Synopsis of Original Research Paper

Analysis of melanosome transport mechanism by small GTPase Rab27A

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Rab27A is responsible for melanosome transport in melanocytes tethering melanosome to myosin Va, an actin-dependent motor protein, through Slac2-a/Melanophilin. For understanding the precise mechanism of melanosome transport, it is important to clarify how Rab27A is activated/inactivated. Furthermore, the regulatory mechanism of Rab27A is also important based on the clinical standpoint, since mutation in Rab27A causes an inherited disease of human "Griscelli syndrome". Exhaustive screening among TBC domain containing proteins revealed that EPI64 is the GAP (GTPase activating protein; inactivator) of Rab27A. EPI64 inactivates Rab27A in vivo and in vitro and overexpression of EPI64 results in melanosome aggregation in melan-a cells probably through intactivation of Rab27A. Interestingly, there are two close homologues of EPI64, FLJ13130 and mFLJ00332, in mammalian genome including human. Therefore, I investigated functional difference among these three TBC proteins.

As a consequence, I found that FLJ13130 and mFLJ00332 have other functions than EPI64. FLJ13130 inactivated and mislocalized Rab3A in PC12 cells. mFLJ00332 was involved in formation of immunological synapse in T cells. Furthermore, in vitro GAP assay revealed that FLJ13130 exhibited somewhat broad specificity and that mFLJ00332 showed specific GAP activity toward Rab35. These data indicate that there are significant differences even in the closest members among TBC proteins. These basic data will be useful for application to medical care like a drug discovery against EPI64.