Role of Rab32 in Endolysosomal Pathways

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Rab32 is a small Ras-like GTPase that has been implicated in regulating subcellular membrane trafficking events. Emerging evidence suggests that Rab32 also plays a role in innate immune functions and mitochondrial dynamics. Notably, a rare missense mutation in Rab32, resulting in a serine-to-arginine substitution at position 71 (S71R), has been identified in familial cases of Parkinson's disease (PD). This S71R variant is associated with a markedly increased risk of PD by up to 65-fold. Despite this strong genetic link, the molecular mechanisms by which Rab32 and its S71R mutation contribute to PD pathogenesis remain poorly understood. In this study, we demonstrate that Rab32 is predominantly expressed in microglia within the substantia nigra. Immunocytochemistry and subcellular localization experiment reveal that Rab32 localizes primarily to endolysosomal membranes in phagocytic cells. Upon lysosomal damage, Rab32 is rapidly recruited to the compromised lysosomes, a process mediated by its interaction with the lipid raft-associated protein stomatin. While the S71R mutation does not disrupt Rab32's association with stomatin or its recruitment to damaged lysosomes, it significantly enhances the interaction between Rab32 and the PD-associated kinase LRRK2. This aberrant interaction promotes increased LRRK2-mediated phosphorylation of downstream Rab substrates, including Rab10, which has been implicated in vesicle trafficking and inflammatory signaling. Our findings uncover a novel role for Rab32 in the cellular response to lysosomal damage and provide mechanistic insight into how the S71R mutation may potentiate LRRK2 activity, contributing to endolysosomal dysfunction and potentially to pro-inflammatory microglial activation in PD.