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Review article

MicroRNAs: New regulators of IL-22

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ABSTRACT

Interleukin-22 (IL-22) is a cytokine that belongs to the IL-10 family of interleukins. It can be produced by T helper 22 (Th22) cells, T helper 1 (Th1) cells, T helper 17 (Th17) cells, natural killer 22 (NK22) cells, natural killer T (NKT) cells, innate lymphoid cells (ILCs), and γδ T cells. IL-22 acts via binding to a heterodimeric transmembrane receptor complex that consists of IL-22R1 and IL-10R2 and mainly contributes to the tissue repair and host defense. Transcription factors such as retinoid orphan receptor γt (RORγt) and signal transducer and activator of transcription 3 (STAT3), have been reported to play important roles in regulation of IL-22 expression. Recently, it has been demonstrated in several studies that microRNAs (miRNAs) potently regulate expression of interleukins, including production of IL-22. Here, we review current knowledge about regulators of IL-22 expression with a particular emphasis on the role of miRNAs.

Contents

Abbreviations: IL-22, interleukin-22; Th22, T helper 22 cell; Th1, T helper 1 cell; Th17, T helper 17 cell; NK22, natural killer 22; NKT, natural killer T cell; ILCs, innate lymphoid cells; RORγt, retinoid orphan receptor γt; STAT3, signal transducer and activator of transcription 3; miRNAs, microRNAs; 3′ UTR, 3′ untranslated region; RA, rheumatoid arthritis; RISC, RNA-induced silencing complex; *IL22RA1*, IL-22R1-encoding gene; *IL10RB*, IL-10R2-encoding gene; IL-22BP, IL-22 binding protein; MAPK, mitogen-activated protein kinase; ConA, concanavalin A; IBD, inflammatory bowel disease; EAE, experimental autoimmune encephalomyelitis; APAP, acetaminophen; AILI, (APAP)-induced liver injury; DSS, dextran sulfate sodium; AOM, azoxymethane; AH, alcoholic hepatitis; AHR, aryl hydrocarbon receptor; FICZ, 6-formylindolo (3,2-b) carbazole; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; Hsp90, heat shock protein 90; ART, aryl hydrocarbon receptor nuclear translocator protein; bZIP, basic region/leucine zipper; TGF-beta, transforming growth factor beta; ICOS, inducible T cell costimulatory; IRF4, IFN regulatory factor 4; ING4, inhibitor of growth family member 4; IBP, IRF binding protein; BMDMs, bone marrow-derived macrophages; PRC2, polycomb repressive complex 2; MM, multiple myeloma; CIA, collagen-induced arthritis; ALCL, anaplastic large cell lymphoma; ZFL, zebrafish liver; OLP, oral lichen planus; SOCS1, suppressor of cytokine signaling 1; IGF-1R, insulin-like growth factor-1 receptor; NFAT5, nuclear factor of activated T cells 5; PTEN, phosphatase and tensin homolog.

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1. Introduction

IL-22 was discovered by Dumoutier et al. in 2000 [1]. The primary structure of IL-22 is similar to that of the well-known anti-inflammatory cytokine IL-10. Because it was initially found in murine BW5147 T lymphoma cells, it was named IL-TIF for "IL-10-related T cell derived inducible factor" [2,3]. Shortly thereafter, IL-TIF was identified in human and its gene was localized to human chromosome 12 [1,4]. Then, this interleukin was renamed IL-22 according to interleukin nomenclature rules. Since its discovery, biological functions of IL-22 have been extensively studied. IL-22 has been identified as a crucial player in tissue repair and host defense [5–7]. However, IL-22 has also been reported to act as a pro-inflammatory cytokine leading to pathological changes [3]. Therefore, regulation of IL-22 expression may help to control development of such conditions. Classical regulators of IL-22 include retinoid orphan receptor γt (RORγt), signal transducer and activator of transcription 3 (STAT3), and a number of other transcription factors [3,5]. Recently, miRNAs (microRNAs) have been suggested to strongly affect IL-22 expression.

A considerable attention to functions of miRNAs in the past few years is explained by their proven crucial regulatory role in gene expression and, in particular, their close relation to aberrant expression of various genes in many diseases [8–10]. MiRNAs are small noncoding RNAs. Mature miRNAs are ~22nt in length. Generally, they are derived from larger precursors. It takes several steps to get mature miRNAs after transcription catalyzed by RNA polymerase II. The original transcripts, called pri-miRNAs, are cleaved by the RNase III endonuclease Drosha in the nucleus. The cleavage liberates stem-loop intermediates called pre-miRNAs. After cleavage, pre-miRNAs are transported out of the nucleus into the cytoplasm by Ran-GTPase and Exportin-5. Subsequently, pre-miRNAs are processed by Dicer, an RNase III endonuclease that cleaves away the loop and several base pairs from the terminal, leading to formation of double-stranded miRNAs, which have a 2-nucleotide long overhang on the 3′-ends of both strands [11]. The double-stranded miRNA duplex is loaded onto the RNA-induced silencing complex (RISC). Some RISC subunits can unwind the duplexes because the complex may have helicase activity. After the duplex is unwound, only one strand gets integrated into the RISC, while the other one is peeled away and degraded. The remaining strand usually binds to the 3′ UTR of the target mRNA to repress its expression (which is a typical process in mammals) or directly cleaves the target mRNA [12,13] (Fig. 1).

In this review, we will consider biological functions of IL-22 and summarize transcriptional and post-transcriptional regulators of its expression. We will focus on the role of miRNAs that have been recently discovered to modulate IL-22 production.

2. Cellular sources of IL-22

IL-22 is predominantly produced by $CD4^+$ T cells. Two subsets of $CD4^+$ T cells, Th1 and Th17, are the main sources of IL-22. High levels of secreted IL-22 were initially detected in Th1 cells. Later, Th17 cells were reported to produce IL-22 as well [1]. Recently, Th22 cells, a new subset of $CD4^+$ T cells enriched in inflammatory skin lesions, were also found to secrete high levels of IL-22 [14,15]. In addition to adaptive immune cells, innate immune cells, includ-

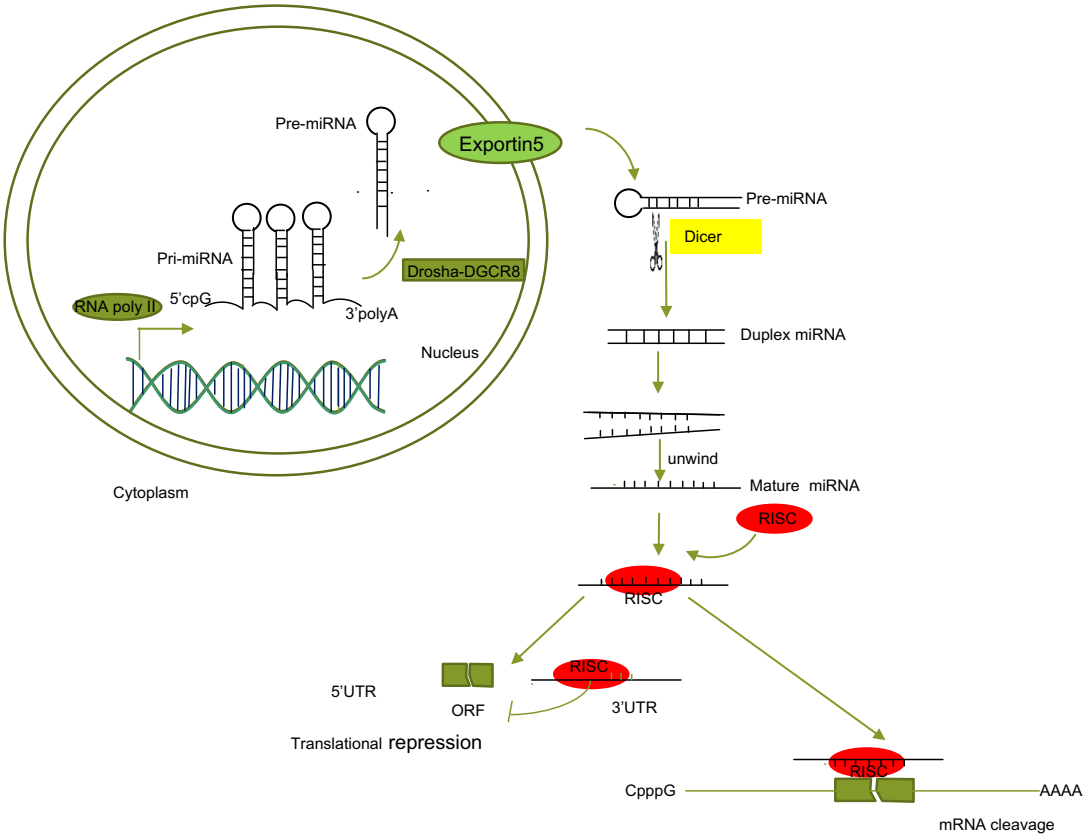

Fig. 1. Generation process and functional mechanisms of microRNAs. MicroRNAs (miRNAs) are small noncoding RNAs with approximately 22 nucleotides. The precursors (pri-miRNA) are transcribed by RNA polymerase II and cleaved into stem-loop intermediates (pre-miRNA) by an RNase III endonuclease (called Drosha) in the nucleus. Then the pre-miRNAs are exported into the cytoplasm by Ran-GTPase and Exportin-5, wherein they have their loops and a few base pairs from the terminal cleaved away and become double-stranded miRNAs with 2nt over-hang on the 3′ terminal of both strands. Double-stranded miRNAs bind to RISC which can unwind the duplexes. The strand remained usually bind to the 3′UTR of the target mRNA to repress the gene expression or lead to cleavage of the target mRNA directly.

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