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Original Article

Hylonome

Small leucine-rich proteoglycans in the aging skeleton

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Abstract

Small Leucine-Rich Proteoglyans (SLRPs) are major skeletal extracellular matrix (ECM) components that comprise a family of 13 members containing repeats of a leucine-rich motif. To examine SLRP function, we generated mice deficient in one or more member and analyzed them at the tissue, cell and molecular levels. This review outlines the novel research findings uncovered using these new animal models.

Keywords: Small Leucine Rich Proteoglycans (SLRPs), Biglycan, Bone, Osteoblasts

Mice deficient in biglycan (a class I SRLP) acquired early onset osteopenia due to a decreased ability to make new bone[1]. Experiments using normal and biglycan deficient calvarial cells showed that biglycan controls BMP binding and activation[2]. To attain a comprehensive picture of downstream effectors controlled by the presence of biglycan, microarray analyses were performed using mRNA from biglycan-deficient osteoblasts treated with or without BMP. Numerous differentially regulated mRNAs were identified related to cell cycle, differentiation and apoptosis. New molecular circuits potentially connecting biglycan to osteoblast function were uncovered and are currently under investigation[3]. The observed defects in biglycan-deficient osteoblasts led us to speculate that biglycan could also modulate osteoclast function. Osteoblast-osteoclast co-culture and induced osteolysis experiments using normal and biglycan-deficient mice confirmed this theory[4].

The SLRP decorin is closely related to biglycan and is upregulated in the context of biglycan deficiency. To test whether there is redundancy/compensation in SLRP function, we made mice deficient in biglycan and decorin. These mice displayed a more profound osteopenia compared to mice deficient in only one of the SLRPs[5]. To examine the molecular mechanisms that caused this osteopenia we cultured osteogenic bone marrow cells from the doubly deficient mice. We found that these cells proliferate faster than normal cells but, unlike the singly biglycan-deficient, they were not defective in differentiation. Moreover we found a "hypersensitivity" to TGF-beta that eventually led to premature apoptosis. This premature cell death appeared to deplete osteogenic precursors, and is likely the cellular basis for decreased osteogenesis in this animal model[6].

To test compensation in distantly related SLRPs mice deficient in both biglycan and fibromodulin (a class II SLRP) were made[7]. They acquired early onset osteoarthritis instigated by weak tendons that ossified prematurely. These abnormalities became worse when the mice were subject to forced treadmill running indicating that biomechanical stress could influence this pathological process. Based on the observation that tendons ossified in the absence of biglycan or fibromodulin we theorized that tendons contain stem cells whose fate could be influenced by their ECM niche. Several approaches are currently underway to test this hypothesis. In summary using mice deficient in one or more SLRP we have been able to identify early molecular events causing skeletal abnormalities that are dependent on SLRP function.

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