THE MIRNA NETWORK AND THE INTERPLAY BETWEEN GROWTH AND CANCER REGULATING PATHWAYS IN PREPUBERTAL PATIENTS WITH IDIOPATHIC ISOLATED GROWTH HORMONE DEFICIENCY (IGHD) ON GROWTH HORMONE (GH) TREATMENT

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INTRODUCTION

GH and IGF1 regulate cell proliferation, differentiation and apoptosis playing a key role in growth, and leading to consider potential oncogenic effects of GH.

To evaluate possible oncogenic risks in GHD patients who underwent GH replacement therapy, the SAGhE Consortium was created. The data collected have not yielded definite conclusions and continuous surveillance is yet required.

MiRNAs are regulators of gene expression, and are involved in many biological processes including genes involved in cancer.

AIM

We aimed at identifying miRNAs varying on GH treatment using a profiling approach, and at evaluating whether these miRNAs had an impact on pathways involved in cancer.

METHOD

Ten prepubertal normal weight patients with IGHD were enrolled (5 Males, 5 Females; CA: 8,79 ± 0,82yr). miRNA profiles were evaluated at -3,0 and at +3 months on treatment.

MiRNA expression levels at -3 and 0 months were compared and miRNAs showing a p-value ≤0.05 were excluded allowing to identify those miRNAs changing only in response to treatment.

MiRNAs were analysed using the DDCt method and only the ones differing by either a factor 2^{-DDCt} >+1.5 or 2^{-DDCt} < -1.5 (up- or down-regulated, respectively) were considered of interest. MiRNetv.2.0 platform was used for gene target and pathway analyses.

RESULTS

Sixteen miRNAs were found to be up-regulated and 2 down-regulated by GH treatment.

Pathway analysis showed that they were significantly involved in the regulation of 100 different pathways.

Among these, the most significant were: Oncogene-induced senescence, SHC-related events triggered by IGF1R, and Cyclin D associated events in G1 pathways. The first involved CDK6, MDM2, MAPK1, and TNRC6A genes; the second IGF1R, KRAS, and MAPK1 genes; the third CCND1, CDK6, and CDKN1A genes (**Table 1**).
These are all involved both in longitudinal growth and cancer.

Specifically, CDK6/CCND1 regulates chondrocyte maturation and cell cycle progression. MDM2 increases bone mineralization and is a negative regulator of p53. MAPK1(ERK2) and TNRC6A are involved in many cancers. IGF1R is pivotal for growth but is overexpressed in breast, colon, melanoma and prostate cancers among others. KRAS is an oncogene mutated in RASopathies which present both short stature and increased risk of cancer. CDKN1A (p21) regulates chondrocyte development but is also expressed in malignancies.

Table 1 The most significant pathways that involve the target genes of the differentially expressed miRNAs.

Pathway	Genes
Oncogene Induced Senescence	CDK6 MDM2 MAPK1 TNRC6A
SHC-related events triggered by IGF1R	IGF1R KRAS MAPK1
Cyclin D associated events in G1	CCND1 CDK6 CDKN1A

CONCLUSIONS

GH regulates miRNAs that in turn modulate genes and pathways commonly dysregulated in cancer. Interestingly, 16 out of 18 miRNAs were up-regulated suggesting inhibition of gene expression which is encouraging in terms of safety for treatment.

We have validated three up-regulated miRNAs in 25 treated subjects, and are performing specific experiments in bone cell lines to provide new insight into these aspects yet unclear in clinical practice.

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