ABSTRACT FROM CORINNA WEHMEYER

Loss of Wnt inhibitor sclerostin promotes TNF-dependent inflammatory bone destruction

Wnt inhibitor sclerostin is a negative regulator of the Wnt/β-catenin pathway and has anti-anabolic effects on bone formation. Mutations in the human sclerostin gene (*SOST*) lead to sclerosteosis with massiv bone growth, and sclerostin deficient mice show increased bone mass and bone strength. Therefore blocking sclerostin antibodies are currently evaluated clinically for the treatment of postmenopausal osteoporosis in humans. However, the impact of sclerostin on bone under chronic inflammatory conditions, such as RA, is not well understood. We could show for the first time that sclerostin expression is not only restricted to osteocytes, but is also induced by the inflammatory cytokine TNFα in rheumatoid arthritis fibroblast-like synoviocytes (RA FLS). We were surprised to find that lack of sclerostin or its antibody-mediated inhibition in the human TNF transgenic mouse model (hTNFtg) of RA did not stop bone loss as expected; it actually aggravated disease severity with enhanced pannus formation, cartilage loss and bone erosion. Inhibition of sclerostin also failed to improve bone destruction in the glucose-6-phosphate isomerase (G6PI)-induced RA mouse model but ameliorated disease severity in the K/BxN serum transfer-induced arthritis model, which is TNF receptor independent, indicating a specific role for sclerostin in TNFα signaling. Furthermore, isolated FLS from sclerostin deficient hTNFtg mice displayed increased TNFα mediated p38 activation, a key step in arthritis development. In turn, sclerostin effectively blocked TNFα but not IL-1 induced activation of p38 mediated by an β-catenin-independent but LRP6-dependent mechanism.

Collectively, these data demonstrated that sclerostin appears to have a protective function in TNF-mediated inflammatory joint destruction and the more as inflammation is driven by TNF the more aggravation of disease can be expected by the inhibition of sclerostin. The possibility that the use of anti-sclerostin antibodies under chronic TNFα-dependent inflammatory conditions may lead to aggrevation of disease severity in mice means that caution should be taken when considering such treatment in RA patients and in patients with chronic TNF-dependent comorbidities.