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Connective tissue disease in MT1-MMP -/- mice

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Keywords

Collagen, MT1-MMP-/- mice, skeletogenesis

Context

Matrix metalloproteinases (MMPs) constitute a family of zinc endopeptidases that are capable of degrading the structural components of the extracellular matrix. They play a role in processes that involve remodeling, such as wound healing, angiogenesis and cell migration. Hence MMPs may be important in diseases such as cancer, arthritis, and atherosclerosis. In addition, they may have a role in embryonic development and growth. Most MMPs are secreted, but MT-MMPs are membrane-bound and thus particularly suited for pericellular proteolysis. MT1-MMP is highly expressed in embryonic (peri)skeletal tissues, and has been suggested as an activator of MMP-2 and MMP-13.

To address the physiological role of MT1-MMP by generating mutant mice deficient in MT1-MMP activity.

Significant findings

1. *MT1-MMP-/-* mice were viable but displayed severe wasting and increased

   mortality.

2. *MT1-MMP-/-* mice showed abnormal cranial morphogenesis due to impaired

   removal of primordial calvarial cartilage, which interfered with membranous bone formation and suture closure. This suggests that timely removal of the cartilage primordia is critical in cranial morphogenesis and suture formation.

3. Limb bones were 65% shorter in mutants than in controls by day 45 and there was severe osteopenia. Prenatal and early postnatal metaphyseal growth plates developed normally, but the

postnatal development of epiphyseal growth plates was delayed due to impaired vascularization. This was followed by a progressive disorganisation of the metaphyseal growth plates.

4. Increased osteoclastic resorption and decreased bone formation were associated with progressive fibrosis of periskeletal soft tissues. The periosteum showed fibrosis, reduced cell proliferation, and structural disorganization.

5. Collagenolytic activity and osteogenic potential of osteoblasts were impaired. Osteoprogenitor cells were loaded onto type I collagen carriers (Gelfoam) and implanted in the subcutis. Cells from control mice efficiently degraded Gelfoam and replaced it with ectopic bone, but mutant cells formed only scarce amounts of bone and a large fraction of the collagenous carrier remained undegraded.

6. Skin fibroblasts from newborn mice were seeded on a type I collagen film. Cells from normal mice degraded the collagen film when stimulated with TNFa and IL-1?. Mutant cells failed to degrade the film, indicating that the degradation of type I collagen fibrils is dependent on MT1-MMP in this system.

7. Aging mutant mice developed arthritis. All joints were affected by overgrowth of a hypercellular vascularized synovium and destruction of the articular cartilage.

Comments

Methods

A 3.35 kb segment of *MT1-MMP* was replaced with a phosphoglycerate kinase (PGK) controlled HPRT minigene. This removed amino acids 6-274 from the mature MT1-MMP protein, including most of the prodomain and the catalytic domain, thus rendering any polypeptide expressed from this mutant gene catalytically inactive. The targeting vector was transfected into (HM-1)HPRT-deficient mouse embryonic stem cells. Chimeric offspring derived from two individual cell clones were mated to Swiss Black mice. Heterozygous mice were interbred. No MT1-MMP mRNA was detected in total neonatal RNA by northern blot in *MT1-MMP-/-* mice.

Additional information

For the molecular biologist' perspective, see related report

References

1. Holmbeck K, Bianco P, Caterina J, Yamada S, Kromer M, Kuznetsov SA, Mankani M, Robey PG, Poole AR, Pidoux I, Ward JM, Birkedal-Hansen H: MT1-MMP-deficient mice develop dwarfism, osteopenia, arthritis, and connective tissue disease due to inadequate collagen turnover. Cell. 1999, 99: 81-92.