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Review Article

Progress on the relationship between miR-125 family and tumorigenesis

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ABSTRACT

miRNA-125 family, which is a highly conserved miRNA family throughout evolution, is consist of miRNA-125a-3p, miRNA-125a-5p, miRNA-125b-1 and miRNA-125b-2.The aberrant expression of miR-125 familyis tightly related to tumorigenesis and tumor development. The downstream targets of miRNA-125 include transcription factors like STAT3, cytokines like IL-6 and TGF-β, tumor suppressing protein p53, pro-apoptotic protein Bak1 and RNA binding protein HuR et al. Through regulating these downstream targets miR-125 family is involved in regulating tumorigenesis and tumor development. Nowadays, miR-125b have already became a putative and valuable biomarker for cancer diagnosis, treatment and prognosis. In this review, we mainly summarize the dual function of miRNA-125 family in suppression and promotion of cancer cells and further elaborate its regulatory mechanisms from four facets, proliferation, apoptosis, invasion or metastasis and immune response.

Contents

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1. Introduction

microRNAs are a class of endogenous single-stranded small noncoding RNAs with the length of 19～25 nucleotides, which mainly regulate the abundance of mRNAs and the expression level of their corresponding proteins by directly binding with target mRNAs on the 3' UTR (untranslated region) or 5' UTR [1]. Current studies revealed that miRNAs ubiquitously exist in various species and are mainly evolutionarily conserved but still possess tissue specificity and species specificity to some extent. miR-125 family is the human homolog of the microRNA lin-4, which was the first microRNA being discovered by Lee RC in C. elegans development [2]. In normal cells, miR-125 family has been reported to be implicated in a wide variety of physiological processes, including cell differentiation, immune response, pain signaling, cell metabolism. The aberrant expression of miR-125 family is closely related to proliferation, apoptosis, invasion, metastasis and immune response of cancer cells. Thus, miR-125 family has been validated of possessing the potential possibility of being a therapeutic target for cancer treatment and becoming a biomarker.

2. MicroRNA biogenesis and function

As naturally occurring small noncoding RNAs, microRNAs regulate physiological processes through modulating the translation of target mRNAs and the expression level of target proteins. The biogenesis of miRNA mainly go through three processes, being respectively intranuclear processing of pri-miRNA, pre-miRNA exporting out of nuclear and intracytoplasmic cleaving of pre-miRNA [3] (in Fig. 1). MicroRNAs are mostly transcribed by RNA polymeraseII and the direct product is pri-miRNA, a long RNA with several hair pin structures [4]. Then endoribonuclease Drosha and splice site recognizing protein DGCR8 (DiGeorge syndrome critical region 8) cooperate to process pri-miRNA into small double-stranded pre-miRNA with only 70–80 nucleotides [5]. When finished processing pre-miRNA starts to be exported into cytoplasm by shuttle protein exportin-5 [6]. In cytoplasm, the RNase III enzyme Dicer cleaves the stem loop of pre-miRNA to produce a mature miRNA with approximately 22 nucleotides in length. Then Argonaute2 (Ago2) and Tar RNA binding protein (TRBP) binds to mature miRNA to form a multiprotein complex called RISC (RNA induced silencing complex) [7]. This is the canonical miRNA biogenesis. Evidence showed that except of the canonical pathway, miRNA biogenesis can occur through other ways [8]. Jakub et al. found that some miRNAs could be derived from introns [9]. The initial spliced introns product possess a lariat structure in which the 3' branch point is ligated to the 5'end of the intron. However, introns entering mirtron pathways must go through splicing and debranching by lariat debranching enzyme, after which they are folded into hairpins, which is structurally identical to pre-miRNA [10].

Mature miRNA inhibits mRNA translation through three ways: inhibiting translation initiation, inhibiting peptide elongation and inducing mRNA degradation [11]. The seed sequence located in 5'end 2-7nt of miRNA plays an important role in determining target mRNA while which way to modulate mRNA chosen by miRNA depends on the complementary degree between miRNA and mRNA [12]. When the sequences are perfectly complementary, miRNAs trigger target mRNA degradation or deadenylation [13]. When the sequences are only partly complementary, miRNAs induce translation repression [14]. Recent research revealed that GW182 and RCK/p54 are two protein played important role in miRNA mediated mRNA degradation [15]. GW182 protein recruits CCR4-NOT deadenylation complex through binding with Ago2 [16], which further accelerate mRNA deadenylation and degradation [17]. RCK/p54 protein mainly promotes the formation of P-body (processing body), which supports mRNA degradation by offering a place and needed enzymes or proteins [18]. Compared with the former, miRNA mediated mRNA translation repression merely take up approximately 20% of all miRNA modulating measure [19]. Such translation repression could occur in initiation stage and elongation stage. In initiation stage miRNA mostly inhibits ribosome assembling; while in elongation stage, inducing ribosome disassociating and promoting nascent peptide hydrolysis are two measure chosen by miRNA [20].

3. MicroRNA-125 family

3.1. miR-125 family chromosome location and expression

MicroRNA-125 family is a group of highly conserved microRNA, consisting of two sub-family, miR-125a and miR-125b, which has distinct seed region and chromosomal location. MiR-125a could further divided into miR-125a-3p and miR-125a-5p, which respectively derives from the 3' end (passenger strand) and the 5'

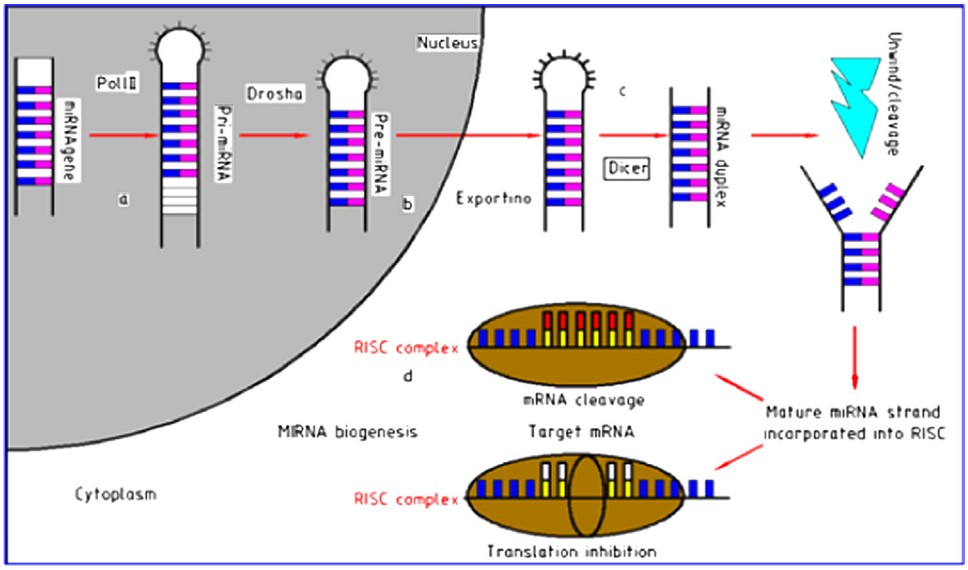

Fig. 1. MicroRNA biogenesis and function.