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The prostaglandinE2-pathway as a new player in the pathogenesis of non-syndromic craniosynostoses

Wanda Lattanzi[1,2], C. Cicione[1], Luca Massimi[3], Gianpiero Tamburrini[3], M. Barba[1], C. Bernardini[1], G. Di Taranto[1], F. Michetti[1,2], Concezio Di Rocco[3], Massimo Caldarelli[3]

[1] *Insitute of Anatomy and Cell Biology, Università Cattolica del Sacro Cuore, Rome, Italy*

[2] *Latium Musculoskeletal Tissue Bank, Rome, Italy*

[3] *Institute of Pediatric Neurosurgery, Università Cattolica del Sacro Cuore, Rome, Italy*

Introduction: The etiopathogenesis of midline nonsyndromic craniosynostosis remains still largely unclear. We attempted to clarify this issue using microarray comparative gene expression profiling. Among the differentially expressed genes, we focused particularly on the hydroxyprostaglandin dehydrogenase (HPGD) gene which encodes the PGE2 catabolizing enzyme, whose pathway is involved in osteogenic differentiation. Also, mutations in this gene result in primary autosomal recessive hypertrophic osteoarthropathy and cranioosteoarthropathy.

Methods: RNA and calvarial cells were isolated from calvarial specimens of both patent and fused sutures collected during surgical cranial remodeling of NSC patients. RNA was used for exon-level microarray analysis; gene expression and alternative splicing events were confirmed using real time PCR and RT-PCR. For functional validation, calvarial cells isolated in primary culture were treated with scalar concentrations of PGE2; after 10 days of treatment cells were alternatively lysed to extract RNA or stained with Alizarin Red to analyze osteogenic differentiation.

Results: The gene expression profiling allowed the identification of 114 significantly modulated genes and 150 alternatively spliced genes, including HPGD. Exon level analysis of HPGD revealed that the active isoform was significantly downregulated in fused suture-calvarial tissues. Cells treated with the highest PGE2 concentrations showed higher osteogenic differentiation rates and osteoblast-specific gene expression levels. As expected, cells isolated from fused sutures displayed a higher amount of osteogenic differentiation compared to patent suture-derived cells, possibly due to the reduced activity of HPGD.

Conclusions: The results of this study may provide the original description of an impairment in the PGE2-signaling pathway in the pathogenesis of premature suture fusion in NSC patients. Translational implications may further derive from these data.