Synopsis of Original Research Paper

Role of Wnt signaling in the regulation of melanin biosynthesis

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Microphthalmia-associated transcription factor (MITF) consists of many isoforms that differ at their N-termini but share a basic helix-loop-helix and leucine-zipper (bHLH-LZ) structure. Among the isoforms, melanocyte-specific MITF (MITF-M) is of particular interest, because expression of MITF-M is under the regulation of the melanocyte-specific promoter (*M* promoter) of the *MITF* gene, and transcription from the *M* promoter is induced by Wnt signals through a nuclear mediator, lymphoid-enhancing factor 1 (LEF-1). Wnt, a group of secretory signaling molecule, evokes a signal to regulate the melanocyte differentiation. The binding of Wnt to its receptor Frizzled leads to inactivation of glycogen synthase kinase-3β (GSK3β), followed by the accumulation of β-catenin and its translocation to nucleus. LEF-1/TCF transcription factors can bind to the β-catenin, and the formed complexes transactivate the target genes. Recently, we have shown that functional cooperation of MITF-M with LEF-1 could lead to transcriptional activation of the *M* promoter and the dopachrome tautomerase (*DCT*) gene, an early melanoblast marker. The bHLH-LZ region of MITF-M is responsible for the physical interaction with LEF-1, and β-catenin is required for the collaboration between LEF-1 and MITF-M. Importantly, MITF-M could function as a non-DNA-binding cofactor for LEF-1. These results suggest that MITF-M may function as a self-regulator of its own expression to maintain a threshold level of MITF-M at a certain sensitive stage of melanocyte development, which could account for dominant inheritance of Waardenburg syndrome type 2 (WS2) that is characterized by deafness and hypopigmentation due to lack of melanocytes in the inner ear and skin. MITF-M therefore plays dual roles in the Wnt signaling pathway; MITF-M represents a downstream target and a nuclear mediator of Wnt signals in melanocytes.