論 文 要 旨

CDC5L promotes early chondrocyte differentiation and proliferation by modulating pre-mRNA splicing of SOX9, COL2A1, and WEE1

（CDC5L は SOX9, COL2A1, WEE1 の pre-mRNA スプライシングを調整し初期軟骨細胞分化と増殖を促進する）

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【abstract】

Ossification of the posterior longitudinal ligament (OPLL) of the spine is a common pathological condition that causes intractable myelopathy and radiculopathy, mainly the result of an endochondral ossification-like process. Our previous genome-wide association study identified six susceptibility loci for OPLL, including the cell division cycle 5-like (CDC5L) gene region. Here, we found CDC5L to be expressed in type II collagen-producing chondrocyte-like fibroblasts in human OPLL specimens, as well as in differentiating ATDC5 chondrocytes. Cdc5l siRNA transfection in murine chondrocytes decreased the expression of the early chondrogenic genes Sox9 and Col2a1, diminished the cartilage matrix production, and enhanced the expression of parathyroid-hormone-related protein (a resting chondrocyte marker). We also showed that Cdc5l shRNA suppressed the growth of cultured murine embryonal metatarsal cartilage rudiments and that Cdc5l knockdown suppressed the growth of ATDC5 cells. Fluorescence-activated cell sorting analysis revealed that the G2/M cell cycle transition was blocked; our data showed that Cdc5l siRNA transfection enhanced expression of Wee1, an inhibitor of the G2/M transition. Cdc5l siRNA also decreased the pre-mRNA splicing efficiency of Sox9 and Col2a1 genes in both ATDC5 cells and primary chondrocytes; conversely, loss of Cdc5l resulted in enhanced splicing of Wee1 pre-mRNA. Finally, an RNA-binding protein immunoprecipitation assay revealed that Cdc5l bound directly to these target gene transcripts. Overall, we conclude that Cdc5l promotes both early chondrogenesis and cartilage growth and may play a role in the etiology of OPLL, at least in part by fine-tuning the pre-mRNA splicing of chondrogenic genes and Wee1, thus initiating the endochondral ossification process.

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