



Antenatal Corticosteroid Therapy Attenuates Angiogenesis Through Inhibiting Osteoclastogenesis in Young Mice

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Antenatal corticosteroid therapy (ACT) has been shown to reduce morbidity and mortality rates in preterm delivery, but the fetus is more likely to face the risk of low bone mineralization and low fetal linear growth. However, the mechanism of ACT inducing low bone mineralization remains largely unknown. Pre-osteoclasts, which play an important role in angiogenesis and osteogenesis, are specifically regulating type H vessels (CD31^{hi}Erms^{hi}) and vessel formation by secreting platelet-derived growth factor-BB (PDGF-BB). We find that the number of pre-osteoclasts and POC-secreted PDGF-BB is dramatically decreased in ACT mice, contributing to the reduction in type H vessels and bone mineralization during the mouse offspring. Quantitative analyses of micro-computed tomography show that the ACT mice have a significant reduction in the mass of trabecular bone relative to the control group. Mononuclear pre-osteoclasts in trabecular bone decreased in ACT mice, which leads to the amount of PDGF-BB reduced and attenuates type H vessel formation. After sorting the Rank+ osteoclast precursors using flow cytometry, we show that the enhancer of zeste homolog 2 (Ezh2) expression is decreased in Rank+ osteoclast precursors in ACT mice. Consistent with the flow data, by using small molecule Ezh2 inhibitor GSK126, we prove that Ezh2 is required for osteoclast differentiation. Downregulating the expression of Ezh2 in osteoclast precursors would reduce PDGF-BB production. Conditioned medium from osteoclast precursor cultures treated with GSK126 inhibited endothelial tube formation, whereas conditioned medium from vehicle group stimulated endothelial tube formation. These results indicate Ezh2 expression of osteoclast precursors is suppressed after ACT, which reduced the pre-osteoclast number and PDGF-BB secretion, thus inhibiting type H vessel formation and ACT-associated low bone mineralization.

Keywords: ACT, angiogenesis, osteoclastogenesis, EZH2, pre-osteoclasts

The Official Patients Sourcebook On Antenatal Corticosteroid Therapy

Nelson Mark Braslow



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