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BMP-2 induces osteoblast apoptosis mediated by PKC

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Keywords

apoptosis, BMP-2, osteoblasts, PKC, TGF-?

Context

Apoptosis of osteoblasts is a key to controlling osteoblast life span and bone formation, in addition to differentiation of progenitor cells. There are two types of regulators of osteoblast apoptosis: osteotropic hormones and local regulatory cytokines, such as tumor necrosis factor-a, interleukin-1 and -6, insulin-like growth factor-1, and fibroblast growth factor. Although it is well known that bone morphogenic proteins (BMPs) play a pivotal role in the commitment and differentiation of osteoblastic lineage, their role in apoptosis induction remains unknown.

Significant findings

BMP-2 promotes apoptosis in primary human calvariae and immortalized neonatal osteoblasts, while TGF-? inhibits apoptosis. BMP-2 increases the release of mitochondrial cytochrome c to the cytosol, the Bax/Bcl-2 ratio, and caspase-9, -3, -6, and -7 activity. When mutant Smad-1 is transfected in a dominant-negative fashion BMP-2-induced expression of osteoblast transcription factor Runx2 is downregulated, whereas the caspase activation and apoptosis is not affected. BMP-2 upregulates PKC activity and its inhibitor blocks osteoblasts-apoptosis induced by BMP-2, indicating that the proapoptotic effect of BMP-2 is PKC-dependent.

Comments

A novel role for BMP-2 in the induction of apoptosis in human osteoblasts has been demonstrated, although the ability to induce apoptosis by BMP-2 was not compared with other pro-inflammatory cytokines. The signaling pathway leading to apoptosis induction is not dependent on Smad, which is necessary for BMP-2-induced osteoblast differentiation, but on PKC. Given that the regulation of apoptosis in osteoblasts is pivotal to the control of bone formation, the results introduce a possibility that one can selectively modulate the BMP-2/apoptosis pathway without affecting osteoblast differentiation. It would be of interest to know whether apoptosis induced by proinflammatory cytokines other than BMP-2 can be inhibited by a selective PKC inhibitor.

Methods

TUNEL-staining, *in vitro* enzyme activity measurements, western blot, *in vitro* transfection

Additional information

References

1. Hay E, Lemonnier J, Fromigue O, Marie PJ: Bone morphogenetic protein-2 promotes osteoblast apoptosis through a Smad-independent, protein kinase C-dependent signaling pathway. J Biol Chem. 2001, 276: 29028-29036.