 5-aza-2'-deoxycytidine (5-Aza-CdR), were approved by FDA to treat myelodysplastic syndromes (MDS) and AML. In 2006, the FDA first approved the HDAC inhibitor suberoylanilide hydroxamic acid (SAHA) to treat cutaneous T-cell lymphoma (CTCL).

MicroRNA and immune system:

Recent work from a number of laboratories has revealed that miRNAs play an important role in this intricate system. The first step toward this understanding was the identification of multiple miRNAs in hematopoietic cells, many of which are expressed specifically in cells and tissues of immune relevance. In fact, cells of the hematopoietic system can be selectively identified from other tissues by their miRNA expression profile; they all express five highly specific miRNAs: miR-142, miR-144, miR-150, miR-155, and miR-223[27].

Different lineages of immune cells can also be distinguished by their unique miRNA expression profiles. For example, erythrocytes show higher expression of miR-451, whereas B and T lymphocytes express miR-223. Additionally, although it may seem that similar expression patterns of miRNAs exists in two different forms.A deficiency in miRNAs also affects B cell development was first suggested by the conditional deletion of Ago2, a component of RISC, in hematopoietic cells, which resulted in a partial deficiency in miRNAs and compromised development of B and erythroid cells[28]. When *Dicer* was deleted in the B cell lineage from the earliest stage of B cell development, an almost complete block at the proto pre-B transition resulted, which was at least in part due to apoptosis of *Dicer* deficient pre-B cells[29]. In an attempt to elucidate the molecular basis of this phenotype, gene expression profiles of *Dicer*

deficient andproficient pro-B cells were established, and a bioinformatic search was conducted for conserved nucleotide hexamers complementary to miRNA seed regions in the 3' untranslated regions (UTRs) of genes upregulated in *Dicer* deficient pro-B cells[30-31]. Surprisingly, only a few such motifs were identified, with a corresponding small group of miRNAs predicted to be critical players at the pro-B cell stage. Tuning miRNA functions in immune cells, through gain- and loss-of-function approaches in mice, may reveal a novel approach to restore immune equilibrium from pathogenic conditions, such as autoimmune disease and leukemia.miRNAs may also play an important role in host viral interactions and may participate in the antiviral activity. For e.g miR-32 counteracts the accumulation of primate foamy virus type 1 (PFV-1) in human cells by targeting the PFV-1 genome and resulting in translation inhibition[32,33]. Thus such examples show insights into mechanisms of adaptive immune responses and suggest potentially new therapeutic capabilities.

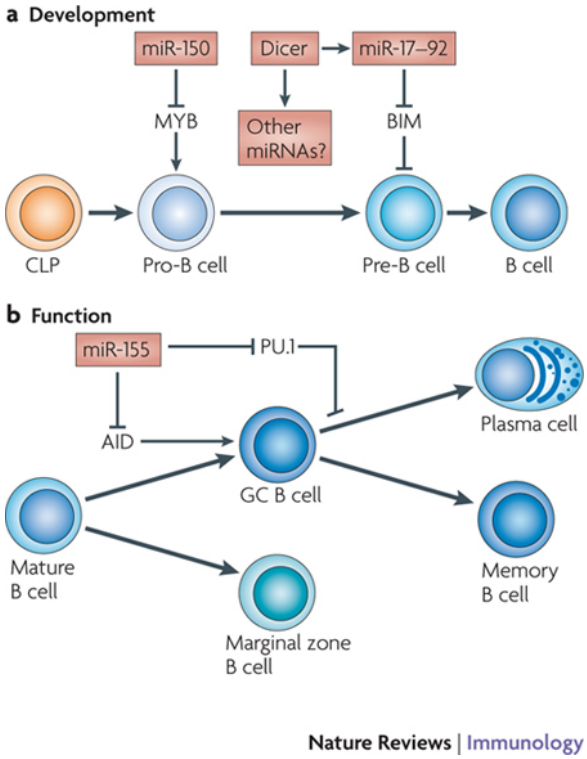

Fig.1: Role of miRNA in development of immune cells

Fig.1 Courtesy: R M. O'Connell, D S. Rao, A A. Chaudhuri & D Baltimore. Nature Reviews Immunology, 10, 111-122, 2010

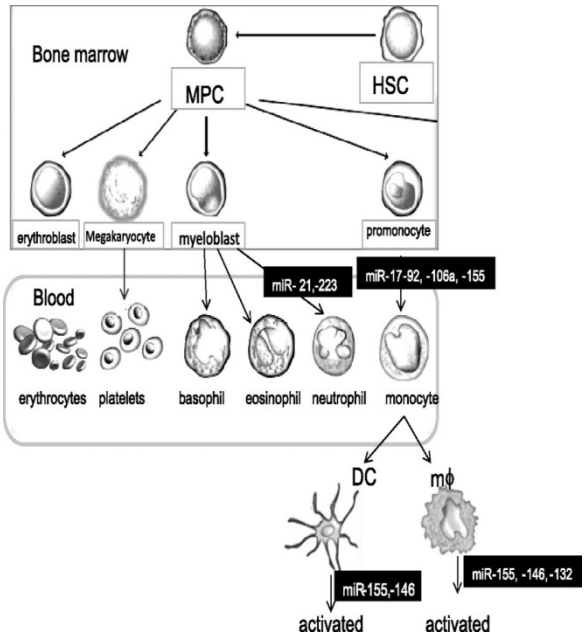

Fig.2: miRNA and myeloid cell differentiation

Fig.2 Courtesy: Sashwati Roy, and Chandan K. Sen. Physiol. Genomics, 2011 Vol. 43 no. 10, 557-565

Conclusion:

MicroRNAs have distinct characteristics that make them an intriguing candidate for cell protection. As advances in the field of miRNA-mediated gene regulation are being made, it is apparent that miRNAs are a crucial component of gene regulatory networks. While, most studies dedicated a downregulation role for miRNA-mediated post transcriptional gene regulation,recently increasing research work reveal an adverse role for miRNAs as activators of gene expression. miRNPs increase protein yield of target mRNA by mRNA degradation and/or translational repression. With the identification of specific miRNAs that play important roles in negative or positive regulatory pathways in innate and adaptive immunity and with the demonstration that dysregulation of specific miRNAs is associated with inflammatory diseases, the field has opened new avenues for uncovering novel targets in treating pathological inflammatory conditions.

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