

OSTEOSCOOP

News on current events in osteoporosis and rheumatology

Lifelong accumulation of bone in osteoblasts lacking Pten

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The development and maintenance of the mammalian skeleton are controlled by actions of morphogens and growth factors on bone cells. Skeletal growth factors such as insulin-like growth factor-1 (IGF-1) affect bone formation and induce osteoblast proliferation and lifespan by activating antiapoptotic pathways, increasing cell proliferation, and influencing differentiation. A key control point in many antiapoptotic pathways is a kinase named phosphatidylinositol (PI) 3-kinase (PI3K), which is activated in response to various extracellular signals and leads to generation of lipidic second messengers. A key downstream target of this pathway is another kinase named Akt. When activated, Akt promotes cell growth and cell survival by regulating numerous downstream pathways.

This pathway is controlled by a phosphatase named PTEN which negatively regulates PI3K. Loss of PTEN in either embryonic stem cells or human cancer cell lines results in persistent activation of Akt, leading to increases in cell proliferation, survival, and migration.

To directly investigate the role of PTEN in osteoblasts in vivo, Liu et al. [1] disrupted the gene encoding PTEN in mice. Mice carrying an osteoblast-specific deletion of PTEN had normal body size but demonstrated progressive increases in bone volume and density throughout life. In vitro osteoblasts lacking PTEN differentiated more rapidly than controls and exhibited greatly reduced apoptosis in association with markedly increased levels of activated Akt and activation of signaling pathways downstream of Akt.

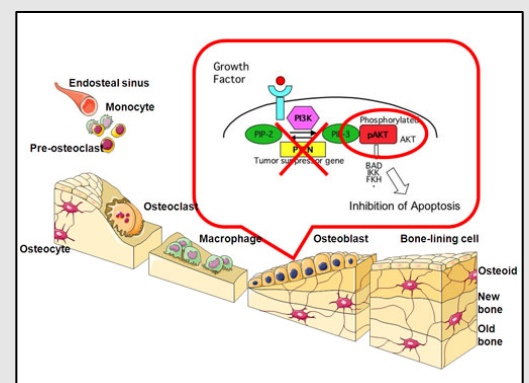
These findings support a critical role for this tumor-suppressor gene in regulating osteoblast lifespan and likely explain the skeletal abnormalities in patients carrying germ-line mutations of PTEN.

1. Liu X et al. *Proc Natl Acad Sci USA*. 2007;104: 2259-2264.

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A key control point in many antiapoptotic pathways is PI3K, which is activated in response to various extracellular signals and leads to generation of lipidic second messengers. The PTEN gene encodes a phosphatase which negatively regulates PI3K. Loss of PTEN function results in persistent activation of Akt, leading to increases in cell proliferation, survival, and migration.

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