Microphthalmia associated transcription factor

The Microphthalmia-associated transcription factor (MITF) is a basic helix-loop-helix leucine zipper family factor that is essential for terminal osteoclast differentiation. Previous work demonstrates that phosphorylation of MITF by p38 MAPK downstream of Receptor Activator of NFkB Ligand (RANKL) signaling is necessary for MITF activation in osteoclasts. The spontaneous Mitf cloudy eyed (ce) allele results in production of a truncated MITF protein that lacks the leucine zipper and C-terminal end. Here we show that the Mitf(ce) allele leads to a dense bone phenotype in neonatal mice due to defective osteoclast differentiation. In response to RANKL stimulation, in vitro osteoclast differentiation was impaired in myeloid precursors derived from neonatal or adult Mitf(ce/ce) mice. The loss of the leucine zipper domain in Mitf(ce/ce) mice does not interfere with the recruitment of MITF/PU.1 complexes to target promoters. Further, we have mapped the p38 MAPK docking site within the region deleted in Mitf(ce) . This interaction is necessary for the phosphorylation of MITF by p38 MAPK. Site-directed mutations in the docking site interfered with the interaction between MITF and its co-factors FUS and BRG1. MITF-ce fails to recruit FUS and BRG1 to target genes, resulting in decreased expression of target genes and impaired osteoclast function. These results highlight the crucial role of signaling dependent MITF/p38 MAPK interactions in osteoclast differentiation [1].

1)

Carey HA, Bronisz A, Cabrera J, Hildreth BE 3rd, Cuitiño M, Fu Q, Ahmad A, Toribio RE, Ostrowski MC, Sharma SM. Failure to Target RANKL Signaling Through p38-MAPK Results in Defective Osteoclastogenesis in the Microphthalmia Cloudy-Eyed Mutant. J Cell Physiol. 2016 Mar;231(3):630-40. doi: 10.1002/jcp.25108. PubMed PMID: 26218069; PubMed Central PMCID: PMC4664053.