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Immunomodulation: A definitive role of microRNA-142

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Immunomodulation: A definitive role of microRNA-142

Abstract:
Majority of microRNAs are evolutionarily conserved in vertebrates. This is suggestive of their similar roles in regulation of gene networks. In addition to their conserved mature sequences and regulatory roles, a few microRNAs show very cell or tissue specific expression. These microRNAs are highly enriched in some cell types or organs. One such microRNA is microRNA-142 (miR-142). The classical stem-loop structure of miR142 encodes for two species of mature microRNAs; miR142-5p and miR142-3p. MiR-142 is abundant in cells of hematopoietic origin, and therefore, aptly plays a role in lineage differentiation of hematopoietic cells. Interestingly, over the years, miR-142 has gained considerable attention for its quintessential role in regulating immune response. This mini-review discusses the important functional roles of miR-142 in inflammatory and immune response in different physiological and disease setting.

Keywords: MicroRNA; Hematopoiesis; Gene Expression Control; Immune Regulation; Cytokine Signaling.

Contents:

1. Introduction:

MicroRNAs are a class of noncoding RNA molecules. As their name suggests, they are small single-stranded molecules, approximately 19-25 nucleotides long that have recently emerged as pivotal gene-expression regulatory molecules in multicellular organisms. The founding member of microRNAs is lin-4. It was the first microRNA discovered to play a regulatory role in the transition from one larval stage to another in the nematode *Caenorhabditis elegans.* It does that by translation repression of lin-14 gene involved in the larval development programs (Bartel, 2004). MicroRNAs are encoded in several ways such as independent transcription units, in the introns of pre-mRNAs, or multi-cistronic clusters. The suppressive action of microRNAs on their target genes can be achieved in many ways. If there is perfect complementarity between the microRNA binding sequence and the seed region on the untranslated region of the mRNA, mRNA transcripts undergo cleavage and degradation. In contrast, imperfect base pairing results in translational inhibition at the level of initiation and elongation of mRNA (Bartel, 2009; Stefani and Slack, 2008). One essential feature of microRNAs is that their suppressive function is not limited to one-microRNA—one-mRNA paradigm. In fact, one microRNA can target multiple mRNA targets, and conversely, one mRNA can be targeted by multiple microRNAs(Bracken et al., 2016). Hundreds of microRNAs have been cloned and discovered in many organisms till date. Therefore, to understand gene expression regulation, spatiotemporal regulation of microRNAs is an active field of research. Diverse functional roles of many of these microRNAs have been delineated in a variety of physiological and pathological conditions(Lin and Gregory, 2015; O'Connell et al., 2010; Sayed and Abdellatif, 2011; van Rooij and Olson, 2012).

Majority of microRNAs display a ubiquitous expression, but a few are more enriched in specific tissues than others. The pre-microRNA-142 has the signature stem-loop structure, which encodes for two microRNA species (miR-142-3p and miR-142-5p). Both miR142-5p and -3p are well conserved in many species including mouse, rat and human (Figure 1)(Griffiths-Jones, 2004; Griffiths-Jones et al., 2006; Griffiths-Jones et al., 2008; Kozomara and Griffiths-Jones, 2011, 2014). MiR142 is essentially expressed in hematopoietic tissues(Chen et al., 2004). Its primary role in hematopoietic tissue was discovered to be lineage differentiation(Merkerova et al., 2008). Over the years, plenty of literature has emerged that collectively underscores the role of miR-142 in immune and inflammatory response. Although, studies have also explored diverse functional effects of miR-142 in different biological conditions, the critical regulatory role of miR-142 on different aspects of immunity remain predominant.

2. MiR-142 is a hematopoietic tissue-enriched microRNA

MiR-142 (miR-142-3p and miR-142-5p) is preferentially expressed in hematopoietic tissues. Chen et al. made the very first attempt to characterize the hematopoietic tissue-rich microRNAs in mice. Their study shows that miR-142 is enriched in the adult hematopoietic tissues: bone marrow, spleen and liver, and fetal liver, an embryonic hematopoietic organ (Chen et al., 2004). Many transcription factors (TFs) such PU.1, Runx, C/EBP, GATA, PAX5, Ikaros, and FLI1 are involved in the differentiation lineage of hematopoietic cells. These TFs regulate gene expression changes specific to hematopoiesis. To explore the mechanisms governing specific expression of miR-142 in hematopoietic cells, Sun et al demonstrated that the promoter of miR-142 contains separate binding sites for three TFs, PU.1, C/EBPb, and Runx1 only in the hematopoietic cells. Of these, PU.1, either alone or in synergy with C/EBPb and Runx1, has a predominant role in driving the expression of miR142(Sun et al., 2013). This study identifies the upstream elements that are important for driving miR142 expression in hematopoietic cells, thus modulating many immune regulatory functions of miR-142 as discussed in this review.

2.1 MiR-142 is involved in lineage differentiation of hematopoietic cells

Mildner et al characterized the different cells of myeloid lineage based on their differential microRNA expression. Their study specifically focused on mononuclear phagocytes that are involved in multiple aspects of innate and adaptive immunity. In particular, microRNA signatures were identified in three bone marrow myeloid precursor subsets, monocytes, plasmacytoid dendritic cells (pDC) and splenic classic dendritic cells (cDCs). Interestingly, miR142 is highly expressed in cDCs, most prominently in $CD4^+$ DCs. In a murine model, with splenic deficiency of miR-142 in DC, many costimulatory molecules were activated causing disruption of DC homeostasis. Thus, high expression of miR-142 in DC population appears to be crucial for homeostasis and tonic function of DCs (Mildner et al., 2013).

Since then, many scientific studies have shown agreement between the hematopoietic origin of miR142 with its functional regulation of hematopoiesis. MiR142-3p was shown to play a pivotal role in the lineage differentiation of hematopoietic stem cells (HSCs) in zebra fish. Its loss led to defects in HSC differentiation. This study identified interferon regulatory factor 7 (irf7) as the direct functional target of miR142-3p, and concluded that miR142-3p-irf7 inflammatory axis is potentially involved in lineage differentiation of HSCs in zebrafish. Similar findings in the HSCs development were discovered in mice, reinforcing the conserved role of miR142-3p(Lu et al., 2013). Along similar lines, miR142-3p positively regulates the monocytic and granulocytic differentiation, commonly referred to as myeloid differentiation. MiR142-3p promotes myeloid