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Role of PKG II in osteoblast mechanotransduction

Hema Rangaswami, Nisha Marate Shunhui Zhuang, Yongchang Chen and Renate B Pilz*

Address: Department of Medicine University of California, San Diego, La Jolla, CA 92093, USA

Email: Renate B Pilz* - rpilz@ucsd.edu

* Corresponding author

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Background

Mechanical stress is a primary determinant of bone growth and remodeling: weight bearing and locomotion stimulate interstitial fluid flow through the bone canalicular system, and the resultant shear stress is a major mechanism whereby mechanical forces stimulate bone growth [1]. In response to fluid shear stress and other types of mechanical stimulation, osteoblasts produce large amounts of NO, and genetic and pharmacologic studies indicate an important role of NO in osteoblast biology, but little is known about signaling downstream of NO in osteoblasts [1,2].

Results

In primary human osteoblasts and murine MC3T3-E1 cells, we found that fluid shear stress induced rapid expression of *c-fos*, *fra-1*, *fra-2*, and *fosB*/*ΔfosB* mRNAs; these genes encode transcriptional regulators important for osteoblast proliferation and differentiation, as demonstrated by severe osteosclerotic or osteoporotic phenotypes of mice that over-express or lack these proteins, respectively. Fluid shear stress increased osteoblast nitric oxide (NO) synthesis, leading to increased cGMP production and activation of cGMP-dependent protein kinases (PKG), as demonstrated by phosphorylation of the PKG I/II substrate VASP. Pharmacological inhibition of the NO/cGMP/PKG signaling pathway blocked shear-induced expression of all four *fos* family genes. Induction of these genes required signaling through MEK/Erk, and Erk activation was NO/cGMP/PKG-dependent. Treating cells with a membrane-permeable cGMP analog partly mimicked the effects of fluid shear stress on Erk activity and *fos* family gene expression, and it appears that cGMP co-operates with increased intracellular calcium in shear-stressed osteoblasts. In cells transfected with siRNAs specific for membrane-bound PKG II, shear- and cGMP-induced Erk activation and *fos* family gene expression was nearly abolished and could be restored by transducing cells with a virus encoding an siRNA-resistant form of PKG II; in contrast, siRNA-mediated repression of the more abundant cytosolic PKG I isoform was without effect.

Conclusion

Thus, we report a novel function for PKG II in osteoblast mechanotransduction, and propose a model whereby NO/cGMP/PKG II-mediated Erk activation and induction of *c-fos*, *fra-1*, *fra-2*, and *fosB*/*ΔfosB* play a key role in the osteoblast anabolic response to mechanical stimulation. Defective PKG II regulation of *fos* family transcription factors in osteoblasts may contribute to the developmental bone defects observed in PKG II-deficient rodents [3].

References

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