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Short Commentary Open Access

Tissue Specific Actions of Glucocorticoid Treatment in Bone and Cartilage

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Corticosteroids are potent medications widely used not only to treat many inflammatory and autoimmune conditions but also in a variety of life threatening and disabling disorders and have saved or improved many lives. In the UK alone, more than 250,000 people are taking systemic steroids and at least 10% of all children require some form of Glucocarticoids (GCs) during childhood [1]. Systemic GCs in pediatrics are given for different indications such as rheumatoid arthritis, ulcerative colitis, Crohn´s disease, and asthma. Negative side effects of GCs have always been a concern and it is recommended to carefully monitor children who are treated with high doses of systemic steroids [2,3]. Numerous side effects on various body systems have been reported in GC treated patients. Mary Leonard and colleagues studied 60 children and adolescents with nephrotic syndrome intermittently treated with high-dose GCs and found that these children were significantly shorter, had high body-mass index, and the prevalence of obesity was also significantly higher than in control subjects [4]. In fact, children are more vulnerable to GC-induced side effects. Since, GCs are among the most common and important drugs used in routine clinical practice it is of great importance to identify strategies to prevent such side-effects without compromising the desired anti-inflammatory effects. To achieve this, it is essential to characterize the underlying mechanisms for GC-induced side-effects such as osteoporosis and longitudinal bone growth retardation. In a recent review in the *New England Journal of Medicine*, vascular endothelial growth factor A (VEGF-A) was highlighted as an unusual new potential target for the treatment of osteoporosis [5]. The authors suggest that we may have focused too narrow on already known conventional signaling cascades such as bone morphogenetic protein (BMP)-signaling and Wnt-signaling pathways while ignoring some of the non-conventional targets. The question is what other potential non-conventional targets could be explored against osteoporosis and longitudinal bone growth retardation? We have recently reported that lack of Bax prevents from GC-induced bone growth impairment in young mice [6]. In this study, we used an array of model systems, both *in vitro* (cultures of human growth plate biopsies obtained from children after surgery, human HCS-2/8 proliferative chondrocytes, organ cultures of fetal rat metatarsal bones) and *in vivo* (Bax deficient male/female mice, and rats), and treated these with the GC dexamethasone for up to 4 weeks. We showed that dexamethasone induces dissipation of mitochondrial membrane potential with release of apoptogenic cytochrome c into the cytosol of human chondrocytes. Interestingly, human growth plate biopsies (obtained from children undergoing epiphyseal surgery to prevent extreme tall stature) treated with dexamethasone for 24 hrs *in vitro*, also showed increased levels of apoptosis, pro-apoptotic proteins Bid [7] and Bax activity with conformational changes. Finally, when we treated Bax deficient (-/-) mice with a clinical relevant dose of dexamethasone, we observed that Bax deficient mice were well protected from growth retardation caused by dexamethasone, compared to wild type mice. Furthermore, growth velocity of Bax deficient mice treated with dexamethasone was not significantly altered, when compared to wild type mice treated with vehicle [6]. Indeed, the significance of our findings for bone physiology is supported by previous findings showing that Bax-deficiency is associated with increased bone mineral density [8], and increased cartilage production during fracture repair [9].Interestingly, in tissue specimens obtained from rheumatoid arthritis patients, higher levels of Bax has been reported than in healthy controls and strong Bax staining was also found in chondrocytes at sites of cartilage degradation [10]. In addition, some recent studies show that GC treatment also induces autophagy in lymphoid leukemia cells thereby triggering cytotoxicity [11,12]. These reports suggest that GCs are capable of targeting multiple intracellular signaling pathways depending on cell types and thereby trigger cell death, inhibit cellular proliferation and differentiation. All together, these findings suggest that novel treatment regimens consisting of small molecules/peptides targeting pro-apoptotic proteins such as Bax, may succeed in minimizing long-term negative side effects on bone tissue in patients treated with GCs.

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