BS9 GENE IN NONSYNDROMIC CRANIOSYNOSTOSIS: ROLE OF THE PRIMARY CILIUM IN THE ABERRANT OSSIFICATION OF THE SUTURE OSTEOGENIC NICHE

Di Pietro L. (1,2), Barba M. (1,2), Massimi L. (2,3), Frassanito P. (2,3), Caldarelli M. (2,3), Tamburrini G. (2,3), Bernardini C. (1,2), Ceci P. (4), Falvo E. (4), Boyadjiev S.A. (5), Arcovito A. (2,6), Parolini O. (1,2,7), and Lattanzi W. (1,2)

(1) Istituto di Anatomia Umana e Biologia Cellulare, Università Cattolica del Sacro Cuore, Roma (Italy)
(2) Fondazione Policlinico Universitario "Agostino Gemelli" IRCSS, Roma (Italy)
(3) Istituto di Neurochirurgia, Università Cattolica del Sacro Cuore, Roma (Italy)
(4) Istituto di Biologia Molecolare e Patologia, Consiglio Nazionale delle Ricerche, Roma (Italy)
(5) Section of Genomics, Department of Pediatrics, University of California, Sacramento, CA (USA)
(6) Istituto di Biochimica e Biochimica Clinica, Università Cattolica del Sacro Cuore, Roma (Italy)
(7) Centro di Ricerca E. Menni, Fondazione Poliambulanza-Istituto Ospedaliero, Brescia (Italy)

Nonsyndromic craniosynostosis (NSC) is a congenital malformation due to the premature ossification of skull sutures, with an unclear molecular etiopathogenesis. Our study aimed at characterizing the molecular signaling implicated in the aberrant ossification of NCS patients' sutures.

Comparative microarray gene expression profiling of NCS patient sutures allowed identifying a fused suture-specific signature, including 17 genes involved in primary cilium signaling and assembly. Immunofluorescence showed that mesenchymal stromal cells (CMSC) isolated from fused sutures of NCS patients have a reduced potential to form primary cilia, compared with CMSC isolated from patient-matched control sutures. The microarray dataset included the overexpression of specific splice variants of the Bardet Biedl syndrome-associated gene 9 (BBS9), which encodes a member of the well-characterized class of BBS proteins that interact through their C-term to form an octameric complex named BBSome, necessary for ciliogenesis and ciliary function. BBS9 expression increased during in vitro osteogenic differentiation of CMSC of NCS patients and a siRNA-mediated functional knockdown of BBS9 affected the expression of primary cilia on patient suture cells and their osteogenic potential. Computational modeling of the upregulated protein isoforms (observed in patients) predicted that their binding affinity within the BBSome may be affected, and the impaired ciliogenesis provide a possible explanation for the aberrant NCS suture ossification.

Taken together, our data suggested a functional role of BBS9 in the osteogenic commitment of suture-derived cells, highlighting a key role of the primary cilium in the abnormal osteogenic process underlying NCS pathogenesis. We are currently validating the feasibility of targeting the aberrant ciliary signaling in CMSC with nanocarriers for drug delivery, towards the development of innovative therapeutic strategies exploitable for craniofacial bone remodeling.