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Scoliosis

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Recent progress in genetics of adolescent idiopathic scoliosis

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Introduction

Scoliosis is a three-dimensional deformity of the spine with lateral curvature combined with vertebral rotation. Occurrence of a melatonin signaling dysfunction in cells derived from patients with adolescent idiopathic scoliosis (AIS) was reported by Moreau et al. It was shown that serine phosphorylation of Gi proteins α-subunits was involved although the source of such aberrant phosphorylation remains unknown. The goal of this research project is to identify the kinase(s) and/or phosphatase(s) involved in the melatonin signaling defect observed in AIS. We have used a candidate gene driven approach and found the Tyrosine Phosphatase x (PTPx) and a second molecule termed HSJ-1, which controls the activity of this tyrosine phosphatase.

Materials and methods

Primary osteoblast cell cultures derived from AIS patients and control subjects biopsies were used to determine the expression profiles of the PTPx and HSJ-1 genes by RT-PCR and at the protein level by immunoprecipitation followed by Western blot. In parallel, cDNA and genomic DNA coding for PTPx or HSJ-1 were sequenced to search for possible mutations associated with AIS. PTPx knockout mouse was used as bipedal animal model and primary cell cultures derived from the spine of these mice were used to assess Gi protein signaling through a functional assay termed Cellular Dielectric Spectroscopy (CDS).

Results and discussion

Bipedal PTPx knockout mice develop more often scoliosis (80%) in number and severity than control C57Bl/6 mice (45%). Interestingly, functional analysis of osteoblasts derived from PTPx KO mice by CDS method showed a flaw in the transmission of Gi protein coupled receptor signaling similar to a specific AIS patient subgroup. PTPx inactivation seems to be involved in melatonin signaling dysfunction, as seen in these AIS patients. Interestingly, analysis of the coding region of PTPx led us to discover known and novel SNPs. In the other hand, there is a decrease in the protein level of HSJ-1 in some AIS patients when compared to control subjects.

Conclusion and relevance

Our data support the potential role of PTPx and HSJ-1 in AIS etiopathogenesis as disease modifying factors exacerbating scoliosis development. Additional work must be undertaken to validate the association of specific SNPs in a larger cohort of AIS patients and their functional consequences at the cellular level to understand the role of HSJ-1 and its interaction with PTPx.

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