UNSW SYDNEY

Neuroscience & Non-Communicable Diseases WEBINAR – All welcome

Friday 23 April 2021, 3pm

'Intravital imaging of osteoclasts in vivo reveals novel OSTEOCLAST FATE which may underlie the therapeutic response to Denosumab withdrawal'

Speaker: Dr Michelle McDonald, Garvan Institute of Medical Research

Abstract:

The anti-RANKL treatment Denosumab (Dmab) is an effective agent for the treatment of osteoporosis. However rapid bone loss and increased risk of fracture have been associated with treatment withdrawal. We hypothesised that a rebound in osteoclast activity occurs following removal of Dmab. To examine this in real time in vivo, we developed a novel intravital imaging methodology to visualize osteoclast dynamics on the intact endocortical surface of tibia in live mice. We generated mixed bone marrow chimeras in which osteoclasts were both LysMtdT+ and Blimp-1gfp+ or CSF1Rgfp+ through cell fusion. Using sRANKL to stimulate osteoclasts and osteoprotegerin-Fc (OPG:Fc) to mimic Dmab we examined osteoclast dynamics and function.

We showed that multi-nucleated LysM+Blimp-1+Osteosense+ osteoclasts form syncytial network on bone. Following stimulation with sRANKL we visualized osteoclast fusion and for the first time osteoclast fission in vivo, which was shown to be morphologically distinct to apoptosis. Interestingly we observed osteoclast fission products re-fusing with parent cells or other osteoclasts, a process we termed osteoclast recycling. Following OPG-Fc treatment, small round LysM+Blimp-1+ cells (recycling osteoclasts) accumulated. Critically, 3-4 weeks following OPG-Fc withdrawal (OPG:W), recycling osteoclasts had re-fused to form active osteoclasts, resembling stimulation with sRANKL. This increase in osteoclasts with OPG:W resulted in increased serum TRAP and subsequent loss in bone microarchitecture. Following FACS isolation from bone marrow, LysM+CSF1R+ recycling osteoclasts re-fused to form large active osteoclasts in vitro or on ex vivo calvarial explants. RNA sequencing revealed that LysM+CSF1R+ recycling osteoclasts have a unique transcript profile compared to cells which had not fused, suggesting they are a distinct cell population from osteoclast pre-cursors.

These data demonstrate that intravital imaging of the endosteal bone surface reveals novel osteoclast dynamics in vivo. In addition to apoptosis, we visualised osteoclasts recycling their cellular constituents, and using RNAseq defined recycling osteoclasts as a novel cell population. Osteoclast recycling not only provides a new paradigm for understanding the behaviour of these cells in vivo, but importantly, the rapid re-fusion of these cells following withdrawal of RANK inhibition explains the paradoxical acceleration of bone loss and fractures observed upon discontinuation of Dmab.

All welcome!

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