A fresh look at the function of Rabaptin5 on endosomes

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Rab GTPases act as organizers of protein networks defining identities and functions of organelles of the endocytic and secretory pathways. Various modes of coordination between different Rabs drive the timely maturation and conversion of membranes. Endosomal Rab5 has been known as the prime example for self-activation via a feedback loop recruiting Rabaptin5, which is complexed with the Rab5 exchange factor Rabex5, and couples to Rab4-GTP. Among other effectors, Rab5 also recruits the Mon1/SAND1-Ccz1 complex that both activates Rab7 and dissociates Rabex5 for Rab5-to-Rab7 conversion of early-to-late endosomes. A detailed deletion analysis now revealed 2 separate binding sites each for Rab4-GTP and Rab5-GTP and indicates a feedforward mechanism of Rab5 activation. Rabaptin5/Rabex5 is recruited to endosomal membranes positive for Rab4-GTP and ubiquitinated cargo (binding to the ubiquitin binding site of Rabex5). This mechanism also suggests additional criteria for Rab5 inactivation concomitant with increasing Rab7-GTP levels. The disappearance of ubiquitinated cargo upon ESCRT-mediated formation of intraluminal vesicles and inactivation of Rab4 may also contribute to loss of Rab5 activation. Rabaptin5/Rabex5 thus may integrate several cues of maturation to perform Rab conversion. Furthermore Rab5 binding to Rabaptin5 appears to prevent uncontrolled progression to late endosomes.
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