INVESTIGATING MOLECULAR PATHOGENESIS OF CAMPOMELIC DYSPLASIA

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Two decades after the discovery that sequence alterations within and around *SOX9* cause Campomelic Dysplasia (CD) - a rare skeletal malformation syndrome characterized by severe bowing of long bones (campomelia), the underlying molecular pathogenesis leading to bone dysmorphism remains unclear. $SOX9^{Y440X}$ is the most recurrent mutation identified in CD patients. In $Sox9^{+/Y440X}$ mice that recapitulate the human CD syndrome, an expanded population of osteoblasts was detected in the bowed tibiae, suggesting a causative relationship between altered osteogenesis and campomelia. As hypertrophic chondrocytes (HCs) was recently shown as a major source of endochondral osteoblasts, we hypothesized that the CD-associated $Sox9^{Y440X}$ mutation may impact this chondrocytes-to-osteoblasts lineage progression in causing campomelia. To test this, we utilized *Col10a1-Cre* to conditionally activate the $Sox9^{Y440X}$ mutation in HCs and to trace their fates by lineage analyses utilizing fluorescent protein Cre-reporters. Remarkably, homozygous mutants expressing $Sox9^{Y440X}$ specifically in HCs were markedly dwarfed and exhibited congenital anterolateral bowing of tibiae. While the mutant $Sox9^{Y440X}$ protein did not evidently impair or promote HCs differentiation into osteoblasts, it elevated Ihh signaling in the growth plate to induce excessive periosteal ossification. The aberrantly formed periosteal mass in consequence caused mispositioning of the primary ossification center to prompt campomelia. Intriguingly, genetic inactivation of *β-catenin* in the conditional $Sox9^{Y440X}$ mutants greatly ameliorated campomelia, implying the phenotype was consequential to a neomorphic function of Sox9Y440X in enhancing β-catenin activity. In conclusion, these findings propose that aberrant periosteal ossification owing to dysregulation of Hh signaling may underlie campomelia phenotype in CD patients.