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# Emerging Role of MicroRNAs in the Pathophysiology of Immune System

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## 1. Introduction

### 1.1. Overview of MiRNA biology

MicroRNAs are small (22 nucleotides), noncoding, double-stranded RNA molecules, that can regulate gene expression primarily by reducing the abilities of specific mRNAs to be transduced to their encoded proteins. The first recognized miRNA found in 1993 is lin-4, that controls the cell fate at larval stages in *Caenorhabditis elegans* [1, 2]. Bioinformatic approaches suggested that the mammalian miRNA repertoire is involved in regulation of 30% of all protein-encoding genes [3].

Human miRNAs are encoded within introns of coding genes and introns and exons of noncoding transcripts [4]. Generation of mature miRNAs is due to a series of endonucleolytic steps starting from long primary transcripts (pri-miRNAs). The pri-miRNAs are cleaved in the nucleus to a 70 nt intermediate with the typical stem-loop hairpin structure, precursor miRNAs (pre-miRNAs) by the Drosha- DGCR8 microprocessor complex [5, 6]. The pre-miRNAs are further processed into 22 nt double-stranded miRNA duplex by the cytoplasmic RNase III enzyme Dicer [7]. One strand of this miRNA duplex (the guide strand) incorporates into a large protein complex, RNA-induced silencing complex (RISC), formed by Dicer, TRBP (a dsRNA-binding domain protein) and Ago2 (the Argonaute protein 2), and finally becomes the mature miRNA. The other strand, the so-called passenger strand, is degraded.

Each mature miRNA interacts with a specific mRNA in the mRNA's 3'-untranslated region (3'UTR), leading to translational repression or mRNA degradation. Besides, some evidences have shown that miRNA can increase translation [8].

## 2. The role of MiRNAs in hematopoietic cell development

The development of hematopoietic and immune system requires an integrated network of survival, proliferation and apoptotic signals that are finely tuned along differentiation. miRNAs represent efficient modulators of such a system as they can affect the expression of multiple genes at different stages. The identification of putative miRNA involved in hematopoietic ontogeny has been one of primary topic of miRNA studies since their discovery. To clarify the role of specific miRNAs, Chen et al. [9] first cloned about 100 previously identified miRNAs and analyzed only those expressed in hematopoietic cells (miR181, 142 and 223). miR181 was found in lineage negative (Lin<sup>-</sup>) mouse bone marrow undifferentiated cells and strongly upregulated in mature B cells and within the thymus; miR142 was more ubiquitously expressed, while 223 was mostly confined to myeloid lineage. miR181 was then cloned into a GFP gene carrying retroviral vector and ectopically expressed in Lin<sup>-</sup> bone marrow cells. Infected cells were then followed in vitro to check their lineage commitment. A preferential development of B cells was observed. When Lin<sup>-</sup> miR181<sup>+</sup> cells were transplanted in irradiated mice, lymphoid repopulation showed a prevalence of B cell population as compared to control (80% vs 32%, respectively). This study was of primary relevance as it has shown the effects of a single miRNA in lymphopoiesis and addressed a method to study next candidate miRNAs. De Yebenes and colleagues [10] observed that miR181b is involved also in immunoglobulin class switch at activated B cell level. Hence, miR 181 family is involved in early (switch from pro B cell to pre B cell) and late (from centroblasts to activated B cells) stages of B cell development.

The expression of miR181 in mouse thymus prompted investigators to evaluate their role in T cell selection. Interestingly, miR181 is expressed at higher levels in early T cell differentiation as its expression drops from double negative/double positive cells to single positive CD4/CD8 cells [11]. MiR17-92 cluster (miR17, 18a, 19a, 20a, 19b and 92) has been implicated in B cell lymphopoiesis (transition pro B to pre B cells) by Ventura et al. [12]. Interestingly, in mice this cluster is homologous to the miR-106a-63 (except miR18 and 19), although only mice lacking miR17-92 show a relevant phenotype, including B cell differentiation arrest. It is likely that miR17-92 cluster controls apoptotic signals through suppression of Bim and PTEN [13]. miR-150 has been involved in the transition pro B to pre B cells through suppression of c-Myb [14-16], a transcription factor that leads this phase. miR-150 is strongly upregulated along T cell development beginning from double positive stage and modulates expression of NOTCH3 [17]. NOTCH3 gene is known to be involved in T cell differentiation and leukemogenesis.

Overall, these data indicate that miR181/miR17-92/miR150 are among the main regulators of early T and B lymphopoiesis from the common lymphoid precursor.

An analogue role is played by miR 223 in myeloid lineage. Chen et al [9] observed that miR223 is highly expressed in mouse bone marrow. Indeed, miR223 tunes granulocytic differentiation both at an early and late phase [18]. MiR223 knock out mice show expansion

of granulocyte precursors and hyper mature circulating granulocytes. miR223 targets ELF-1-like factor (mef) 2c, a transcription factor that promotes myeloid differentiation and IGFR1, thus affecting expansion of myeloid precursors committed to granulocytic differentiation [18].

Granulocytic differentiation is further regulated through a critical transcription factor, GFI1 (growth factor independent-1). GFI1 expression depends upon miR21 as demonstrated in a knockout model [19].

### **3. MiRNAs at the cross-roads between innate and adaptive immune responses**

#### **3.1. Innate immune responses**

Innate responses imply the final differentiation and interaction of intervening cells to the site where inflammatory stimuli were generated. Several miRNAs have been described as implicated in a complex network, that controls the on and off phases of the response.

miR146a is upregulated upon LPS stimulation in monocytes and is likely to be responsible of the phenomenon known as hyporesponsiveness to prolonged LPS exposure. Indeed, miR146a acts as a negative regulator of LPS induced responses. LPS-induced NF Kb promotes miR146a upregulation, which in turns suppresses TRAF6 (TNF receptor associated factor 6), IRAK1/2 (Interleukin 1 receptor associated kinase 1). These genes encode key adaptor molecules along TLR related pathways and are involved in innate responses through TNF activation and production of IL-1 dependent molecules such as IL-8 and RANTES [20-22]. Therefore, monocytes become hyporesponsive to further stimulation with LPS and relevant pro inflammatory molecules are reduced in the microenvironment.

miR155 seems to act on the same pathways but with opposite effects to miR146a. Indeed, engagement of several TLRs (3,4 and 9) promotes miR155 transcription through AP1 and NFkb. miR155 main targets are SOCS1 (suppressor of cytokine signaling 1) and SHIP1(Src Homology-2 domain-containing inositol-5'-phosphatase 1) that lead to release of proinflammatory cytokines in the microenvironment such as TNF alpha and IFN gamma [23-26].

miR223 can regulate also monocyte-macrophage differentiation by targeting IKK-alpha (IKb kinase) and leaving NFkb to promote inflammatory genes transcription. The final result is the transition of monocyte to macrophage [27].

The emerging data suggest that miRNA regulation of inflammatory and innate responses is timely tuned according to microenviromental stimuli. Indeed, TLR stimulation evokes miR155 upregulation within 2hr , while other miRNAs, such as miR21 are produced according to a delayed time frame. These observations are likely related to a differential role

of miRNAs in turning on and off the inflammatory/innate responses. In this setting, miR21 should turn off the response, by increasing IL-10 levels [28].

### 3.2. Adaptive responses

Immune responses require an integration between the innate/inflammatory and adaptive arm. According to their specific functions, miRNAs represent a perfect set of molecules to finely regulate and coordinate also adaptive responses. miRNAs that are involved in developmental stages of hematopoiesis can show additional functions in differentiated immune cells. Indeed, miR181a, which is implicated in thymic selection, is able to strengthen TCR signaling and reinforce T cell activation upon antigen engagement [11]. This effect likely relies on phosphatase suppression and increase in ERK phosphorylation. A member of the same family, miR181b has been proposed as regulating CSR (class switch recombination) of B cells. CSR is induced by activation induced cytidine deaminase (AID) and is likely targeted by miR181b. Indeed, IgG switch promoted by LPS and IL-4 stimulation is impaired when levels of endogenous miR181b are increased [10].

The role of miRNAs in T cell responses can be also variable according to its endogenous levels and/or contemporary expression in antigen presenting cells (APCs). This might be the case of miR155. miR155 is encoded within the BIC region (B cell integration cluster), which is often involved in lymphomas. BIC deficient mice, which lacked miR155 production, did not show significant impairment in hematopoiesis. When immunization with different bacterial strains and subsequent challenge with the same pathogens were administered to BIC deficient mice, the animals died of infection. Indeed, immunizations did not translate into protective immunity as compared with wild type mice. The authors have shown that T cell activity was compromised because there was a shift towards Th2 phenotype due to downregulation of c-Maf, which is a transcription factor that drives Th2 cytokine secretion [29]. Furthermore, BIC deficient DCs failed to adequately activate T cell responses. In this model, B cells were not able to differentiate to plasmablasts and showed alterations in CSR (class switch recombination). This phenomenon may be due to miR155, that targets AID [30].

Overall, these data indicate that miR155 has a pivotal role in sustaining adaptive immune responses.

However, these data are partly in contrast with the study from Mao et al. [31], who showed that miR155 is upregulated upon TLR stimulation in murine bone marrow derived dendritic cells. Furthermore, transfection of murine epidermal DCs with miR155 coding plasmid increased its endogenous levels and attenuated T cells responses driven by DCs. These effects were reverted when a miR155 antisense sequence was co-transfected into epidermal DCs. The authors try to reconcile these conflicting data, explaining that endogenous levels may induce different effects of the same miRNA in different cell types. However, since

epidermal DC population is heterogeneous and not pure, it is possible that high levels of miR155 promote attenuation of T cell responses through APCs different from differentiated DCs.

The plasticity of miRNAs in controlling overall immune responses is further demonstrated by the miR29 activity. Interestingly, recent findings of Ma et al. [32], who have shown that miR29 suppresses IFN- $\gamma$  secretion in NK and T cells, thereby linking together innate and adaptive responses. Indeed, responses to pathogen are mainly regulated through this mechanism as for the case of *L. Monocytogenes* and *M. Tuberculosis*.

#### 4. MiRNAs and autoimmune diseases

The emerging picture of a central role played by miRNAs in the onset, development and turning off of immune responses is strictly related to the findings of their involvement in autoimmune diseases. In some cases, the functions of specific miRNAs have been first elucidated in the disease and then in immune system physiology. The possibility to use murine models of autoimmunity allows investigators to study the selected miRNAs *in vivo* in order to understand how they facilitate or attenuate the disease. However, the identification of a specific miRNA in the mouse model does not mean a direct translation into human disease. Overall, dysregulation of miRNAs observed in autoimmunity promote either activation of immune effectors and/or suppression of immune regulatory cells, thus contributing to disease development. In the following section, the contribution of miRNAs will be discussed according to the specific autoimmune disorder.

### 5. Systemic Lupus Erythematosus (SLE)

SLE is a chronic autoimmune disease with a complex pathogenesis, involving different organs [33]. Since systemic inflammation is the hallmark of the disease, deregulation of critical pro inflammatory pathways have been described [34]. Indeed, miRNAs deregulated in SLE target genes involved in the inflammatory responses

#### 5.1. miR146a

Type I IFN pathway is widely recognized as a primary deregulation of inflammatory responses in SLE pathogenesis [34]. IFN I pathway is elicited by TLR engagement. Among TLRs, TLR-7 contributes the most to this phenomenon. In 2009, Tang et al. [35] have shown that underexpression of miR146a is tightly related to the upregulation of type I IFN pathway. They analyzed 52 patients with SLE, 6 with Behcet's disease and 29 normal subjects and evaluated miR146a levels from PBMCs. Interestingly, miR146a was proportionally decreased according to disease state (no disease, inactive SLE and active SLE, with active SLE having the lowest levels). miR146a levels were inversely related to IFN score, which was calculated considering the expression of three representative



inducible genes. Finally, IFN pathway could be downregulated when overexpression of miR146a was attained in PBMCs taken from normal donors and SLE patients. The same group [36] has identified a genetic variant of the miR146a promoter region, that confers reduced binding affinity to the transcription factor ETS1, thus leading to reduced levels of miR146a and increased susceptibility to SLE. These data have been further confirmed by a genomic analysis, where a SLE associated polymorphic SNP variant, rs2431697, was found to be related to low expression levels of miR146a gene [37]. Overall, these findings suggest a pivotal role of miR146a in SLE susceptibility and development.

## 5.2. miR125a, 126, 21 and 148a

Autoimmune disorders are often characterized by dysregulated expression of pro-inflammatory chemokines and its receptor that drive and sustain unchecked immune responses, favoring autoimmunity. This is the case for RANTES (Regulated upon Activation, Normal T-cell Expressed, and Secreted), also known as CCL5, whose elevated levels are observed in the context of chronic systemic inflammations such as arthritis and nephritis. Renal damage is initiated by RANTES over-expression in mouse models of SLE [38].

Zhao et al. [39] have shown that miR125a levels are underexpressed in T cells of SLE patients, while its predicted target KLF13 (Kruppel like factor 13) was upregulated. KLF13 directly controls the expression of RANTES in T cells. Interestingly, prolonged mitogenic stimuli evoke miR125a upregulation in normal T cells, providing a negative feedback loop that controls chemokine expression and helps to turn off inflammatory responses. The deficiency of this mechanism in SLE patients provide further insights on the onset and progression of the disease.

DNA methylation is a relevant mechanism to regulate gene transcription in eukaryotic cells [40] and any perturbation of these pathways can have crucial impact in health and disease. T cells from SLE patients suffer of a global hypomethylation [41], which is related to disease activity. The reduction of DNA methylation depends upon the reduced levels of Dnmt1 (Dna methyl transferase-1), the key enzyme that transfers methyl groups to CpG islands. The paired analysis of CD4 T cells from normal donors and SLE patients revealed the presence of an upregulated miRNA in SLE-T cells, miR126, that was independent from costimulatory signals [42]. miR126 targets Dnmt1 and reduces its levels in SLE- CD4 T cells. miR126 downstream effects include hypomethylation of critical genes in autoimmune pathogenesis such as TNSFS7 and ITGAL, that encode CD70 and CD11a [43], respectively. Indeed, CD70 [44] is the cellular ligand for the tumor necrosis factor receptor family member CD27, and is required on activated T cells and B cells to stimulate the synthesis of IgG. CD11a, also known as lymphocyte function-associated antigen 1, belongs to the integrin family of cell surface receptors and can strengthen the adhesion of T lymphocytes to other immune cells. These events could be reverted by miR126

inhibition. A similar activity of Dnmt1 suppression in CD4 T cells from SLE has been ascribed to miR21 and 148a [45]

## 6. Rheumathoid Arthritis (RA)

RA is a systemic inflammatory disorder, primary involving synovial joints. The inflammatory milieu is the base for disease onset and progression. Several groups reported an increase of miR155 and 146a in synovial fibroblasts and PBMCs from RA patients [46, 47]. Interestingly, these miRNAs can be stimulated by inflammatory stimuli, though promoting opposite effects. miR155 sustains inflammation, while miR146a attenuates through TNF $\alpha$  suppression. In this setting, miR146a seems not able to promote its action. A possible explanation is that both miRNAs are elicited by the pro-inflammatory environment of RA, with miR155 enforcing inflammation, while miR146a should shut off it, but it is unable to exert its activity.

## 7. Multiple Sclerosis (MS)

MS is an autoimmune disease of the central nervous system characterized by chronic inflammation, demyelination, and axonal damage. Demyelination is due to pro inflammatory T cells. Mireia Guerau-de-Arellano et al. [48] identified increased levels of miR128 and 27b in naive and miR340 in memory CD4 T cells from MS patients, favoring switch to Th1 phenotype. Gain-of-function experiments with these micro-RNAs enhanced the encephalitogenic potential of myelin-specific T cells in experimental autoimmune encephalomyelitis, while treatment with specific oligonucleotide miRNA inhibitors reverted to normal Th2 shift. These data further clarified the role of these miRNAs in MS pathogenesis and suggested a therapeutic strategy based on miR suppression by selected inhibitors.

## 8. Conclusions

The increasing evidences on the role of miRNAs in pathophysiology are radically changing the established paradigms of disease onset and development. However, we can assert that our understanding of miRNA functions is still preliminary and further work is awaited to better define how these molecules integrate with known intracellular pathways. Indeed, we know that miRNAs exert a very finely tuned regulation of intracellular pathways. This effect is attained through a modulation of miR levels, that is very complex to study in simplified models both in vitro and in vivo. Indeed, the best method to study miRNAs is to over express or completely inhibit its expression, but it is unlikely that this method can perfectly mirror the real intracellular conditions. Immune responses represent an attracting system to explore miR functions, since they have to be tightly regulated. The data have shown that miRNA modulation is an efficient way to rapidly turn on and off immune responses, both preceding and integrating with the classical gene mastered pathways. Therefore, we believe that the study of miRNAs within



immune system may represent an excellent model to understand miRNA pathophysiology, providing critical insights to be extended to the other branches of biopathology.

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