Synopsis of Original Research Paper

Functional analysis of a GAP for Rab32/Rab38 that regulate melanogenic enzymes trafficking in melanocytes

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Rab32 and Rab38 (Rab32/Rab38) have been proposed as regulating the trafficking of melanogenic enzymes, including tyrosinase and tyrosinase-related protein 1 (Tyrp1), to melanosomes in melanocytes. Rab32/Rab38 are known to function as switch molecules that cycle between a GDP-bound inactive form and a GTP-bound active form; the cycle is thought to be regulated by an activating enzyme, guanine nucleotide exchange factor (GEF), and an inactivating enzyme, GTPase-activating protein (GAP), which stimulates the GTPase activity of Rab32/Rab38. Although BLOC-3 has already been identified as a Rab32/Rab38-specific GEF that regulates the trafficking of tyrosinase and Tyrp1, physiological GAP for Rab32/Rab38 in melanocytes has never been identified, and it has remained unclear whether Rab32/Rab38 are involved in the trafficking of dopachrome tautomerase (Dct), another melanogenic enzyme, in melanocytes. In this study, we investigated RUTBC1, which was originally characterized as a Rab9-binding protein and GAP for Rab32 and Rab33B *in vitro*, and the results demonstrated that RUTBC1 functions as a physiological GAP for Rab32/Rab38 in the trafficking of all three melanogenic enzymes in melanocytes. The results of this study also demonstrated the involvement of Rab9A in the regulation of the RUTBC1 localization and in the trafficking of all three melanogenic enzymes. We discovered that either excess activation or inactivation of Rab32/Rab38 achieved by manipulating RUTBC1 inhibits the trafficking of all three melanogenic enzymes. These results collectively indicate that proper spatiotemporal regulation of Rab32/Rab38 is essential for the normal trafficking of all three melanogenic enzymes in melanocytes.