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TGF-beta regulates *Ank*expression

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Keywords

Ank, chondrocyte hypertrophy, metatarsal culture, mineralization, transforming growth factor-?

Context

The *Ank* gene encodes a multipass transmembrane protein that is thought to function as a transporter that regulates the balance of inorganic pyrophosphate between intracellular and extracellular chondrocyte compartments (see additional information). Mice with progressive ankylosis carry a G?T substitution in the *Ank* gene, which results in a truncated and defective protein. These animals develop arthritis-like disease characterized by articular cartilage erosion, ectopic joint calcification, osteophyte formation and joint immobility and fusion. Mutations in the human homolog are associated with autosomal dominant craniometaphyseal dysplasia. The transforming growth factor-? (TGF-?) superfamily of growth and differentiation factors includes the bone morphogenetic proteins (BMP). Members of this superfamily have diverse and pleiotrophic functions. Interestingly, a genetically engineered mouse model expressing a dominant-negative form of TGF-? receptor in skeletal tissues exhibits an osteoarthritis-like phenotype. Furthermore, TGF-? has been shown to regulate inorganic pyrophosphate levels *in vitro*. Therefore, this investigation tested the hypothesis that *Ank* is expressed in a restrictive pattern during cartilage hypertrophic maturation and is regulated by TGF-? signaling.

Significant findings

In both E15.5 and E17.5 mouse embryos, *Ank* mRNA expression was localized to sites of endochondral and intramembraneous ossification. In particular, *Ank* was detected in hypertrophic chondrocytes, and inner lining cells of the perichondrium and periosteum at the bone collar. During postnatal development, *Ank* was detected in hypertrophic chondrocytes at the transition zone between the articular cartilage and the secondary ossification center. *Ank* expression overlapped in part with that of type X collagen. *Ank* was also detected in the perichondrium and periosteum at the metaphysis. Using an *ex vivo* culture system for E15.5 mouse metatarsal, 10ng/ml TGF-?1 promoted *Ank* expression by 3.64-fold after 5 days in culture, as determined by RT-PCR. This data was corroborated by

morphological observations of *Ank* expression in cultured metatarsal. In addition to the *in vivo* pattern of expression, *Ank* expression was observed in prehypertrophic chondrocytes in TGF-?-treated cultures, suggesting that TGF-? can induced ectopic *Ank* expression. Taken together, these results suggest that *Ank* is expressed, and may be significantly involved, in cartilage hypertrophy. Ank expression is regulated by TGF-?.

Comments

The most significant finding was the demonstration that TGF-? regulates *Ank* expression. This regulation includes both the promotion of *Ank* mRNA levels at sites of normal *Ank* expression, and also the induction of ectopic *Ank* expression. Therefore, this finding supports a mechanistic relationship among TGF-? signaling, *Ank* expression pattern, and arthritis and other joint calcification disorders. The *Ank* expression pattern during embryonic and early postnatal development is consistent with the phenotype of diseases and disorders associated with defective *Ank* protein. Although it may be possible to regulate pyrophosphate levels by intervention with small molecules, this study suggests that TGF-? may be an earlier and additional therapeutic target.

Methods

Polymerase chain reaction (PCR) cloning, sequencing, *in situ* hybridization, metatarsal culture, reverse-transcription-polymerase chain reaction (RT-PCR)

Additional information

Ryan LM: **The%20ank%20gene%20story***Arthritis Res* 2001, **3**(2):77-79

References

1. Sohn P, Crowley M, Slattery E, Serra R: Developmental and TGF-beta-mediated regulation of *Ank*mRNA expression in cartilage and bone. Osteoarthritis Cartilage. 2002, 10: 482-490.

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