MITR IS A SWITCH THAT PROMOTES OSTEOGENESIS AND INHIBITS ADIPOGENESIS OF MESENCHYMAL STEM CELLS BY INACTIVATING PPARγ-2

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Background

EZH2, a catalytic subunit of Polycomb repressive complex 2 (PRC2), is a histone lysine methyltransferase (HKMT) that methylates lysine 27 of histone H3, resulting in gene silencing. It has been shown that EZH2 plays a pivotal role in fostering self-renewal and inhibiting the differentiation of embryonic stem cells. Mesenchymal stem cells (MSCs) can be induced to differentiate into adipogenic and osteogenic lineages, which are mutually exclusive. However, it is not clear whether the molecular events of EZH2-mediated epigenetic silencing may coordinate differentiation between osteoblasts and adipocytes.

Methods

Disruption of the balance between adipogenesis and osteogenesis is associated with many diseases; thus, identifying a switch that determines the MSC's fate is critical. In this study, we used EZH2-ChIP-on-chip assay to identify differential EZH2 targets in the two differentiation stages on a genome-wide scale. After validating the targets, we found that MITR/HDAC9c was expressed in osteoblasts while greatly decreased in adipocytes.

Results

We demonstrated that MITR plays a crucial role in the acceleration of MSC osteogenesis and attenuation of MSC adipogenesis through interaction with PPARγ-2 in the nucleus of osteoblasts, which interrupts PPARγ-2 activity and prevents adipogenesis. Together, our results demonstrated that MITR plays a master switch role to balance osteogenic and adipogenic differentiation of MSCs through regulation of PPARγ-2 transcriptional activity. (JBC in press)