COMMENTARIES

Matrix Metalloproteinases in Cartilage Remodeling in Development

T. John Martin

St. Vincent’s Institute of Medical Research, Melbourne, Australia

February 2005

Commentary on:


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 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
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 Col1α1 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

