

**Dysregulated chondrocyte formation as a novel mechanism of lambdoid synostosis**

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Craniosynostosis affects approximately 1 in 2,500 infants, with lambdoid synostosis being a rare subtype involving premature fusion between the parietal and occipital bones. Its underlying mechanisms remain poorly understood due to its rarity and lack of suitable models. Previously, we reported that Pdgfra overactivation leads to premature coronal suture fusion in mice. In this study, we found that mesodermal expression of an autoactivated PdgfraK allele induces lambdoid synostosis, establishing PdgfraK/+;Mesp1Cre mice as a relevant disease model. Histological analysis revealed excessive cartilage formation prior to suture fusion, implicating chondrocytes in the process. To test this, we activated Pdgfra in chondrocytes using Col2a1Cre, which also resulted in lambdoid synostosis. This confirmed that dysregulated chondrogenesis contributes to the condition. Spatial transcriptomics (10X Visium) revealed that Pdgfra activation promotes chondrocyte proliferation and differentiation toward endochondral ossification. These findings were validated by immunostaining and proliferation assays. Two types of cartilage are involved in calvarial development: one undergoes endochondral ossification, while the other is typically resorbed. Our results suggest that Pdgfra activation alters the fate of the latter, redirecting it toward ossification and leading to premature suture fusion. This study presents a novel model for lambdoid synostosis, identifies chondrocyte abnormalities as a key pathological factor, and elucidates how Pdgfra signaling regulates this process.

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