Immune-Related miRNAs

Subjects: Pathology

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MicroRNAs (miRNAs) are small non-coding regulatory RNA family that play pivotal roles in physiological and pathological conditions, including immune response. Immune-related miRNAs might on one side trigger the innate and adaptive immune response and regulate the expression of immune cells. On the other side, miRNAs can be diferentially expressed due to activated immune cells. All of this makes them valuable promising diagnostic, prognostic and predicative markers as well as potential therapeutic targets.

Keywords: microRNA (miRNA) ; immune response

1. MicroRNAs

MicroRNAs (miRNAs) are short non-coding and regulatory RNAs. Through formation of silencing complex with proteins, they act mainly as posttranscriptional repressors of gene expression. The most known canonical way is through inhibition of translation. They are regulating physiological and contributing to pathological conditions, including regulation of immune response [1]. Detailed description on their biogenesis is beyond the scope of this entry and can be found elsewhere [2].

In multicellular organisms, different mechanisms of regulation of miRNA biogenesis are used, not only to generate the spatiotemporal specificity of miRNA, but also to achieve the necessary levels and dynamics of expression. There is a variety of silencing complexes that produce different molecular effects on miRNAs targets. And higher organisms, including humans, have taken advantage of this variability to ensure the required differences in specific cell types or even in different subcellular compartments [2]. Many miRNAs are expressed in a tissue-specific manner, e.g., *miR-208* is cardiac specific [4], *miR-122* is liver specific [5] and/or cell type specific, e.g., *miR-223* is primarily expressed in granulocytes [2].

In repressing translation of mRNAs under normal cell conditions, miRNAs act in different ways. For mRNAs that should not be expressed in a particular cell type, miRNAs reduce protein production, resulting in silencing of the targets. In another way, miRNAs can adjust protein production, leading to tailored expression in certain cell types but more uniform levels in other cell types, serving as a fine-tuning of target expression. Another mechanism of miRNAs is that they can act as a bystander, where downregulation by miRNAs is tolerated or negated by feedback processes, resulting in neutral target expression [6].

miRNA functions are mainly postulated by in vivo experiments, through the phenotypic consequences of a mutated miRNA or an altered mRNA complementarity site, both of which can disrupt miRNA regulation. In some cases, function has been inferred from the effects of transgenic constructs leading to ectopic expression of miRNA [6]. Canonical and non-canonical mechanisms in miRNA biology, their specific expression and variations influence different developmental stages of immune cells and physiology of multicellular organisms. Disruption of these mechanisms can lead to undesirable pathogenesis of various diseases [2]. miRNAs are important in the regulation of morphogenesis and maintenance of undifferentiated or incompletely differentiated cell types, such as in stem cell differentiation, cardiac and skeletal muscle development, neurogenesis, haematopoiesis, control of cell fate decision, cell proliferation, cell death, neuronal patterning, modulation of hematopoietic lineage differentiation, and control of the timing of developmental transitions [2][3][6]. Under physiological conditions, miRNAs are involved in metabolism, the regulation of insulin secretion, cholesterol metabolism, resistance to viral infections and oxidative stress, immune response, etc. [7]. Therefore, each cell type at each developmental or physiological stage might have a different miRNA expression profile. It is believed that miRNA biogenesis and function is one of the most important regulatory mechanisms in maintaining tissue identity during embryogenesis and adult life [2].

2. miRNAs' Contribution to Disease Pathogenesis—Causes of Aberrant Expression of miRNAs

miRNAs are associated with various pathological conditions due to the disruption of miRNA biogenesis or its complex that results in dysregulation of miRNAs, leading to inappropriate expression and consequently function [8]. An abnormal miRNA expression profile is usually the consequence of their regulation by aberrantly expressed transcription factors, genomic rearrangements, alterations in genes encoding miRNAs, or epigenetic mechanisms. All of this could contribute to inappropriate regulation of protein-coding genes and ultimately to the development of disease, e.g., genetic disorders, cancer, autoimmune and inflammatory diseases and neurodegenerative and cardiovascular diseases [2][8].

Disruption of miRNA-target interaction in the form of single nucleotide polymorphisms (SNP), both in the miRNA gene or its target site in the mRNA, can lead to a complete gain or loss of miRNA function, thereby establishing a disease state [9]. In contrast to miRNA target sites in mRNA transcripts, where the potential for variation is very large (e.g., *AT1R* and *miR-155*) [9], the variants identified in miRNA precursor sequences are extremely rare (e.g., *miR-196* [10]). The presence of SNP in pri-miRNA or pre-miRNA can also affect the processing of miRNAs and their expression, which can also lead to different disease outcomes [11].

Aberrant methylation or de-methylation of any gene (protein-coding or protein-non-coding) can lead to repression and silencing of a physiologically activated gene or de-repression of a physiologically silenced gene, respectively. In the case of miRNAs, this mechanism leads to the inappropriate expression of miRNAs, either de-methylation and expression of miRNAs that should be silenced or methylation and silencing of miRNAs that should be expressed. All of these aberrant expressions can be the cause of disease development [12].

3. miRNAs in Immune Response

Based on experimental models and human samples, there is an ample evidence that miRNAs also play important roles in the development of various immune-response related disease, suggesting that aberrant miRNA regulation might be a cause of disease. There is an increasing evidence that different miRNAs represent disease-specific signatures not only in tissue samples but also in liquid samples. Moreover, since these molecules are stable and can be easily detected in body fluids, such as blood and urine, they are even more interesting and promising as potential prognostic and diagnostic markers for non-invasive monitoring of various diseases [1].

miRNAs have been shown to play a role in a broad spectrum of diseases, ranging from various infectious diseases, systemic (auto)immune diseases to isolated immune-related diseases [13], which not only cause native organ damage, but can sometimes recur after organ transplantation [14].

Solid organ transplantation is a highly immunological complex process associated with the need to optimize donor-recipient MHC (major histocompatibility complex) antigen matches to achieve graft acceptance. Many different components of the immune system are involved in graft tolerance or rejection, including antibodies, antigen-presenting cells, subsets of helper and cytotoxic T-cells, immune cell surface molecules, signalling mechanisms, and cytokines [15]. The development of pharmacological agents that interfere with the alloimmune response has been instrumental in the success of organ transplantation, leading to improved graft survival, lower doses of necessary, albeit toxic, immunosuppressive drugs, and better long-term outcomes for patients. Immune response plays a crucial role in the most common complications that may occur after allograft transplantation, i.e., rejection and non-rejection complications (e.g., antibody-mediated rejection, T-cell-mediated rejection, delayed graft function, viral infections, drug toxicity, systemic diseases, recurrent or de novo diseases, etc.). miRNAs are involved in all aspect of immunity, from inflammation and innate to adaptive [16].

There are numerous suggestions that miRNAs are important regulators of all these outcomes, becoming new class of promising diagnostic, prognostic and predictive biomarkers as well as therapeutic targets [1].

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