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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

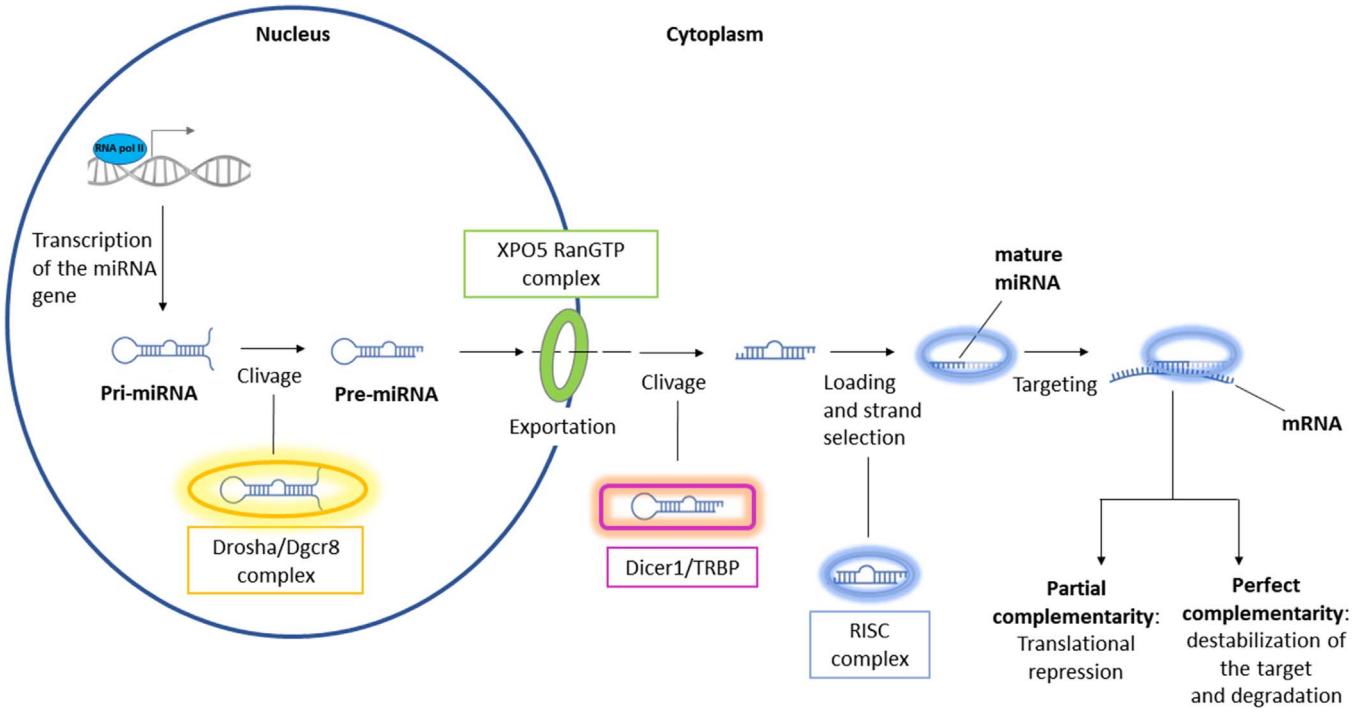

Fig. 1. Biogenesis and action of miRNAs.

are also essential in B- and T-cell development, regulation and functions [29–31]. Perturbations in the immune system are associated with insulin-resistance and growth impairment and the concomitant aberrant expression of miRNAs in these conditions could represent an interesting link among these aspects.

1.2. Longitudinal growth and insulin regulating pathways

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) are pivotal hormones for the regulation of growth in humans. GH promotes growth plate chondrogenesis and longitudinal bone growth with its stimulatory action mediated mainly by IGF-I both systemically and locally [32]. GH binds to two GH receptors (GHRs), causing a dimerization process that activates the GHR-associated Janus kinase (JAK) tyrosine kinase, and tyrosine phosphorylation of both JAK and GHR. These events activate a series of other signaling molecules, such as mitogen-activated protein kinases (MAPKs), insulin receptor substrate proteins (IRS), phosphatidylinositol-3-phosphate kinase (PI3K), diacylglycerol, protein kinase C, intracellular calcium, and Signal Transducer and Activator of Transcription (STAT) factors [33]. These signaling molecules lead to changes in enzymatic activity, transport function, and gene expression that determine final changes in growth and glucose metabolism [34,35]. IGF-I is critical for human prenatal and postnatal development and growth. Synthesis of IGF-I mainly occurs in the liver and is secreted in response to activation of the GHR by GH (GH-IGF-I axis), although some IGF-I synthesis occurs in peripheral tissues also, as bone and cartilage. Defects in this axis traditionally present with GH deficiency and/or IGF-I deficiency. Both IGF-I and IGF-II signal through the IGF-1 receptor (IGF-1R) which regulates proliferation, differentiation, and apoptosis in many cell types by a tyrosine kinase activity. Both ligands and the IGF-1R are similar to insulin and the insulin receptor [36,37]. The IGF system includes these transmembrane receptors *i.e.* IGF-1R and insulin receptor (INSR), their respective ligands, IGF-I, IGF-II and insulin (INS), and six major high affinity IGF binding proteins (IGFBP1-6) that regulate IGF bioavailability and distribution. In particular, IGF-I is stored mainly in the blood bound with IGFBP-3/5 and with a protein named acid-labile subunit (ALS) in a ternary complex, which further increases IGF-I's half-life, while it is released upon a cleavage mediated by pappalysin2 metalloproteinase (PAPP-A2) [38–40]. ALS and PAPP-A2 abnormalities should be considered as factors responsible for growth failure since they affect IGF-I bioavailability even in absence of absolute defect in IGF-I [41–43].

Insulin sensitivity in humans is dependent mainly on the binding of INS to its own transmembrane receptor. INS is a peptide hormone produced and secreted by pancreatic β-cells and it has pleiotropic actions on glucose metabolism. INS controls blood glucose concentrations inhibiting hepatic glucose release while enhancing glucose uptake into muscle and adipose tissue. INSR and IGF-1R have a tyrosine-kinase activity and their activation initiates a cascade of phosphorylation events ending into the activation of intracellular enzymes. In particular, the binding of INS and IGF-I to their own homo/hetero tetrameric receptors leads to autophosphorylation on specific tyrosine residues and, in turn, these phosphorylate downstream substrates like IRS 1–4 and Shc proteins [44]. IRS 1–4 proteins are involved in the activation of the PI3K-Akt pathway leading to phosphatidylinositol production. Shc activates Ras-MAPK which is involved mainly in cellular growth, survival and differentiation. Akt mediates most of insulin metabolic effects regulating glucose transport, adipogenesis gluconeogenesis/glycogen synthesis. Furthermore, growth factor receptor-bound protein 10 (Grb10) is an adapter protein which interacts with tyrosine-kinase receptors. It acts as partner of PI3K and mediates insulin induced- INSR degradation [45,46].

1.2.1. Effects of inflammation on growth

Poor linear growth with subsequent reduction in adult height is a frequent complication in childhood chronic inflammatory diseases. Moreover, growth failure may be worsened by delayed onset of puberty and attenuated pubertal growth spurt, which both commonly occur in these patients [47]. The underlying mechanisms for the disruption of growth are complex and comprise chronic inflammation itself, prolonged use of glucocorticoids and suboptimal nutrition and/or malabsorption [48,49]. The pathophysiology of growth impairment is secondary to both a disruption of the GH/IGF-I axis and to direct effects on the growth plate. Chronic inflammation is associated with a broad spectrum of abnormalities in the GH/IGF-I axis, including GH/IGF-I insufficiency, GH/IGF-I resistance, down regulation of GH/IGF-I receptors, disruption in downstream GH/IGF-I signaling pathways and dysregulation of IGFBPs. Proinflammatory cytokines seem to be key factors for the onset of these abnormalities. In recent years, interactions between proinflammatory cytokines and the IGF system have been described [35,50]. One of the first studies *in vivo* that confirmed that inflammation determined growth impairment used interleukin (IL)6 overexpressing transgenic mice to mimic rheumatoid arthritis, and showed that chronic inflammation was associated with low IGF-I serum levels and stunted growth [51]. IL6, to date, is known to antagonize GH actions through disruption of JAK/STAT signaling by induction of Suppressor of cytokine signaling (SOCS)-3 protein [52]. Recent evidences suggest a role for SOCS family proteins in these mechanisms as well as SOCS proteins are stimulated by proinflammatory cytokines and reduce JAK2 and STAT activation [53]. Similarly, IL1β can disrupt GH signaling through its action on STAT5 and STAT3 expression, both downstream effectors of the GHR [54]. Tumor Necrosis Factor Alpha (TNFα), IL6 and IL1β impair IGF-I intracellular transduction by a dysregulation of MAPK/Extracellular signal regulated kinase (ERK) and PI3K in chondrocytes and by inactivating other downstream intracellular mediators [55,56].

1.2.2. Effects of inflammation on insulin sensitivity

Children with inflammatory conditions may also be at risk of developing insulin-resistance as a result of the inflammatory process [57]. Immune and metabolic system integrity are pivotal for homeostasis and survival. Evidences show how metabolic and immune response pathways are strongly connected and how they have been evolutionarily conserved throughout species [58]. As a consequence, proper function of one is dependent on the other and a dysregulation in this balance may lead to chronic metabolic disorders. When an inflammatory response is activated, the coordinated regulation of metabolic pathways guarantees advantages in terms of optimization of energy resources. In these conditions, major anabolic pathways, such as insulin and IGF-I pathways, are switched off, diverting energy sources from synthetic pathways.

Potentially, every stress and inflammatory state is therefore involved in the disruption of INS action [58]. Many studies have shown that insulin-resistance is associated with chronic inflammation through the inhibition of the INSR signaling cascade [59]. In insulin resistant conditions, circulating levels of acute phase response cytokines, such as TNFα [60], IL1β [61], and IL6 [62], are increased, and tyrosine phosphorylation of IRS proteins is frequently altered both in experimental models and in humans [63]. Among the IRS modifying enzymes, c-Jun N-terminal kinase (JNK), Inhibitor of NF-kappa B kinase (IKK) and Protein Kinase C (PKC) are crucial mediators of insulin-resistance in response to stress and inflammation. In addition, proinflammatory cytokines and intracellular damage, such as endoplasmic reticulum stress, lead to an impaired INS signaling [64]. Increased activation of mammalian target of rapamycin (mTOR), a serine/threonine kinase, is also a feature of conditions characterized by insulin insensitivity. In hyperinsulinemic conditions or obesity mTOR induces serine phosphorylation of IRS-1, mediated by S6 kinase 1 resulting in a feedback inhibition of insulin signaling [65,66]. Furthermore, mTOR regulates several downstream components such as Grb10 by phosphorylation, leading to a feedback inhibition of the PI3K and ERK-MAPK pathways [67].

Table 1
Current knowledge on circulating miRNAs dysregulated in chronic inflammatory diseases.

Inflammatory disease	Studied miRNAs	Regulation	Effects	Inflammatory target	References
Cystic Fibrosis	miR-126	down	Suppresses TOM1 expression	IL1B, IL8, NFKB	[91]
	miR-155, miR-1	up	Lowers SHIP1 expression, PI3K/Akt activation	IL8	[92]
	miR-17	down	Increases expression of interleukines	IL8	[94]
	miR-145	down	Regulates SMAD3 expression	TGFB1	[95]
Inflammatory Bowel Diseases	miR-199a, miR-340, miR-362	up	unknown	unknown	[108]
	miR-505, miR149	down	unknown	unknown	
	miR-188, miR422a, miR-378, miR-500, miR-501-55, miR-769, miR-874	up	unknown	unknown	[109]
	miR-16, let-7b, miR-195, miR-106a, miR-20a, miR-30e, miR-140, miR-484, miR-93, miR-192, miR-21	unknown	unknown	unknown	[110]
	miR-127, miR-491, miR18, miR145, let7b, miR-185, miR29c, miR-19b, miR20b, miR106a, miR17, miR-222	up	unknown	unknown	[111]
	miR-135a	down	unknown	unknown	
	miR16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-191, miR-199a, miR-200c, miR-362, miR-532, miR-21, miR-28, miR-151, miR-155	up	unknown	unknown	[112]
	Let-7d, let-7e	up	Increases after anti-TNF therapy	unknown	[113]
	miR-19a, miR-21, miR-101, miR-375	unknown	unknown	unknown	[114]
	miR-146a, miR-31	up	Increases suppressing inflammatory response	unknown	
	miR-223	up	unknown	unknown	[115]
	miR-223, miR-23a, miR-302, miR-191, miR-22, miR-17, miR-30e, miR-148b, miR-320e	up	unknown	unknown	[116]
	miR-1827, miR-612, miR-188	down	unknown	unknown	
	miR-4454, miR-223, miR-23a, miR-148b, miR-320e, miR-4516	unknown	Correlates wih inflammatory status	unknown	
	miR-155	up	Increases in APC cells, is elicited by B and T cells	unknown	[117]
Juvenile Idiopathic Arthritis	miR-223	up	Correlates with ESR	unknown	[139]
	miR-132	up	unknown	unknown	
	miR-155	down	unknown	unknown	
	miR-16	up/down	Correlates with MMP3	IL6	[140]
	miR-146a	unknown	Correlates with MMP3	TNFA	
Celiac Disease	miR-449a	up	Reduces Notch-1 signaling in vitro	unknown	[155]
	miR-31, miR-192, miR-194, miR-551a, miR-551b, miR-638, miR-1290, miR-192/194 cluster	unknown	Duodenal fibroblast matrix remodeling	unknown	[156]
	miR-192-5p	down	NOD2 and CXCL2 regulation in adults	unknown	[157]
	miR-31, miR-338	down	Regulates FOXP3 and RUNX1 expression and T cells function	unknown	
	miR-21	unknown	unknown	STAT3	
Intrauterine Growth Restriction	miR-424	up	Reduces MEK1 and FGFR1 expression	unknown	[169]
	miR-194	down	unknown	unknown	[170]

2. Current knowledge on miRNAs related to inflammation in chronic diseases in childhood associated with growth impairment and insulin-resistance

Impaired linear growth is commonly encountered in children with chronic inflammatory conditions such as Cystic Fibrosis [68], Inflammatory Bowel Diseases [69], Juvenile Idiopathic Arthritis [70], Celiac disease and in Intrauterine Growth Restriction. MiRNAs reported as dysregulated in these diseases and their contribution to inflammation are listed in the following sections and are resumed in Table 1.

2.1. Cystic Fibrosis (CF)

CF is the most frequent life-threatening autosomal recessive disorder in Caucasians, caused by mutations in a gene that encodes for the Cystic Fibrosis transmembrane conductance regulator protein (CFTR), an epithelial chloride channel that is widely expressed and is involved in the homeostasis of ions and other metabolites. In Europe, the prevalence of CF is 1 in 2000–3000 newborns, whereas the incidence in the USA is estimated to be 1 in 3500 births according to the World Health Organization [71]. CF is well known to be characterized by chronic inflammation [72–76]. People affected by CF have several important endocrine abnormalities including poor linear growth and diabetes [77]. There is now sufficient evidence to suggest that poor growth in CF is already seen in the neonatal period [48]. Adolescents with CF show lower peak height velocity with pubertal delay and a later pubertal growth spurt and this growth pattern is influenced by disease severity [78,79]. The existing recent literature on growth in CF suggests that nutritional issues and pulmonary exacerbations are not sufficient to explain the growth abnormalities observed. Other factors involved in the determinism of growth failure in CF patients include chronic inflammation, chronic infection and treatment with inhaled and systemic glucocorticoid medications. The cytokine profile in CF impacts the GH/IGF-I axis as demonstrated in studies relating inflammatory cytokines to changes in the GH/IGF-I axis and IGF system [35,80]. Studies of GH secretion report that approximately 50% of these patients have blunted peak GH levels after stimulation tests and low IGF-I levels, suggesting co-existence of GH insufficiency and GH resistance [81]. According to data published by our group, CF patients have increased serum IL1β, IL6, TNFα and IGFBP2 concentrations, and low IGF-I and IGF-II, and we concluded that inflammation was an important modulator of the IGF system leading to an overall reduction in IGF bioactivity [75].

Insulin-resistance and impairment of insulin secretion are also features of CF [82] and with time develop into Cystic fibrosis related diabetes (CFRD), to date the major co-morbidity of CF [74,83]. CFRD is related to the basic genetic defect as well as to changes in INSR signal transduction and to other described mechanisms as reduced autophagy, and endoplasmic reticulum stress [84]. We described for the first time impaired insulin signal transduction in CF cells mainly due to reduction in total and activated Forkhead box O1 (FOXO1), downstream the insulin receptor [85]. FOXO1 is a transcription factor that activates gluconeogenic genes in the liver and inhibits adipogenesis, and is thought to play a key role in the development of type 2 diabetes mellitus [86]. More recently, we have shown that HMGB1, actively secreted mainly by granulocytes upon inflammatory *stimuli*, increases as a consequence of CFTR malfunctioning and is directly related to blood glucose control [87].

Significant heterogeneity exists between CF patients, suggesting potential roles for epigenetic regulation, including miRNA alterations [88]. Although many studies have focused on the role for miRNAs in regulating CFTR gene expression, little attention has been directed to other aspects, such as inflammation, glucose metabolism, and growth. Different approaches have been used to assess miRNA-mediated regulation of inflammation in CF patients.

Table 1 summarizes current knowledge on human circulating miRNAs, altered in CF, related to inflammation. Currently the first set of evidence of miRNAs dysregulation in CF was provided by a global profiling approach [89]. MiR-126 was then one of the first investigated miRNAs, and was recognized as a suppressor of the Translocase of the outer membrane 1 gene (TOM1), negative regulator of IL1β [89]. An expression screen of a miRNA library in ΔF508 CFTR and wild-type CFTR lung epithelial cell lines identified miRNAs associated with the proinflammatory phenotype in the CF lung [90]; this study evidenced up regulation of miR-155. These authors proved also that high levels of miR-155 contributed to the proinflammatory expression of IL8 by lowering Src homology-2 domain-containing inositol 5-phosphatase 1 protein (SHIP1) expression that activates the PI3K/Akt signaling pathway [90]. MiR-1 was then described as a regulator of miR-155 synthesis in CF lung epithelial cells [91]. We subsequently described miR-155 to be up-regulated in CF patients and to be dependent on both genotype and glucose tolerance state and we showed that it decreased at onset of CFRD. MiR-155 was also predicted to be an insulin sensitivity regulator as it targeted the FOXO1 gene [72]. MiR-17 was described to be decreased in CF bronchial brushings, resulting in increased expression of its proinflammatory target, IL8 [92]. Furthermore, CF patients present dysregulation of the Transforming growth factor beta 1 (TGFβ1) signaling pathway *via* SMAD which is a key element of the inflammatory pathway mediated by this cytokine. By using a candidate miRNA approach, miR-145 was found to regulate SMAD3 expression *in vitro* [93].

2.2. Inflammatory Bowel Diseases (IBDs)

IBD is a broad term that describes conditions with chronic or recurring immune response and inflammation of the gastrointestinal tract [94]. IBDs are conditions that cause severe gastrointestinal symptoms that can affect quality of life. The two most common IBDs are ulcerative colitis (UC) and Crohn's disease (CrD). Both illnesses are characterized by an abnormal response to the body's immune system. CrD potentially involves any location of the gastrointestinal tract, but it often affects the end of the small bowel and the beginning of the large bowel. UC is a chronic gastrointestinal disorder that occurs in the top layers of the colon. It is believed that IBDs result from complicated interactions between environmental factors, genetic predisposition, and immune disorders. As many as 1.4 million persons in the United States and 2.2 million persons in Europe suffer from these diseases [95]. Linear growth retardation is a frequent extraintestinal complication of IBDs in children and adolescents. Impaired linear growth is a presenting symptom in 19–31% of children with CrD and UC [96–98]. Moreover, early growth delay has been associated with permanent stunting in 17% of patients [99]. In rats with experimental colitis it was demonstrated that approximately 30–40% of linear growth impairment occurred as a direct result of the inflammatory process [100]. Stimulated and spontaneous GH secretion in children with CrD and growth failure are found to be usually normal whereas there is a reduction in plasma IGF-I concentrations, compatible with a certain degree of GH resistance [75]. The precise cytokines mediating growth failure in patients with IBDs are not known. However, studies in rats with experimental colitis suggested that IL6 and TNFα played key roles [101]. In IBDs, IGF-I and IGFBP2 levels are related to IL levels, such as IL6 and IL1β, consistent with active inflammation and changes in the IGF system, possibly relevant to the disturbance of growth [102,103].

Epidemiological studies in children have described a higher prevalence of insulin-resistance in both CrD and UC up to five times higher than that of the general population [104]. In patients with UC, intestinal inflammation leads to elevated circulating levels of insulin [105]. CrD is associated with an increase in central fat accumulation and this adipose tissue distribution is a well-known contributor to both the metabolic syndrome and insulin-resistance [106]. Defects in intestinal barrier function are characterized by an increase in intestinal permeability and contribute to intestinal inflammation. Aberrant miRNA expression in IBDs has been recently documented in peripheral blood and the possibility of utilizing these miRNAs as biomarkers and as potential therapeutic targets is at present object of discussion. Table 1 summarizes current knowledge on human circulating miRNAs, altered in IBDs, associated with inflammation. Specifically, an increased expression of miR-199a-5p, miR-340-3p, miR-362-3p, and reduced expression of miR-505-5p and miR-149-3p was described [107]. After fractionating platelets from peripheral blood miR-188-5p, miR-422a, miR-378, miR-500, miR-501-55, miR-769-5p, and miR-874 were reported to present an increased expression in UC [108]. Eleven circulating miRNAs were described to have an altered expression in pediatric CrD (miR-16, let-7b, miR-195, miR-106a, miR-20a, miR-30e, miR-140, miR-484, miR-93, miR-192, and miR-21) [109]. Thirteen serum miRNAs were reported to be expressed both in CrD and UC patients: twelve of these (miR-127-3p, miR-491-5p, miR-18a, miR-145, let-7b, miR-185, miR-29c, miR-19b, miR-20b, miR-106a, miR-17, and miR-222) were found to be elevated and one (miR-135a) to be reduced in serum compared with healthy controls [110].

A further study documented eleven miRNAs (MiR-16, miR-23a, miR-29a, miR-106a, miR-107, miR-126, miR-191, miR-199a-5p, miR-200c, miR-362-3p and miR-532-3p) to be increased in serum of CrD patients and six miRNAs (miR-16, miR-21, miR-28-5p, miR-151-5p, miR-155 and miR-199a-5p) to be increased in UC [111]. Recently, the effects of an anti-TNFα drug on miRNA expression in the serum of CrD patients was investigated and an elevated expression of let-7d and let-7e was described in patients who remitted on treatment compared with the nonresponders [112]. A further study identified a set of six miRNAs (miR-19a, miR-21, miR-31, miR-101, miR-146a, and miR-375) as candidate biomarkers to distinguish between CrD and UC [113]. MiR-223 expression has also been reported to be increased in CrD and UC and serum levels of miR-223 were correlated with several indicators of disease activity both in CrD and UC [114]. Polytarchou et al. reported a signature of 12 circulating miRNAs that differentiated patients with UC from controls: 9 miRNAs were up-regulated (miR-223a-3p, miR-23a-3p, miR-302-3p, miR-191- 5p, miR-22-3p, miR-17-5p, miR-30e-5p, miR-148b-3p, miR-320e) whereas 3 miRNAs were down-regulated (miR-1827, miR-612, miR-188-5p). Moreover, 6 miRNAs (miR-4454, miR-223-3p, miR-23a-3p, miR-148b- 3p, miR-320e and miR-4516) significantly correlated with disease activity and 4 miRNAs (miR-4454, miR-223-3p, miR-23a-3p, and miR-320e) showed higher sensitivity and specificity values than serum C-reactive protein levels in detecting the inflammatory status [115]. One of the most studied miRNAs associated with epithelial barrier and immune function in IBDs pathogenesis is

miR-155. Upon inflammatory *stimuli* as Interferon beta (IFNβ) and TLR ligands exposure, miR-155 expression is induced in antigen presenting cells. Moreover, B and T cells rapidly express miR-155 in response to the presence of antigen [116].

2.3. Juvenile Idiopathic Arthritis (JIA)

JIA is a common childhood rheumatic disease, with an incidence of 20–30/100000. JIA is defined as arthritis beginning before the age of 16 years with the highest frequency occurring in children aged 1–3 years [117]. This age distribution is evident mostly in girls with oligoarticular JIA and psoriatic arthritis. The subtypes classified under JIA (systemic arthritis, polyarthritis, oligoarthritis, enteritis-related arthritis, psoriatic arthritis and undifferentiated arthritis) have distinct features and varying spectrums of disease severity [118]. Growth impairment is a well known long term complication in patients with JIA and its likelihood increases in children with systemic or polyarticular JIA (about 30–40% of all JIA cases) [119]. Patients with JIA are affected by different types of growth abnormalities, ranging from growth delay to limb length discrepancy due to accelerated growth of metaphysis adjacent to affected joints [120,121]. Prolonged periods of active disease and long-term treatment with systemic steroids seem to be the main determinants of growth retardation. Moreover, these patients may present pubertal delay [122]. Several mechanisms may be involved in the impairment of GH/IGF-I axis: resistance to GH as a consequence of reduced GHR expression, changes in the GHR intracellular signaling (deactivation of GHR/JAK2 complex, inhibition of JAK/STAT signaling by SOCS) [123,124], and increased in IGF-I clearance [125]. In patients with newly diagnosed rheumatoid arthritis (RA), GH response to Growth hormone-releasing hormone (GHRH) was shown to be blunted compared to healthy controls [126]. Furthermore, in an experimental arthritis model, GH and liver IGF-I gene expression were reduced [127]. Inflammation in arthritis increases circulating IGFBPs (IGFBP1, IGFBP2, IGFBP3, IGFBP4) and decreases ALS in children, thus reducing IGF-I bioactivity [128,129]. Moreover, high levels of cytokines in JIA patients may cause an impairment in target cell sensitivity to GH. At the onset of the disease, GHR mRNA expression has been described to be reduced in mononuclear cells with a restoration of its expression after 2 years of combined therapies based on non-steroidal anti-inflammatory drugs [130]. The interactions among insulin-resistance, inflammation and long-term use of glucocorticoids and other treatments has been actively explored in inflammatory arthropathies in adults, with the evidence of an extremely complex situation [131], while data in children are lacking. According to a recent study, prevalence of undiagnosed diabetes in adult patients with rheumatoid arthritis is increasing especially in patients with longer disease duration [132]. Conversely, data on prevalence of insulin-resistance in patients with JIA are very scarce [133]. JIA patients are at high risk of insulin-resistance and glucose metabolism abnormalities, because both inflammation and glucocorticoid therapy markedly affect insulin sensitivity [134,135]. Body composition could also be involved, as the prevalence of obesity in JIA children is reported around 22% [136]; this condition is a well-recognized risk factor for insulin-resistance and type 2 diabetes mellitus.

The mechanistic link between pathogenesis of JIA and acquisition of the proinflammatory phenotype in the JIA patients is currently unknown, although it is thought to be due to a combination of environmental triggers (including epigenetics) and specific immunogenic factors [137].

Table 1 summarizes current knowledge on human circulating miRNAs, altered in JIA, associated with inflammation. Serum levels of miR-223 were described to be significantly higher in patients in the active phase of systemic onset JIA than in controls, whereas peripheral blood leukocytes miRNA levels did not show any difference in JIA subjects compared with healthy individuals. Moreover, miR-223 and miR-16 positively correlated in both systemic onset JIA and polyarthritis with erythrocyte sedimentation rate and Matrix metalloproteinase 3 (MMP3), commonly used laboratory indicators of disease activity. MiR-146a also positively correlated with matrix MMP3 in polyarthritis. MiR-132 was significantly higher in patients with systemic onset JIA compared with patients with polyarthritis in the inactive phase; whereas miR-155 was lower in patients with polyarthritis without typical symptoms compared with patients with systemic onset JIA with symptoms [138]. Additionally, plasma miR-16 was up-regulated in polyarticular JIA compared to oligoarticular JIA and correlated with circulating IL6 levels. MiR-146a concentrations showed a positive correlation with the JIA Disease Activity Scores in 27 joints, swollen joint count, limited joint count, and hip magnetic resonance imaging scores, whereas it correlated negatively with TNFα serum concentrations [139].

2.4. Celiac disease (CD)

CD is defined as an immune-mediated enteropathy, with characteristic changes in the intestinal histology. It is characterized by a chronic inflammatory state secondary to a permanent sensitivity to gluten, and it occurs in genetically susceptible individuals. Screening for CD in the general population shows a prevalence of 1:300–1:100. About 50% of these children are completely symptomless [140]. CD may present with typical gastrointestinal symptoms (abdominal bloating, chronic diarrhea, constipation, gas, pale, foul-smelling, or fatty stool, stomach pain, nausea, vomiting) associated with growth impairment and delayed puberty, as well as in an atypical fashion. In atypical forms growth failure can be present in 30% of cases [141]. Generally, complete catch-up growth is reported within 2–3 years of starting treatment on a gluten-free diet [142]. In a population based retrospective study from Saari et al. the authors showed how most children with CD developed growth failure prior to the diagnosis and, on average, children with CD were shorter than the healthy reference population [143]. In children with short stature and no gastrointestinal symptoms, the prevalence of growth failure was reported to be 2–8%, and when endocrine causes for short stature were excluded, the prevalence rose up to 59% [144]. The mechanisms underlying impaired linear growth in children with CD are not yet completely clear. Nutritional deficiencies seem to play a major role, although changes in the GH/IGF-I axis and inflammatory cytokines are also involved [145]. Protein and calorie malnutrition are known regulators of the IGF system and deficiency of each reduce IGF-I and IGFBP3 and increase IGFBP2; moreover, IGFBP1 is inversely related to glucose and insulin concentrations [146]. CD may be characterized by GH resistance, as suggested by normal or elevated GH levels and low IGF-I levels [147]. However, during the acute phase of the disease, GH secretion may be blunted, and IGF-I levels are usually decreased during this phase with normalization of these changes after an appropriate gluten-free diet in the majority of patients [148]. Moreover, low IGFBP3 and high IGFBP1 and IGFBP2 have been described at diagnosis of CD and have been reported to change and normalize on gluten-free diet [149]. More recently, our group showed, at diagnosis, lower levels of IGF-I, IGF-II and IGFBP3, and increased IGFBP2, IL6 and TNFα compared with controls. All peptides normalized on gluten-free diet [150].

Data regarding insulin sensitivity in CD patients are quite scarce. According to some authors, the prevalence of insulin-resistance in CD children on a gluten-free diet is 3.5% [151]. More recently, another study reported significantly higher values of insulin and insulin-resistance in CD young adults compared to healthy controls [152]. Despite the growing number of studies concerning the role of miRNAs in autoimmune diseases, data in CD are scarce. In the intestinal mucosa using a high-throughput sequencing approach, miRNA abundance was found to vary considerably. Of the 453 miRNA families identified, miR-192 was the most highly expressed in both the small and large intestinal mucosa. In Dicer1 (an endoribonuclease enzyme involved in the miRNA biosynthesis)-deficient mice, several histopathological abnormalities in

the intestinal epithelium such as a decrease in goblet cells, a huge increase in apoptosis in crypts of both jejunum and colon, and enhanced jejunal cell migration have been described. Moreover, the function of the intestinal barrier was altered resulting in bowel inflammation with infiltration of lymphocytes and neutrophils; the authors concluded that Dicer protein possesses a vital role in the differentiation and function of the intestinal epithelium [153].

Differences in the clinical features and manifestations of CD both in children and adults, could be due to age-related variations in intestinal architecture and inflammatory response potentially secondary to changes in miRNA regulated gene expression.

Table 1 summarizes current knowledge on human circulating miRNAs, altered in CD, associated with inflammation. Using TaqMan low-density arrays, about 20% of miRNAs in small intestinal tissues was found differentially expressed between CD and control children. High miR-449a levels were found to target and reduce the Notch1 pathway *in vitro*. The Notch1 signaling pathway plays a pivotal role in intestinal morphogenesis and homeostasis and controls intestinal development. This could be constitutively altered in the celiac small intestine and could drive the increased proliferation and the decreased differentiation of intestinal cells towards the secretory goblet cell lineage [154]. A more recent report analyzed the expression of miRNA in duodenal mucosa in a group of untreated adult celiac patients (with classic or atypical presentation), a group of treated patients (with or without remission of mucosal damage) and control subjects without CD. Dysregulation of seven miRNAs (miR-31-5p, miR-192-3p, miR-194-5p, miR-551a, miR-551b-5p, miR-638 and miR-1290) was observed in CD patients with respect to controls. These miRNAs were subsequently studied in duodenal fibroblasts from CD patients and incubated with gliadin peptides (13- and 33-mer) showing that these latter were regulators of matrix remodeling. MiRNA cluster miR-192/194, involved in matrix remodeling, was altered in CD and related to clinical manifestations [155]. A panel of miRNAs and their target genes was analyzed in duodenal biopsies of pediatric CD patients [156]: circulating miR-192-5p expression was described to be reduced in the patients, but no variations were found in Nucleotide-binding oligomerization domain containing 2 (NOD2) and Chemokine (C-X-C motif) ligand 2 (CXCL2), both previously identified targets of this miRNA in adults. However, NOD2 plays an important role in immune response at the mucosal level, activating the Nuclear Factor Kappa B (NFKB) pathway, and CXCL2 is a chemokine produced by epithelial intestinal cells after activation of TLR. MiR-31-5p and miR-338-3p were down-regulated and their respective gene targets, forkhead box P3 (FOXP3) and Runt-related transcription factor 1 (RUNX1), involved in regulatory T cells function, resulted up-regulated. Finally, an increased expression in miR-21-5p was detected in CD patients with its putative target STAT3. The analysis in plasma showed similar findings in biopsies, and on gluten-free diet circulating miRNAs values were similar to controls [156].

2.5. Intrauterine Growth Restriction (IUGR)

IUGR is defined as the failure of a fetus to attain its expected fetal growth at any gestational age. It is one of the most important causes of perinatal mortality and morbidity and affects approximately 7–15% of worldwide pregnancies. The prevalence is estimated to be approximately 8% in the general population [157]. The incidence of IUGR varies among countries, populations, races and increases with decreasing gestational age: 14 to 20 million infants are affected annually in developing countries. A large number of IUGR infants are seen in the Asian continent also, followed by the African and Latin American continents [158]. During prenatal life, fetal growth is driven mainly by nutritional factors. In addition to insulin, IGF-I and IGF-II play a role, in an autocrine and paracrine manner, to assure an adequate local nutritional delivery and to induce tissue and organ growth and differentiation. Defects in insulin secretion or action, or defects in IGF-I secretion and signaling lead to impaired fetal growth [159–161]. In developed countries, most of IUGR subjects present complete or partial catch up growth during the first 2 years of life. However, approximately 13% of these subjects fail to present a catch-up growth and remain short after 2 years of life [162]. The IGF system plays a critical role in placental development and function. IGF signaling plays a critical role in trophoblast invasion and increased utero-placental blood flow during implantation, while imbalances or abnormalities in this signaling lead to adverse pregnancy outcomes and have been associated with IUGR [163]. The IGF system interacts with proinflammatory cytokines in IUGR models and these relationships seem to be cell- and tissue-specific and occur within the placenta also. Previous data from our group showed higher placental content in IGF-II, IGFBP1, IGFBP2, and IL6 in IUGR newborns compared with controls [164]. The increased IL6 concentrations proved for the first time that IUGR shared features with conditions characterized by chronic inflammation. An unfavorable *in utero* environment determines adaptive functional and structural modifications in skeletal muscle, such as fiber type distribution, oxygen consumption and oxidative capacity. These changes may induce a derangement in the insulin-signaling pathway which is critical for insulin-resistance [165]. Indeed, subjects born with IUGR have been reported to present an increased incidence of cardiovascular disease, hypertension and type 2 diabetes mellitus later in life compared with the general population. These features are shared with obese subjects, and derive primarily from increased insulin-resistance. At a molecular level, IL6 and other proinflammatory cytokines such as TNFα are responsible for molecular mechanisms of insulin-resistance. In particular IL6 inhibits Akt, blocking downstream insulin signaling as observed in IUGR newborns [166]. We previously showed that activated INSR content in placenta was increased in IUGR newborns [167], but was associated with impaired signal transduction downstream the receptor and increased IL6 placental content. The IL6 lysate concentrations correlated negatively with Akt content [166]. One of the mechanisms leading to inflammation, altered IGF bioactivity and insulin-resistance in placenta and in IUGR subjects may be through the aberrant expression of miRNAs. Data regarding miRNAs related to the regulation of inflammation in fetus are limited. Few studies have reported on miRNAs in IUGR.

Table 1 summarizes current knowledge on human circulating miRNAs, altered in IUGR, associated with inflammation. MiR-424, a hypoxia-regulated miRNA, and its target genes, Mitogen-activated protein kinase 1 (MEK1) and Fibroblast growth factor receptor 1 (FGFR1) were examined in placental tissue [168]; miR-424 levels were significantly increased in placenta from women with IUGR, suggesting a potential regulatory role for miR-424 in IUGR [168]. An implemented cluster algorithm for the identification of molecular signatures allowed the identification of down-regulation of miR-194 in IUGR which is believed to be involved in placental metabolism as its putative target Nuclear factor of activated T cells (NFAT5) was previously reported to regulate placental osmolytes inositol and sorbitol in IUGR animal models [169,170].

3. Linking microRNAs involved in inflammation to the regulation of the GH-, IGF- and insulin-receptor interactomes

Circulating miRNAs associated with the inflammatory components of the selected pediatric chronic inflammatory diseases (Table 1) were analyzed *in silico* to screen the possible targets and their interactions within the GHR, IGF-1R and INSR interactomes. In detail, validated and predicted miRNA target genes were extracted from the Target Scan and DIANA-TarBase databases [171]. TargetScan predicts biological targets of miRNAs by searching for the presence of conserved 8mer, 7mer, and 6mer sites that match the seed region of each miRNA. DIANA-TarBase is the largest available manually curated target database which catalogues published experimentally validated miRNA:gene interactions and reveals the regulatory effect of the single miRNA on a validated target gene [172]. Genes involved within the GHR, IGF-IR and INSR

Table 2
MiRNAs related with inflammation in Cystic Fibrosis targeting genes within the GHR, IGF-1R (**A**) and INSR (**B**) interactomes. *(The STRING analysis has been extended up to 50 interactors).*
Sources: TargetScan, TarBase v7.0 (↓ = down regulation; ↑ = up regulation;? = unknown).

A

miRNAs	Validated	Predicted
	GHR interactome target genes	
miR-126-3p (↓)	PIK3CA (↓)	
miR-155-5p (↑)	STAT3 (↓); PIK3R1 (?)	
miR-17-5p (↓)	JAK1 (↓); PIK3R1 (↓); PIK3CA (?); STAT3 (↓)	
miR-145-5p (↓)	STAT3 (?); IRS1 (↓/↑); IRS2 (↓)	
	IGF-1R interactome target genes	
miR-126-3p (↓)	PIK3CA (↓)	IRS1
miR-155-5p (↑)	IRS2 (↓); PIK3R1 (?)	
miR-17-5p (↓)	PTPN11 (↓); IGF1R (↓); IGFBP5 (?); PIK3R3 (↓); PIK3R1 (↓); PIK3CA (?)	
miR-145-5p (↓)	IGF1R (↓); IRS1 (↓/↑); IRS2 (↓)	GRB10

B

miRNAs	Validated	Predicted
	INSR interactome target genes	
miR-126-3p (↓)	PIK3CA (↓); AKT1 (↓)	IRS1; AKT2
miR-155-5p (↑)	IRS2 (↓); PIK3R1 (?)	
miR-17-5p (↓)	PTPN11 (↓); PIK3R1 (↓); PIK3CA (?); AKT1(↓)	
miR-145-5p (↓)	IRS1 (↓/↑); IRS2 (↓); AKT1(?); PTPN11 (?)	GRB10

interactomes were selected from the target gene list of miRNAs described to date and involved in each chronic inflammatory disease. Target genes described as involved in other biological processes or molecular functions were excluded. In order to carry out this selection, the GHR, IGF-1R and INSR were chosen as query proteins and their associated interactomes were displayed using the STRING tool. STRING is a database of known and predicted protein-protein interactions, including direct (physical) and indirect (functional) associations [173]. The search was carried out extending the analysis to 50 interactors for each receptor.

3.1. Inflammatory microRNAs targeting genes belonging to the GHR and IGF-1R interactomes and their role in growth impairment

Our analysis reported that a subgroup of miRNAs, dysregulated in inflammation in the selected pediatric diseases, targeted genes codifying proteins belonging to GHR and IGF-1R interactomes. Their regulatory effect on the largest part of genes has been experimentally validated while, in some cases it was predicted by an *in silico* analysis only. Indeed, most of the selected target genes are reported in the Literature as pivotal mediators of growth. The single tables (Tables 2A–6A) report the miRNAs known to be altered in each considered disease in relationship to inflammation and their predicted and validated target genes within the GHR and IGF-1R interactomes.

MiR-126-3p (Tables 2A and 3A), miR-17-5p (Tables 2A and 3A), miR-16-1-3p (Tables 3A and 4A) and miR-132-5p (Table 4A) are PI3K Catalytic Subunit Alpha (PIK3CA) regulators which postzygotic gain of function mutations have been described in a group of patients with overgrowth affected by Megalencephaly-capillary malformation and megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndromes [174]. Moreover, Sanger sequencing of PIK3CA exons identified a mutation in PIK3CA present in affected nerve tissue from patients with Macrodactyly consisting in the enlargement of all tissues localized to the terminal portions of a limb [175]. These findings suggest that changes in PIK3CA do affect growth.

MiR-155-5p (Tables 2A4A), miR-17-5p (Tables 2A and 3A) and miR-145-5p (Tables 2A and 3A) miR-223-3p (Tables 3A and 4A), miR-21-3p (Tables 3A and 5A), miR-424-3p (Table 6A) target the STAT3 gene. Gain-of-function mutations in this gene cause growth impairment by exerting their effect on the downstream activation of STAT5 resulting in partial GH insensitivity. Moreover, a reduction in phosphorylated nuclear STAT3 levels with subsequent STAT3 signal transduction alteration, has been reported in patients with Idiopathic Short Stature [176,177]. Furthermore, a repressor of STAT3 expression, Trps1, is capable of promoting the survival and proliferation of growth plate chondrocytes which have a key role in endochondral ossification during longitudinal bone growth [178]. Thus, downregulation of STAT3 by miRNAs could produce similar effects. MiR-155-5p (Tables 2A4A) and miR-17-5p (Tables 2A and 3A) regulate the Phosphoinositide-3-Kinase Regulatory Subunit 1 (PIK3R1) gene which autosomal dominant mutations are reported to be the cause of SHORT syndrome which is a rare, multisystem disease characterized by short stature [179]. Furthermore, a heterozygous missense alteration in PIK3R1 was shown in a patient with short stature associated with multiple endocrinopathies by whole exome sequencing. In this same patient a missense mutation in PIK3CD, catalytic subunit delta of PI3K, was also found (Tables 3A and 4A) [180]. Dysregulation in PIK3R1 gene expression is therefore related with altered growth. MiR-17-5p (Tables 2A and 3A) and miR-424-3p (Table 6A) regulate the expression of JAK1. Autosomal-dominant gain of function mutations in this gene are associated with failure to thrive and short stature in adulthood [181].

MiR-145-5p (Tables 2A and 3A), miR-126-3p (Tables 2A and 3A), miR-16-1-3p (Tables 3A and 4A), miR-145-5p (Table 3A), miR-551b-5p (Tables 3A and 5A) and miR-1290 (Table 5A) target IRS1. Spontaneous mutations in this gene are associated in mice with abnormalities in bone formation, raising the possibility that in humans down regulation of this gene might contribute to short stature [182].

MiR-145-5p (Tables 2A and 3A), miR-155-5p (Tables 2A and 3A), miR-551b-5p (Tables 4A and 5A), miR-1290 (Table 5A) and miR-424-3p (Table 6A) regulate IRS2 expression. IRS2 was described to be highly expressed in cord serum in small for gestational age (SGA) newborns, especially in those with hypoglycemia, compared with adequate for gestational age (AGA) newborns showing an association between intrauterine growth restriction, glucose metabolism and IRS2 [183].

MiR-17-5p (Tables 2A and 3A) and miR-449-5p (Table 5A) target the Protein Tyrosine Phosphatase, Non-receptor Type 11 (PTPN11) gene. This gene encodes Shp2, a cytoplasmic protein-tyrosine phosphatase which is a negative regulator of tyrosine-kinase cascade post-

Table 3
MiRNAs related with inflammation in Inflammatory Bowel Diseases targeting genes within the GHR, IGF-1R (**A**) and INSR (**B**) interactomes. *(The STRING analysis has been extended up to 50 interactors).*
Sources: TargetScan, TarBase v7.0 (↓ = down regulation; ↑ = up regulation;? = unknown).

A

miRNAs	Validated	Predicted
	GHR interactome target genes	
miR-126-3p (↑)	PIK3CA (↓)	
miR-155-5p (↑)	STAT3 (↓); PIK3R1 (?)	
miR-17-5p (↑)	JAK1 (↓); PIK3R1 (↓); PIK3CA (?); STAT3 (↓)	
miR-145-5p (↑)	STAT3 (?); IRS1 (↓/↑); IRS2 (↓)	
miR-146a-5p (↑)	STAT5B (↓)	
miR-223-3p (↑)	STAT3 (↓)	
miR-16-1-3p (↑)	PIK3CA (↓); STAT5B (↓)	IGF1; IRS1; JAK2
miR-21-3p (↑)	STAT3 (↓)	
	IGF-1R interactome target genes	
miR-126-3p (↑)	PIK3CA (↓)	IRS1
miR-155-5p (↑)	IRS2 (↓); PIK3R1 (?)	
miR-17-5p (↑)	PTPN11 (↓); IGF1R (↓); IGFBP5 (?); PIK3R3 (↓); PIK3R1 (↓); PIK3CA (?)	
miR-145-5p (↑)	IGF1R (↓); IRS1 (↓/↑); IRS2 (↓)	GRB10
miR-223-3p (↑)	IGF1R (?); PIK3CD (↓)	
miR-16-1-3p (↑)	PIK3CA (↓); IGF1R (↓)	IGFBP1; IGF1; IRS1; IRS4
miR-31-5p (↑)		IRS4
miR-192-5p (?)	IRS4 (↓); IGF1R (↓)	
miR-21-3p (↑)	PIK3R3 (↓); IGFBP4 (↓)	

B

miRNAs	Validated	Predicted
	INSR interactome target genes	
miR-126-3p (↑)	PIK3CA (↓); AKT1 (↓)	IRS1; AKT2
miR-155-5p (↑)	IRS2 (↓); PIK3R1 (?)	
miR-17-5p (↑)	PTPN11 (↓); PIK3R1 (↓); PIK3CA (?); AKT1 (↓)	
miR-145-5p (↑)	IRS1 (↓/↑); IRS2 (↓); AKT1(?); PTPN11 (?)	GRB10
miR-146a-5p (↑)	AKT2 (↓)	
miR-16-1-3p (↑)	PIK3CA (↓)	IGF1; IRS1; IRS4
miR-31-5p (↑)		IRS4
miR-192-5p (?)	IRS4 (↓)	

receptor signaling and is described to be altered in Noonan Syndrome, characterized by facial dysmorphism, short stature, cardiac defects, and skeletal malformations [184]. Mutations in Noonan syndrome cause mild GH resistance by a post-receptor signaling defect which contributes to the short stature phenotype in these children and their poor response to GH therapy [184]. PTPN11 is also reported to participate in

Table 4
MiRNAs related with inflammation in Juvenile Idiopathic Arthritis targeting genes belonging to the GHR, IGF-1R (**A**) and INSR (**B**) interactomes. *(The STRING analysis has been extended up to 50 interactors).*
Sources: TargetScan, TarBase v7.0 (↓ = down regulation; ↑ = up regulation;? = unknown).

A

miRNAs	Validated	Predicted
	GHR interactome target genes	
miR-155-5p (↓)	STAT3 (↓); PIK3R1 (?)	
miR-146a-5p (?)	STAT5B (↓)	
miR-223-3p (↑)	STAT3 (↓)	
miR-16-1-3p (↑/↓)	PIK3CA (↓); STAT5B (↓)	IGF1; IRS1; JAK2
miR-132-5p (↑)		PIK3CA; GHR
	IGF-1R interactome target genes	
miR-223-3p (↑)	IGF1R (?); PIK3CD (↓)	
miR-16-1-3p (↑/↓)	PIK3CA (↓); IGF1R (↓)	IGFBP1; IGF1; IRS1; IRS4
miR-132-5p (↑)	IRS4 (↓)	PIK3CA; GHR

B

miRNAs	Validated	Predicted
	INSR interactome target genes	
miR-146a-5p (?)	AKT2 (↓)	
miR-16-1-3p (↑/↓)	PIK3CA (↓)	IGF1; IRS1; IRS4
miR-132-5p (↑)	IRS4 (↓)	PIK3CA

Table 5
MiRNAs related with inflammation in Celiac Disease targeting genes within the GHR, IGF-1R (**A**) and INSR (**B**) interactomes. *(The STRING analysis has been extended up to 50 interactors).*
Sources: TargetScan, TarBase v7.0 (↓ = down regulation; ↑ = up regulation;? = unknown).

A

miRNAs	Validated	Predicted
	GHR interactome target genes	
miR-194-5p (?)		STAT5B
miR-551b-5p (?)		IGF1; IRS1; IRS2; JAK2; STAT5B
miR-638 (?)		GHR
miR-1290 (?)		IGF1; GHR; IRS1; IRS2
miR-338-3p (↓)		IGF1
miR-21-3p (?)	STAT3 (↓)	
	IGF-1R interactome target genes	
miR-449-5p (↑)	PTPN11 (↓)	IGFBP3
miR-31-5p (↓)		IRS4
miR-192-5p (↓)	IRS4 (↓); IGF1R (↓)	
miR-194-5p (?)	IGF1R (↓); IGFBP5 (↓)	
miR-551b-5p (?)		IGF1; IGFBP4; IRS1; IRS2; IRS4
miR-638 (?)		IGFBP4; GHR
miR-1290 (?)		IGF2; IGF1R; IGF1; GHR; IRS2; IRS1
miR-338-3p (↓)	IGF1R (↓)	IGF1
miR-21-3p (?)	PIK3R3 (↓); IGFBP4 (↓)	

B

miRNAs	Validated	Predicted
	INSR interactome target genes	
miR-449-5p (↑)	PTPN11 (↓); AKT1(↓); AKT2 (↓)	
miR-31-5p (↓)		IRS4
miR-192-5p (↓)	IRS4 (↓)	
miR-194-5p (?)		AKT2
miR-551b-5p (?)		IGF1; IRS1; IRS2; IRS4
miR-638 (?)		INSR
miR-1290 (?)	AKT2 (↓)	IGF1; IRS2; INSR; IRS1
miR-338-3p (↓)		IGF1

the transition of chondrocytes to osteoblastocytes during endochondral bone formation [185] and specific mutations have been associated with a decrease in IGF-I, IGFBP-3 and ALS levels often reported in children harboring these mutations [186].

MiR-17-5p (Tables 2A and 3A), miR-145-5p (Tables 2A and 3A), miR-223-3p (Tables 3A and 4A), miR-16-1-3p (Tables 3A and 4A), miR-192-5p (Tables 3A and 5A), miR-194-5p (Tables 5A and 6A), miR-1290 (Table 5A) and miR-338-3p (Table 5A) are IGF-1R gene regulators. Mutations in the IGF-1R gene have been well documented to be associated with IUGR and severe postnatal growth failure leading to short stature [187–191].

MiR-145-5p (Tables 2A and 3A) is predicted to target the GRB10 gene which has a suppressive effect on growth, interacting with either the IGF-1R or the GHR. Mutations in GRB10 have been described in Silver-Russell syndrome, which is characterized by pre- and post-natal growth impairment, dysmorphisms and other bone malformations [192–198].

MiR-146a-5p (Tables 3A and 4A), miR-16-1-3p (Tables 3A and 4A)

Table 6
MiRNAs related with inflammation in Intrauterine Growth Restriction targeting genes within the GHR, IGF-1R (**A**) and INSR (**B**) interactomes. *(The STRING analysis has been extended up to 50 interactors).*
Sources: TargetScan, TarBase v7.0 (↓ = down regulation; ↑ = up regulation;? = unknown).

A

miRNAs	Validated	Predicted
	GH interactome target genes	
miR-194-5p (↓)		STAT5B
miR-424-3p (↑)	JAK1 (↓); STAT3 (↓); IRS2 (↓)	
	IGF-1R interactome target genes	
miR-194-5p (↓)	IGF1R (↓); IGFBP5 (↓)	
miR-424-3p (↑)	IRS4 (↓); IGFBP7 (↓); IGFBP5 (↓); IGFBP4 (↓); IGFBP3 (↓); IRS2 (↓); IGF2 (↓)	

B

miRNAs	Validated	Predicted
	INSR interactome target genes	
miR-194-5p (↓)		AKT2
miR-424-3p (↑)	INSR (↓); IRS4 (↓); IRS2 (↓)	AKT1

and miR-194-5p (Tables 5A and 6A) are regulators of STAT5B. STAT5B deletions or mutations are associated with reduced postnatal growth, GH resistance, and reduced IGF-I synthesis as reported in human and showed in mice models [199]. Moreover, in humans, several homozygous and heterozygous STAT5B mutations with an inactivating or a dominant negative effect have been described in patients with a severe grade of growth deficiency, markedly reduced IGF-I expression and immune disorders [200–203].

MiR-16-1-3p (Tables 3A and 4A), miR-551b-5p (Tables 3A and 5A), miR-1290 (Table 5A) and miR-338-3p (Table 5A) target the IGF-I gene which deletions or mutations cause severe intrauterine and postnatal growth retardation and are related to fetal growth in a dose-related manner, independent of GH [160,204].

MiR-17-5p (Tables 2A and 3A), miR-21-3p (Tables 3A and 5A), miR-16-1-3p (Tables 3A and 4A), miR-551b-5p (Tables 3A and 5A), miR-194-5p (Tables 5A and 6A), miR-449-5p (Table 5A), miR-638 (Table 5A) and miR-424-3p (Table 6A) are regulators of IGFBPs which have been well documented to exercise an important role in the regulation of longitudinal growth in humans. At the molecular level, alterations in IGFBPs can result in: decreased IGF-I bioactivity subsequent to inhibiting formation of the circulating ternary complex favoring clearance of IGF peptides reducing feedback action on GH secretion [205–210].

Increased IGFBP-1 has been described in the pathogenesis of growth failure in Turner syndrome as it reduces IGF-I action [211]. In humans there is a description of a boy with extreme short stature associated with increased IGFBP-1 values that were considered the cause of his growth impairment [212].

Increased IGFBP-2 associated with decreased IGFBP-3 and IGF-I has been described in children with inadequate GH secretion [213]; moreover IGFBP-2 is typically increased in IBD and CF in childhood and is associated with impaired growth [[75,80,102]75,80,102]. No mutation or deletion of IGFBP-3, IGFBP-4 and IGFBP-5 has been described to date in humans associated with short stature. However, IGFBP-4 and IGFBP-5 are known to be involved with osteoblast function and bone formation and, thus, could influence longitudinal growth [214]. All IGFBPs are reported to be higher in the placenta from SGA newbors; this has been shown to be dependent on changes in cytosine-phosphate-guanine (CpG) dinucleotide methylation [215]; however, changes in miRNAs regulating these binding proteins have not been reported yet. Interestingly, both IGFBP-1 and IGFBP-2 are closely linked to glucose metabolism and insulin sensitivity [216,217].

MiR-1290 (Table 5A) and miR-424-3p (Table 6A) target IGF-II which expression is reduced in Silver- Russel Syndrome and 3-M syndrome, both genetic disorders which share severe short-stature as a feature [218]. Furthermore, to date a heterozygous mutation in the IGF-II gene has been described in members of a same family, all born SGA with post-natal growth impairment [219].

MiR-132-5p (Table 4A), miR-638 (Table 5A) and miR-1290 (Table 5A) target the GHR gene which inactivating mutations cause Laron dwarfism characterized by complete insensitivity to GH and very low IGF-I levels. Over the years many mutations and deletions in this gene have been reported all associated with different degrees of short stature [220,221]. A heterozygous mutation has been also found in idiopathic short-stature associated with scarce levels of GH binding protein and to a scarce response to GH therapy [222].

3.2. Inflammatory microRNAs targeting genes belonging to the INSR interactome and their role in insulin-resistance

Our analysis reported that a subgroup of miRNAs, dysregulated in inflammation in the selected pediatric diseases, targeted genes codifying proteins belonging to INSR interactome. The dysregulation of the reported inflammatory miRNAs can contribute to insulin-resistance. Indeed, most of these target genes are reported in the Literature as mediators of insulin signaling. The results are shown separately based on single disease entities considered and subsequently subgrouped based on the single components of the INSR interactome (Tables 2B–6B).

MiR-155-5p (Tables 2B and 3B) and miR-17-5p (Tables 2B and 3B) target PIK3R1 gene which mutations were reported in patients affected by SHORT syndrome who develop a severe insulin- resistance, highlighting a causal link between the detected mutations and Syndromic Insulin- Resistance [223–226].

MiR-126-3p (Tables 2B and 3B), miR-17-5p (Tables 2B and 3B) miR-145-5p (Tables 2B and 3B) miR-449-5p (Table 5B) and miR-424-3p (Table 6B) regulate AKT1 gene. Akt1 gene inhibition in mice leads to hyperglycemia owe to insulin insensitivity [227].

MiR-126-3p (Tables 2B and 3B), miR-146-5p (Tables 2B and 4B), miR-449-5p (Table 5B), miR-194-5p (Tables 5B and 6B) and miR-1290 (Table 5B) target the AKT2 gene which alterations cause severe insulin-resistance and diabetes along with metabolic dyslipidemia and lipoatrophy [228,229]. Furthermore, Akt2 knockout mice show extreme insulin-resistance followed by the onset of diabetes [230].

MiR-126-3p (Tables 2B and 3B), miR-145-5p (Tables 2B and 3B), miR-16-1-3p (Tables 3B and 4B), miR-551b-5p (Table 5B) and miR-1290 (Table 5B) regulate the IRS-1 gene Changes in IRS-1 phosphorylation inhibit its interaction with the INSR, interfering with the insulin signaling pathway leading to insulin-resistance [231]. A polymorphism in the human IRS-1 gene has been described to be associated with both insulin-resistance and insulin secretory defects [232]. MiR-155-5p (Tables 2B and 3B), miR-145-5p (Tables 2B and 3B), miR-551b-5p (Table 5B), miR-1290 (Table 5B) and miR-424-3p (Table 6B) target the IRS-2 gene. Interestingly, in IRS-2 knock-out mice hepatocytes insulin is unable to inhibit gluconeogenic gene expression while after restoring IRS-2 function *via* an adenoviral vector, the insulin signaling is reconstituted evidencing the importance of this mediator in normal insulin signaling [233].

MiR-17-5p (Tables 2B and 3B), miR-145-5p (Tables 2B and 3B) and miR-449-5p (Table 5B) regulate PTPN11 which deletion in a mouse model induces insulin-resistance in muscle tissue [234].

MiR-638 (Table 5B), miR-1290 (Table 5B) and miR-424-3p (Table 6B) target the INSR gene for which more than a hundred mutations have been described in humans up to date [235]. The vast majority of causative variations are missense and nonsense mutations which produce different phenotypes with a clinical spectrum ranging from the insulin-resistant syndromes as Leprechaunism and Rabson–Mendenhall syndrome to type A insulin-resistance [236–238].

4. Conclusions and future challenges

Growth impairment and insulin-resistance in children with chronic inflammation have a multifactorial origin, although it is now clear that they share also common mechanisms. Some clinical and laboratory studies over the last decades have started focusing attention on the identification and characterization of miRNAs involved in the regulation of inflammation and insulin signaling. In this review we have reported that miRNAs, which dysregulation is driven by chronic inflammation, have the potential to influence the GHR, IGF-1R and INSR interactomes. In detail, we have screened the miRNAs described to date to show changes in chronic inflammatory diseases in childhood. We found that most of these miRNAs were regulators of genes involved in growth and insulin-sensitivity. Thus, this review provides insight into a novel further explanation for a common epigenetic mechanism linking inflammation to growth and insulin- sensitivity. Fig. 2 summarizes the miRNAs overall identified and the genes targeted within the GHR and IGF-1R signaling cascades. Based on the knowledge available in the individual conditions it is clear that further research is warrented. The miRNA system which represents a shared pathophysiological mechanism in selected groups of diseases, could in addition effectively represent a promising diagnostic tool and represent a new direction for treatment strategies. Indeed, the regulation of miRNAs may be useful

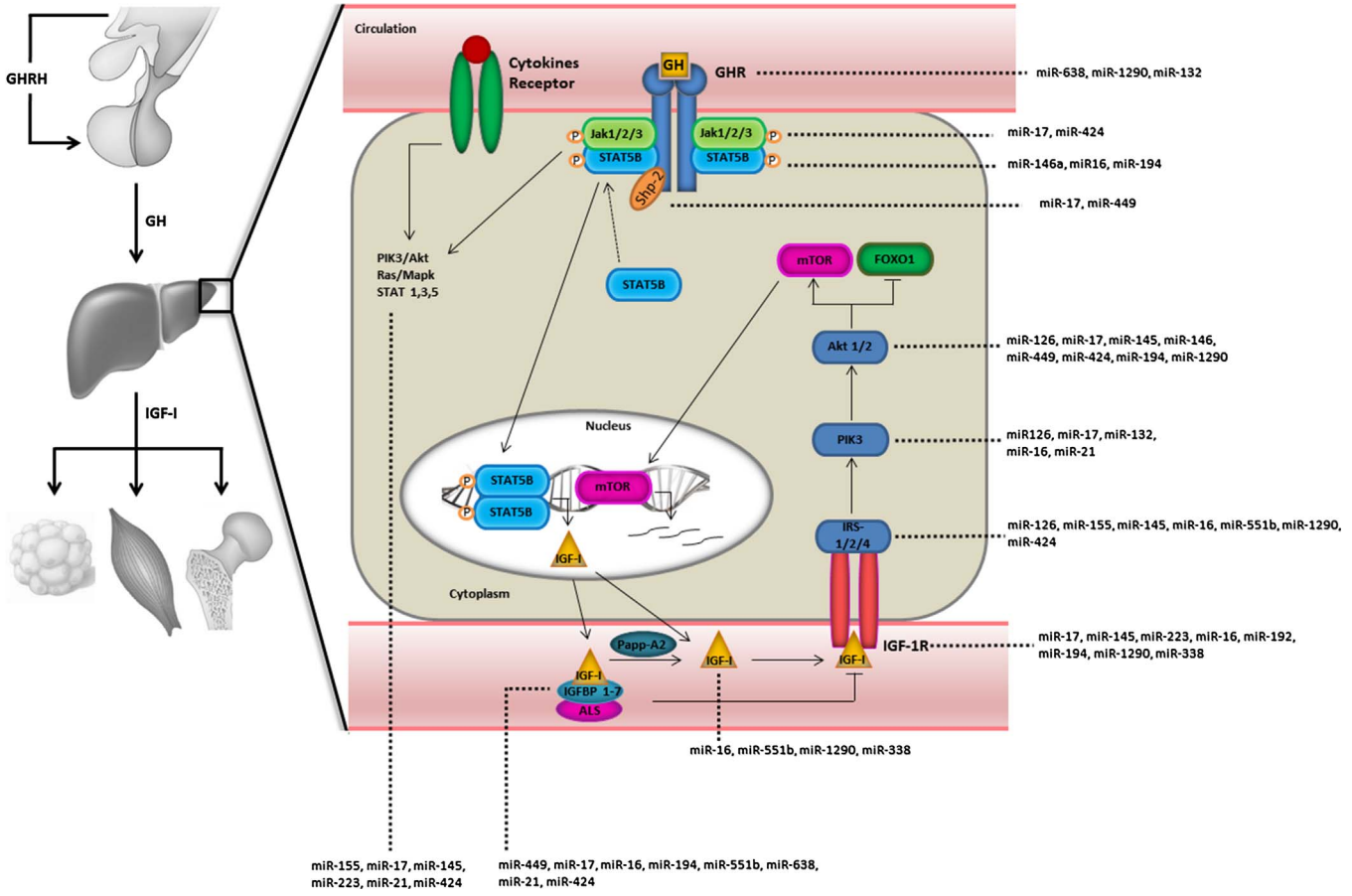

Fig. 2. Currently identified circulating miRNAs in inflammation in humans targeting genes within the GHR and IGF-1R signaling pathways.

for therapeutic gain also: in animal and *in vitro* models activation or inhibition of established miRNAs could be an attractive target for therapeutic modulation [239–241]. Although miRNA-based therapeutics is a promising area in the field of immunometabolism, challenges do remain. These include the effective delivery of the mimic or antagomir to the correct tissue and cell type. In addition, bioinformatic strategies that help to integrate clinical, biochemical data and translational approaches could allow a better understanding of unclear features of human diseases.

Conflicts of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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