Transcriptional and Epigenetic Regulation of Macrophage Activation and Differentiation

The differentiation and activation of macrophages require the timely regulation of gene expression, which depends on the interaction of various factors, including transcription factors and epigenetic modifications. Epigenetic changes also give macrophages the ability to switch rapidly between cellular programs, indicating the ability of epigenetic mechanisms to affect the activation and differentiation. Previously, we focused on key epigenetic events associated with macrophage tolerance, highlighting events related to the formation of innate immune memory and the reprogramming of macrophage epigenome to promote inflammatory activation. Today, we will discuss RANKL-responsive human osteoclast-specific super enhancers (SEs) and SE-associated enhancer RNAs (SE-eRNAs) by integrating data obtained from ChIP-seq, ATAC-seq, nuclear RNA-seq and PRO-seq analyses. Interestingly, we found increased chromatin accessibility in SE regions, where RNA polymerase II was significantly recruited to induce the extragenic transcription of SE-eRNAs, in human osteoclasts. Knocking down SE-eRNAs in the vicinity of the NFATc1 gene diminished the expression of NFATc1, a major regulator of osteoclasts, and osteoclast differentiation. Our genome-wide analysis revealed RANKL-inducible SEs and SE-eRNAs as osteoclast-specific signatures, which may contribute to the development of osteoclast-specific therapeutic interventions.