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MicroRNAs link chronic inflammation in childhood to growth impairment and insulin-resistance

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ABSTRACT

MicroRNAs are involved in multiple pathophysiological networks and in the pathogenesis of a broad spectrum of human disorders, including cancer and inflammatory diseases.

Impaired linear growth is encountered in children with chronic inflammatory conditions such as cystic fibrosis, inflammatory bowel diseases, juvenile idiopathic arthritis, celiac disease and in subjects born intrauterine growth restricted/small for gestational age.

Children with inflammatory conditions may also be at risk of developing insulin resistance as a result of the inflammatory process and concurrent therapy.

Chronic inflammation may lead to a continuum of abnormalities in the Growth hormone/Insulin-like growth factor 1 (GH/IGF-I) axis, including relative GH insufficiency, GH/IGF-I resistance due to down regulation of GH and IGF-I receptors, changes in GH and IGF-I bioavailability due to modifications of binding proteins, and/or impaired GH/IGF-I signaling.

The aim of this review is first to summarize the current knowledge concerning microRNAs involved in inflammation in the most relevant chronic inflammatory diseases in childhood, second to provide new insights into miRNA regulation of growth and insulin sensitivity mediated by the inflammatory processes. We evaluated single microRNAs involved in inflammation in the single conditions mentioned above and verified which had validated and predicted targets within the GH receptor, IGF-I type 1 receptor and insulin receptor interactomes.

The findings show a new link among inflammation, growth and insulin sensitivity mediated by miRNAs that warrants further research in the future.

1. Introduction

Chronic inflammatory diseases are characterized in childhood by growth impairment and, frequently, insulin insensitivity. Genetics and environment are key factors involved in the onset of these conditions, although the precise pathogenetic mechanisms are not clearly understood yet. The most recent chapter which could contribute to fill in some lack of knowledge in the understanding of these diseases is represented by epigenetics. In this context, an important role is covered by miRNAs that could represent a molecular link that binds the inflammatory component underlying these conditions to altered growth and insulin-resistance.

Abbreviations: ALS, acid-labile subunit; APC, antigen-presenting cell; CXCL2, chemokine (C-X-C motif) ligand 2; ESR, erythrocyte sedimentation rate; FGFR1, fibroblast growth factor receptor 1; FOXO1, Forkhed box O1; FOXP3, forkhead box P3; GH, growth hormone; GHR, growth hormone receptor; GHRH, growth hormone-releasing hormone; Grb10, growth factor receptor-bound protein 10; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor-1 receptor; IGFBP, insulin-like growth factor-binding protein; IL, interleukin; INSR, insulin receptor; IRS, insulin receptor substrate; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MEK1, mitogen-activated protein kinase 1; MiR, microRNA; MMP3, matrix metalloproteinase3; mTOR, mammalian target of rapamycin; NF-kB, Nuclear factor Kappa B; NOD2, nucleotide-binding oligomerization domain containing 2; PAPP-A2, pappalysin2; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIK3CA, PI3K Catalytic Subunit Alpha; PIK3R1, Phosphoinositide-3-Kinase Regulatory Subunit 1; PTPN11, Protein Tyrosine Phosphatase, Non-receptor Type 11; RISC, RNA-induced silencing complex; RNA pol, ribonucleic acid polymerase; RUNX1, runt-related transcription factor 1; SHIP1, Src homology-2 domain-containing inositol 5-phosphatase 1 protein; STAT, Signal transducer and activator of transcription; TGF-β1, Transforming growth factor beta 1; TNF, tumor necrosis factor; TOM1, Translocase of the outer membrane 1; XPO5, exportin 5

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1.1. Biology of MicroRNAs: formation and action

Epigenetics is now defined as “the inheritance of variation (-genetics) above and beyond (epi-) changes in the DNA sequence” [1]. Thus, epigenetics refers to inheritable changes of gene function, which do not imply a change in the DNA sequence [2]. Heritability implies that an epigenetic marker has the ability to persist during development and that it is potentially transmitted from generation to generation [3]. The best known mechanisms of chromatin and gene modulation include DNA methylation, histone modification, the positioning of nucleosomes and miRNAs. Within the chapter of epigenetics, miRNAs are becoming increasingly promising because they may provide further molecular explanation for the variability observed, and also have been proven to be potentially useful for diagnosis, prognosis and, to monitor the effect of treatments, and furthermore represent potential therapeutic targets. MiRNAs are endogenous small non-coding RNAs that act as post transcriptional regulators [4]. MiRNA genes are transcribed by an RNA polymerase II generating a primary transcript (pri-miRNA) [5]. Pri-miRNAs are long transcripts which contain many miRNA sequences already folded in hairpin structures. In the nucleus, the pri-miRNA is processed by Drosha, an enzyme member of the RNA polymerase III family which acts with the Dgcr8 protein in the formation of a double stranded pre-miRNA about 70 nucleotides long [6]. The pre-miRNA is exported to the cytosol by the complex XPO5:RAN·GTP [6]. Dicer, a cytoplasmic RNA polymerase III, complexed with its cofactor TRBP, starts the processing of the pre-miRNA [7] ending in the formation of a miRNA duplex about 21–24 nucleotides long. The miRNA duplex is charged in the RNA-induced silencing complex (RISC) which determines a strand displacement and selection. The single stranded mature miRNA is approximately 22 nucleotides (nt) long and contains an approximately 7-nt sequence in the 5'-end (residues 2–8 from the 5'-end) referred as “seed region” which guides recognition of the mRNA target. The miRNA hybridizes to partially complementary binding sites that are typically localized in the 3' untranslated regions (3'UTR) of target mRNAs [8]. Upon binding, miRNAs initiate a pathway that either degrades the transcript or suppresses its translation [9] (Fig. 1). MiRNAs are known to be highly conserved across species and approximately 1100 miRNA genes have been discovered in the human genome [4]. MiRNAs are generally classified as “intergenic” or “intronic” based upon their genomic location. Many of the known miRNAs are encoded in polycistronic transcripts (miRNA clusters) exhibiting coordinated regulation as they are involved in the same gene regulatory network. To date, miRNAs have been predicted to target and control the expression of at least 30% of the entire mammalian genome [10]. Since their discovery, miRNAs have been found to be involved in multiple pathophysiological networks [11,12] and in the pathogenesis of a broad spectrum of human diseases, including cancer and inflammatory diseases [13–18]. The molecular rules governing the targeting of each miRNA to individual genes have been documented [19,20]. A single miRNA can act on several hundreds of target mRNAs and each mRNA can be the target of many miRNAs; this regulatory network provides an explanation for their pivotal functional role [21,22]. Given the pleiotropic action of miRNAs and the complex gene regulation network, a distinctive miRNA signature can be linked to a particular pathological condition. MiRNAs appear remarkably stable in serum and other bodily fluids such as urine and saliva [23]; as they are enclosed in extracellular membrane bound vesicles or combined with high density lipoproteins. Tissue damage in pathologic processes may lead to an aberrant expression of miRNAs; this phenomenon rises the possibility of identifying disease specific miRNA profiles, promoting new strategies for predicting the development and progression of human conditions [24]. Two methods have been employed for miRNA therapeutics: miRNA restoration or inhibition. While restoring miRNAs is achieved through the use of double stranded RNA (mimic), inhibiting miRNAs is obtained through single stranded chemically modified RNA (antagomiR).

1.1.1. microRNAs as mediators of inflammation

Many studies have demonstrated that miRNAs play crucial roles in both adaptive and innate immune responses. MiRNAs regulate the development of various immune cells as well as their immunological functions. Innate immune responses provide the initial defense against pathogens. Pattern recognition receptors expressed on macrophages and dendritic cells, such as Toll-like receptors (TLRs) with their signaling cascade, are regulated by miRNAs [25,26]. MiRNAs have also been shown to regulate macrophage and dendritic cell activation, antigen presenting capacity and costimulation activity [27,28]. MiRNAs

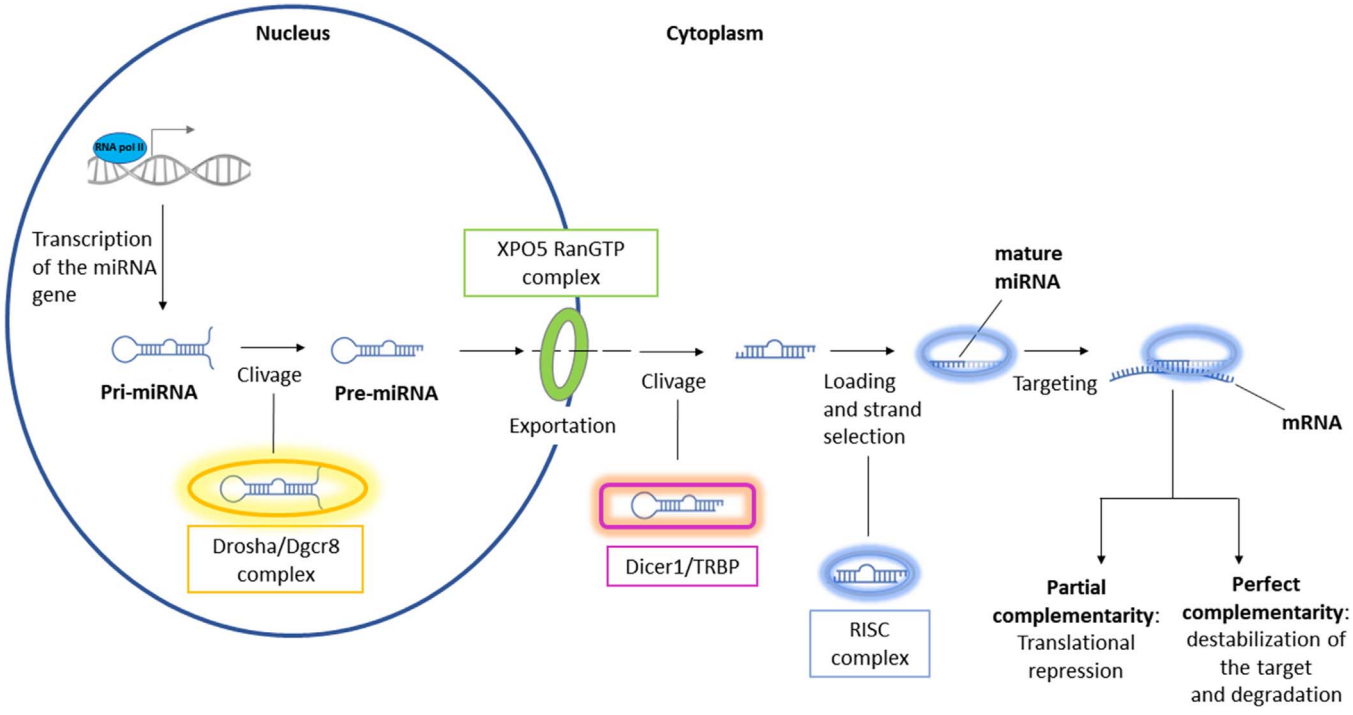

Fig. 1. Biogenesis and action of miRNAs.