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p107 and p130 Coordinately Regulate Proliferation, Cbfa1 Expression, and Hypertrophic Differentiation during Endochondral Bone Development

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Abstract

During endochondral bone development, both the chondrogenic differentiation of mesenchyme and the hypertrophic differentiation of chondrocytes coincide with the proliferative arrest of the differentiating cells. However, the mechanisms by which differentiation is coordinated with cell cycle withdrawal, and the importance of this coordination for skeletal development, have not been defined. Through analysis of mice lacking the pRB-related p107 and p130 proteins, we found that p107 was required in prechondrogenic condensations for cell cycle withdrawal and for quantitatively normal *α1(II) collagen* expression. Remarkably, the p107-dependent proliferative arrest of mesenchymal cells was not needed for qualitative changes that are associated with chondrogenic differentiation, including production of Alcian blue-staining matrix and expression of the collagen IIB isoform. In chondrocytes, both p107 and p130 contributed to cell cycle exit, and p107 and p130 loss was accompanied by deregulated proliferation, reduced expression of Cbfa1, and reduced expression of Cbfa1-dependent genes that are associated with hypertrophic differentiation. Moreover, Cbfa1 was detected, and hypertrophic differentiation occurred, only in chondrocytes that had undergone or were undergoing a proliferative arrest. The results suggest that Cbfa1 links a p107- and p130-mediated cell cycle arrest to chondrocyte terminal differentiation.

Keywords

chondrocyte; chondrogenesis; p107; p130; hypertrophic differentiation; Cbfa1

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