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COMMENTARIES

Matrix Metalloproteinases in Cartilage Remodeling in Development

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Commentary on:

- Stickens D, Behonick DJ, Ortega N, Heyer B, Hartenstein B, Yu Y, Fosang AJ, Schorpp-Kistner M, Angel P, Werb Z. Altered endochondral bone development in matrix metalloproteinase 13-deficient mice. *Development.* 2004 Dec;131(23):5883-95.
- Inada M, Wang Y, Byrne MH, Rahman MU, Miyaura C, Lopez-Otin C, Krane SM. Critical roles for collagenase-3 (Mmp13) in development of growth plate cartilage and in endochondral ossification. *Proc Natl Acad Sci U S A.* 2004 Dec 7;101(49):17192-7.

The papers by Stickens et al. (1) and Inada et al. (2) provide useful insights into the normal development of growth plate cartilage and endochondral ossification and are also relevant to a form of human chondrodysplasia, the Missouri variant of spondyloepimetaphyseal dysplasia, which is caused by a mutation in the Mmp13 gene.

Both papers reported the phenotype of mice in which the *Mmp13* gene was inactivated, and there was agreement in the descriptions of cartilaginous growth plate abnormalities. Furthermore, both papers reported that from the earliest stages, growth plates were increased in length because of increased width of the zone of hypertrophy. In an attempt to understand the mechanism of this increase, consideration was given to decreased proteolysis, apoptosis, and resorption of calcified cartilage and increased chondrocyte proliferation or differentiation.

Both groups of authors identified reduced extracellular matrix remodeling as the crucial factor in determining growth plate width. Inada *et al*. (2) showed decreased proteolysis using antibodies against epitopes in specifically cleaved fragments of type II collagen. They also pointed out increases in the amount of type X collagen and osteopontin accumulation and suggested that increased collagen II and X might mediate cartilage-specific gene expression, manifesting itself in the increased size of the hypertrophic zone. Thus, the authors ascribed prime importance to decreased proteolysis, but also invoked the increased synthesis of collagen. They excluded a contribution from apoptosis and wondered about the role of vascular endothelial growth factor (VEGF), because increased collagen might reduce the availability of VEGF and lead to defective vascularization.

Stickens *et al*. (1) reached the same conclusion as did Inada *et al.* (2) about the role of MMP13 in collagen II degradation. They used a conceptually similar approach, with antibodies against aggrecan cleavage sites, to show that unlike collagen II, aggrecan cleavage requires the cooperative participation of both MMP13 and MMP9. This supports the idea that aggrecan protects cartilage collagen from degradation by proteinases and suggests that aggrecan must first be degraded in the cartilage before cleavage of collagen II by MMP13 can proceed successfully. The much more severe cartilage and bone phenotype in *Mmp9(-/-) : Mmp13(-/-)* mice might reflect the demonstrated strong synergy between the actions of these two proteins, which

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resulted in longer persistence of the increased cartilage matrix and the lack of MMP13 to degrade fragments, together with a slow rate of recruitment of other MMPs to carry out this process.

Stickens *et al*. (1) drew attention to a second important phenotype in the *Mmp13*(-/-) mice, with increased trabecular (but not cortical) bone most evident at birth and until several months of age, but back to wild-type equivalence at 12 months. The authors prepared mice in which the *Mmp13* gene was rendered null conditionally either in chondrocytes (using the *Col2A1* promoter) or osteoblasts (using the *Col1*α*1* promoter). They found that inactivation of the *Mmp13* gene in osteoblasts was required to reveal the trabecular bone phenotype, whereas inactivation in chondrocytes showed the increased growth plate phenotype, but not the increased trabecular bone phenotype. The mechanism responsible for the increased trabecular bone phenotype remains unclear. The authors pointed out that the *Mmp13*(-/-) phenotype differs from the bone phenotype shown by Zhao *et al*. (3) in Col1 collagenase-resistant mutant mice, in which the phenotype was expressed mainly in cortical bone and associated with increased apoptosis of osteocytes. It would have been interesting to have performed histomorphometric analysis to determine whether the trabecular bone phenotype in the *Mmp13*(-/-) mice was the result of increased bone formation or decreased resorption.

An important feature of the two papers is that they draw attention to the need for cooperative interactions among the components of cartilage matrix in determining enzymatic effects. Both papers show that MMP13 is the major collagenase responsible for Col2 cleavage; in addition, Stickens *et al*. show that both MMP13 and MMP9 are needed for aggrecan cleavage. They have used genetic approaches combined with careful biochemistry to demonstrate that remodeling of the cartilage matrix is the rate-limiting step in endochondral ossification. Productive use was made of specific antibodies against Col2 and aggrecan cleavage sites to study the process in development, and maybe such approaches can be applied to work on cartilage turnover in disease.

References

1. Stickens D, Behonick DJ, Ortega N, Heyer B, Hartenstein B, Yu Y, Fosang AJ, Schorpp-Kistner M, Angel P, Werb Z. Altered endochondral bone development in matrix metalloproteinase 13-deficient mice. *Development*. 2004 Dec;131(23):5883-95.

2. Inada M, Wang Y, Byrne MH, Rahman MU, Miyaura C, Lopez-Otin C, Krane SM. Critical roles for collagenase-3 (Mmp13) in development of growth plate cartilage and in endochondral ossification. *Proc Natl Acad Sci U S A*. 2004 Dec 7;101(49):17192-7.

3. Zhao W, Byrne MH, Wang Y, Krane SM. Osteocyte and osteoblast apoptosis and excessive bone deposition accompany failure of collagenase cleavage of collagen. *J Clin Invest*. 2000 Oct;106(8):941-9.

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