

Oral Abstract

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Glucocorticoid signalling through osteoblasts is essential for cranial skeletal development

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Glucocorticoids are important regulators of bone cell differentiation and mesenchymal lineage commitment (1). Using a transgenic model of osteoblast-targeted disruption of glucocorticoid signaling, we investigated the role of endogenous glucocorticoids in murine skeletal development.

Embryonic and neonatal transgenic (tg) mice revealed a distinct phenotype characterised by hypoplasia and osteopenia of the cranial skeleton, disorganised frontal, parietal and interparietal bones, increased suture patency, ectopic differentiation of cartilage in the sagittal suture and disturbed postnatal removal of parietal cartilage. Neonatal transgenic mice develop a distinct cranial phenotype characterised by bone hypoplasia and osteopenia, disorganised and poorly mineralised frontal, parietal and interparietal bones and increased suture patency. These changes were apparent as early as E15.5. In addition, ectopic differentiation of cartilage in the sagittal suture and a postnatal defect in parietal cartilage removal were observed in tg mice, resulting in ectopic cartilage below the sutures and abundant remnant cartilage underneath the parietal and inter-parietal bones. Expression of MMP14, an enzyme essential for calvarial cartilage removal, was markedly reduced in tg parietal bone and cartilage. Concurrently, accumulation of β -catenin, the upstream regulator of MMP14, was decreased in tg osteoblasts, chondrocytes and mesenchymal progenitors in suture areas; probably due to a lack of Wnt signaling from neighbouring osteoblasts. mRNA expression for Wnt9a and Wnt10b was reduced 40% and 50% respectively in osteoblasts of tg parietal bone compared to wild-type (WT) littermates. Also, Wnt9a was undetectable by in-situ-hybridisation in tg calvarial osteoblasts but was strongly expressed in the WT. Supracalvarial injection of Wnt3a protein rescued the cranial phenotype of tg mice (Fig-1).

We conclude that endogenous glucocorticoids stimulate the expression and secretion of Wnt proteins in osteoblasts, in keeping with our previous results (1). Wnt signalling induces a) parietal cartilage chondrocytes to initiate MMP14-mediated cartilage degradation; and b) mesenchymal progenitors to differentiate towards the osteoblast lineage. Thus glucocorticoids and osteoblasts play an essential role in the intricate development of intramembranous bone.

1. Zhou et al JBC 283:1936, 2008

