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Molecular and functional characterization of calvarial stem cells in nonsyndromic craniosynostosis: role of the primary cilium-related signaling in the abnormal osteogenic niche

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Nonsyndromic craniosynostosis (NSC) is a congenital malformation due to the premature ossification of calvarial sutures, representing a paradigm of aberrant osteogenesis, with an unclear multifactorial etiopathogenesis. Through comparative analyses of fused-versus-patent sutures of affected patients, we demonstrated that calvarial stem cells (CSCs) display a constitutively overactive osteogenic potential at the site of premature synostosis, driven by the activation of intracellular osteogenic pathways. Microarray profiling allowed evidencing the significant differential expression of genes involved in the structure and function of the primary cilium, a key sensing organelle involved in cell differentiation and development. Indeed, the Bardet Biedl Syndrome-associated gene 9 (BBS9), encoding a structural component of the primary cilium, has been associated to the NSC phenotype in a recent GWAS. The expression of BBS9 appeared to be increased in CSCs from fused- versus unfused-sutures; moreover, confocal microscopy indicated that BBS9 expression in fused suture-CSCs tended to be scattered within the cytoplasm rather than localized at the transition zone of the primary cilium, as in control cells, indicating a reduced cell polarization. We performed in vitro gene silencing, co-culture assays and in vivo expression analysis in the rat calvarium, to confirm the role of BBS9 and related signaling in the osteogenic differentiation of CSCs and in the ossification of calvarial sutures. Overall our original data point towards the identification of the primary cilium as a key player involved in the abnormal communication of calvarial stem cells with surrounding cells and extracellular matrix within the abnormal osteogenic niche orchestrating the NSC phenotype.

Keywords
Craniosynostosis, primary cilium, osteogenic niche, bone, cranial vault.