Epistatic connections between microphthalmia-associated transcription factor and endothelin signaling in Waardenburg syndrome and other pigmentary disorders

Kayo Sato-Jin, Emi K. Nishimura, David E. Fisher and Genji Imokawa

Waardenburg Syndrome (WS) is an inherited sensorineural deafness condition in humans due to melanocyte deficiencies in the inner ear and forelock. Mutation of MITF is known to produce WS type IIA whereas mutations of either endothelin (EDN) or its receptor endothelin receptor B (EDNRB) produce WS type IV. However, a link between MITF haploinsufficiency and EDN signaling has not yet been established. We demonstrated mechanistic connections between EDN and MITF and their functional importance in melanocytes. Addition of EDN to cultured human melanocytes stimulated the phosphorylation of MITF in an EDNRB-dependent manner, which was completely abolished by a MEK inhibitor. The expression of MITF-M mRNA transcripts was markedly augmented after incubation with EDN1, and was followed by increased expression of MITF protein. Upregulated expression of MITF was found to be mediated via both the MAPK-RSK-CREB and PKC-PKA-CREB pathways. Additionally EDNRB expression itself was seen to be dependent upon MITF. The functional importance of these connection is illustrated by the ability of EDN to stimulate expression of melanocytic pigmentation and proliferation markers in an MITF-dependent fashion. Collectively these data provide mechanistic and epistatic links between MITF and EDN/EDNRB, critical melanocytic survival factors and Wardenburg Syndrome genes.

Reference:
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