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Dlx5 Is a Positive Regulator of Chondrocyte Differentiation during Endochondral Ossification

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Abstract

The process of endochondral ossification in which the bones of the limb are formed after generation of cartilage models is dependent on a precisely regulated program of chondrocyte maturation. Here, we show that the homeobox-containing gene *Dlx5* is expressed at the onset of chondrocyte maturation during the conversion of immature proliferating chondrocytes into postmitotic hypertrophying chondrocytes, a critical step in the maturation process. Moreover, retroviral misexpression of *Dlx5* during differentiation of the skeletal elements of the chick limb *in vivo* results in the formation of severely shortened skeletal elements that contain excessive numbers of hypertrophying chondrocytes which extend into ectopic regions, including sites normally occupied by immature chondrocytes. The expansion in the extent of hypertrophic maturation detectable histologically is accompanied by expanded and upregulated domains of expression of molecular markers of chondrocyte maturation, particularly type X collagen and osteopontin, and by expansion of mineralized cartilage matrix, which is characteristic of terminal hypertrophic differentiation. Furthermore, *Dlx5* misexpression markedly reduces chondrocyte proliferation concomitant with promoting hypertrophic maturation. Taken together, these results indicate that Dlx5 is a positive regulator of chondrocyte maturation and suggest that it regulates the process at least in part by promoting conversion of immature proliferating chondrocytes into hypertrophying chondrocytes. Retroviral misexpression of *Dlx5* also enhances formation of periosteal bone, which is derived from the *Dlx5*-expressing perichondrium that surrounds the diaphyses of the cartilage models. This suggests that Dlx5 may be involved in regulating osteoblast differentiation, as well as chondrocyte maturation, during endochondral ossification.

Keywords

Dlx5; chondrocyte differentiation; chondrocyte maturation; chondrocyte hypertrophy; endochondral ossification; osteoblast differentiation; bone development; limb

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