# Diversity of Osteoclasts Contributes to the Modulation of Their Inflammatory Effect and Resorptive Function

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Osteoclasts (OCLs) are not only bone-resorbing cells but also members of the monocytic family. However, their contribution as innate immune cells remained forsaken until recently. In line with their capacity to permanently fuse with monocytic cells or to undergo fission, we recently demonstrated the existence of different subsets of OCLs. All have an antigen-presenting capacity but divergent effects on T-cells. Anti-inflammatory/tolerogenic OCLs (t-OCLs) emerge in steady state from bone marrow monocytes and induce Treg cells. In contrast, inflammatory OCLs (i-OCLs) emerge from inflammatory monocytes and dendritic cells in inflammatory bone destruction and induce TNFa+CD4+ T cells. We identified the fractalkine receptor CX3CR1 as the first marker of i-OCLs. However, only 25% of i-OCLs are CX3CR1+ while 75% are CX3CR1neg. Our projects are focused on this OCL heterogeneity, and more specifically for this study, to determine the function of CX3CR1+ and CX3CR1neg i-OCLs.
Thanks to the procedure we recently established to sort multinucleated OCLs, we purified CX3CR1+ and CX3CR1neg i-OCLs generated from BM-derived DCs and analyzed them in a comparative RNA-sequencing approach. Data revealed two distinct populations of i-OCLs that differ in various pathways including resorption, antigen presentation and T-cell stimulation. In line with these findings, in vitro functional studies confirmed that CX3CR1neg i-OCLs are more efficient to activate TNFa+CD4+ T cells. In contrast, CX3CR1+ i-OCLs expressed high levels of PD-L1 ($p=0.0023$) and were less efficient than CX3CR1neg i-OCLs in T-cell activation ($p=0.0007$). Furthermore, CX3CR1+ i-OCLs suppressed the inflammatory effect of CX3CR1neg i-OCLs, suggesting a negative feedback mechanism of CX3CR1+ i-OCLs in inflammation. Lastly, we showed that CX3CR1+ i-OCLs have a reduced resorption capacity compared to CX3CR1neg i-OCLs ($p=0.0001$), according to our RNAseq analysis. After ovariectomy-associated osteoporosis, we showed that CX3CR1-GFP/GFP mice have less bone loss than CX3CR1-GFP/+ mice ($p=0.0003$) accentuating the role of CX3CR1 in inflammatory osteoclastogenesis.
Our results demonstrate that i-OCLs are heterogeneous and reveal a new mechanism controlling their inflammatory function. While CX3CR1neg i-OCLs have a clear inflammatory effect, CX3CR1+ i-OCLs control this effect through immunosuppression. A profound understanding of CX3CR1 in i-OCLs will help to elucidate molecular mechanisms leading to inflammatory bone destruction.

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