including rheumatoid arthritis. Our previous work suggests that the immunoglobulin binding protein BiP affects the differentiation of peripheral blood monocytes, so we investigated the effect of BiP on osteoclast differentiation from monocytes in vitro, on resorption of bone explants and the spontaneous onset of arthritis in the human tumour necrosis factor transgenic (hTNFtg) mouse.

Methods Human peripheral blood monocytes were differentiated in vitro in the presence or absence of BiP. Osteoclast development was measured by the presence of F-actin rings and bone resorption by pit formation following culture on dentine slices and staining with toluidine blue. In preliminary in vivo studies, intraperitoneal administration of a single dose of BiP (10 µg/mouse) to the hTNFtg mouse at 5 weeks was investigated. Body weight, grip strength and paw swelling were used to assess arthritis and histomorphometry of the inflamed paw or of the tibia for osteoclast number, function and bone erosion.

Results BiP potently inhibited the differentiation of osteoclasts in a dose-dependent manner when added with macrophage colony-stimulating factor and receptor activator for nuclear factor κB ligand (RANKL) at the start of the culture period (F-actin rings: control 39.3±13.4; BiP µg/ml 5.6±2.2; BiP 20 µg/ml 1.7±1.5; BiP 50 µg/ml 1.3±0.8). When added after 10 days differentiation to semi-mature osteoclasts, BiP caused a significant reduction in the number of F-actin ring-positive osteoclasts (control, 220±48 vs BiP, 52±24; p=0.04) and a concomitant decrease in the number of bone resorption pits on dentine (control, 19±7 vs BiP 2±0.4; p=0.03). In vivo, the BiP-treated hTNFtg mice significantly lost less weight, showed less paw swelling and consequently maintained their grip strength. Histology of the paw revealed that BiP-treated mice had significantly less inflammation and cartilage destruction as well as decreased bone erosion and osteoclast numbers. Histomorphometry analysis indicated an increased systemic bone mass with significantly increased trabecular thickness caused by lower numbers of osteoclasts per bone perimeter.

Conclusion BiP protects against inflammatory arthritis-induced local and systemic bone loss by inhibiting the differentiation and function of osteoclasts.

A53 REGULATION OF OSTEOCLAST DIFFERENTIATION AND FUNCTION BY BIP

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Background Dysregulated bone remodelling is the major cause of the pathology of a number of human diseases,