MicroRNAs change and target genes involved in longitudinal growth in patients with IGHD on GH treatment

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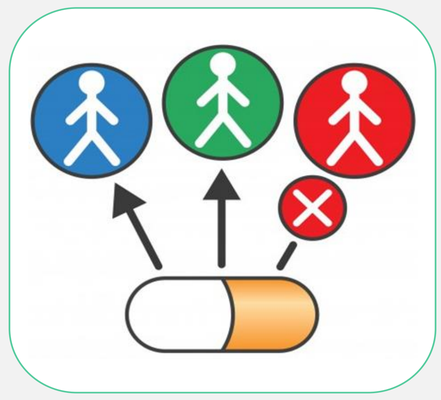
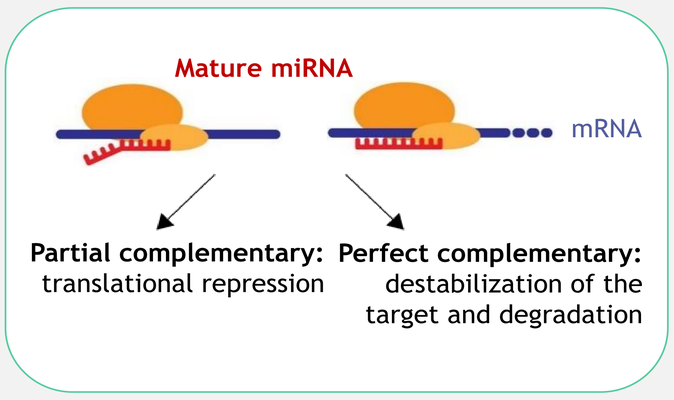
Background

The growth response in patients on GH treatment is extremely variable depending both on the patient's basal conditions and on personal innate sensitivity to therapy. MiRNAs are non-coding RNAs that function as epigenetic regulators of biological and metabolic processes by binding mature mRNA determining the inhibition of protein synthesis or mRNA degradation. MiRNAs could be potential biomarkers of response to GH treatment and could disclose new information on the effects and regulation of GH.

Interindividual variation in GH treatment sensitivity



Mechanism of action of miRNAs



Aim

Identify all the miRNAs varying on GH treatment (Global Profiling approach) and identify the principal pathways/biological processes, within growth, impacted by these miRNAs.

Patients and Methods

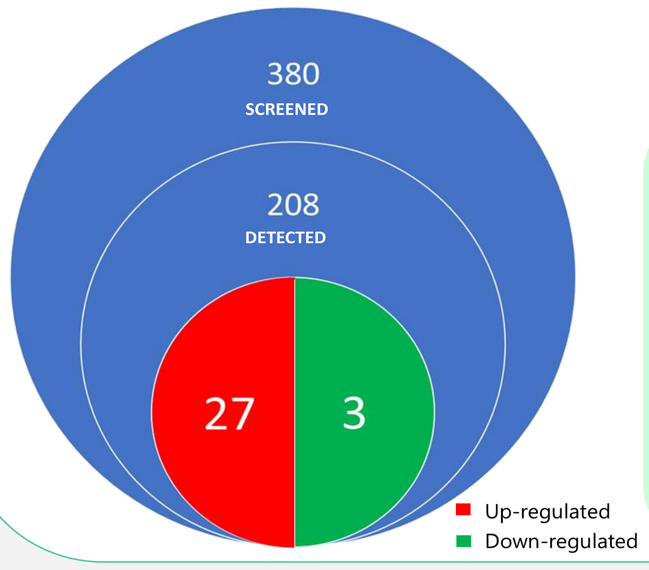
Ten prepubertal normal weight patients with Isolated Idiopathic Growth Hormone Deficiency (IGHD) were enrolled (5 males, 5 females; CA: 8,12 ± 0,73 yr). Global miRNA profiles (TaqMan Advanced Human Card A) were evaluated as follows: miRNA expression levels at -3 and 0 months were compared and the miRNAs showing a p-value≤0.05 were excluded allowing to identify those miRNAs changing only in response to treatment (+3 months) by either a factor $\log_2 2^{-DDCt} > +1.5$ or $\log_2 2^{-DDCt} < -1.5$ (up- or down-regulated, respectively). Single miRNA target genes were evaluated and DIANA-miRPath v3.0 software was used for KEGG pathway and Gene Ontology analyses.

Results

Overall 30 miRNAs were regulated by GH, 27 were up-regulated, and 3 down-regulated.

MiRNA global profiling

MiRNA levels at baseline vs 3 months post- rhGH treatment.



Pathways and biological processes regulated by GH treatment

Single miRNA target gene were evaluated and pathway and biological processes were analysed *in silico*.

GROWTH

Kegg pathways:

ExtraCellularMatrix-receptor, Thyroid hormone, Steroid biosynthesis, mTOR signaling, MAPK signaling, Prolactin signaling, PI3K-Akt signaling, Phosphatidylinositol signaling, and N-Glycan biosynthesis.

Biological processes:

fibroblast growth factor receptor signaling, glycosaminoglycan metabolism, phosphatidylinositol-mediated signaling, insulin receptor signaling, transforming growth factor beta receptor signaling, androgen receptor signaling and the JAK-STAT cascade involved in GH signaling.

Target Genes:

- COL1A1, COL2A1, integrins, laminins, SOX9, NF1;
- THR, ATP1B2, MAP2K2, PIK3R2, RAF1, NOTCH2, AKT, CASP9, STAT1, FOXO1, MAPK1;
- BRAF, AKT, PIK3CD, IGF1, PTEN;
- BRAF, SOS2, FGFR3, RAF1, FGF4, EGFR, TGFB1, FGF11, AKT, FLNB, FGF9, NF1, TGFB2, FGFs, FGFRs, TGFB3;
- PRLR, STAT3, SOS2, SHC1, RAF1, AKT2, JAK2, SOCS1, FOXO3, STAT1, SOCS7;
- FGFR3, FGFR4, COL4A5, IGF1R, EGFR, COL5A1, COL1A1, INSR, IGF1, VEGFB, FGFR1, FGF7, SOS2, RAF1, FGF8;
- PIK3R3, PTEN;
- FGFR3, IGF1R, PTPN11, IGF1, FGF8, FGFR1.

Known genes involved with genetic short stature and regulated by the miRNAs that change on GH treatment

Mutations of 15 of these genes are well known to cause severe short stature in humans.

BRAF	FLNB	RAF1
CBL	IGF1	SHOC2
FGF8	IGF1R	SLC26A2
FGFR1	NF1	SOS2
FGFR3	PTPN11	SOX9

Conclusions

GH treatment regulates miRNAs that in turn regulate genes, pathways and biological processes involved with growth. MiRNAs could be explored as biomarkers of response to treatment, as accurate prediction of growth still represents a considerable challenge for physicians in their daily clinical practice. Further, some novel genes implicated in the regulation of growth could be identified using this approach.

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ESPE European Society for Paediatric Endocrinology

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Azienda Unità Sanitaria Locale di Reggio Emilia
IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

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GH and IGFs

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