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The organelles of the endocytic pathway serve many ‘housekeeping’ functions such as taking up nutrients, controlling signaling pathways and degrading unwanted macromolecules. In addition, these organelles are involved in a diverse range of more specific cellular functions.

The major goals of our research are to gain a better understanding of the biogenesis and functions of two such specialized endosomal organelles: exosomes, which are secreted from multivesicular bodies, and the lysosome-related organelles called melanosomes which synthesize the pigment melanin.

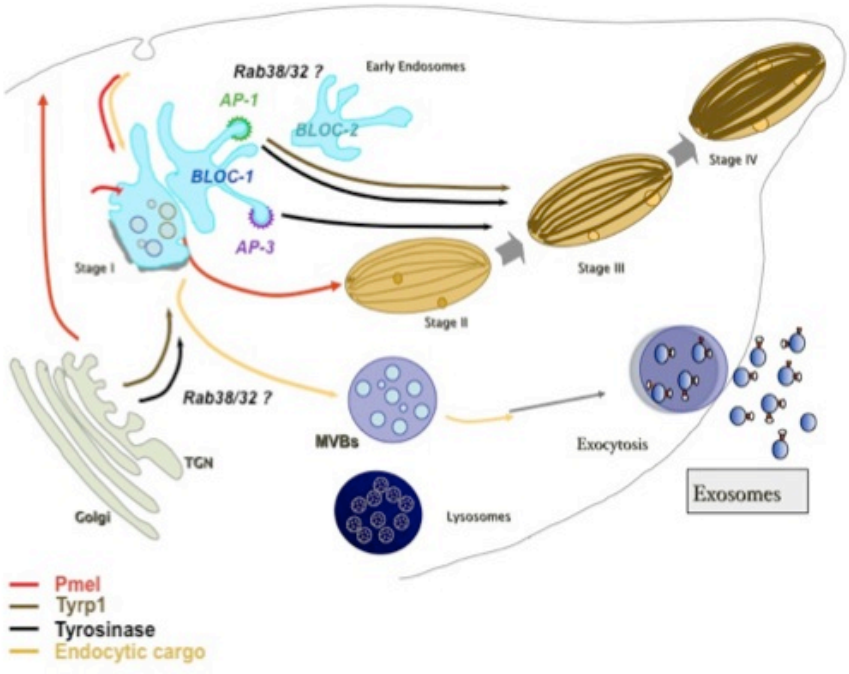

Figure 1: Functional modulations of the endocytic pathway: Melanosomes and Exosomes. Melanosomes originate from the endocytic pathway but remain distinct from lysosomes. PMEL, is transported to Stage II premelanosomes via early endosomes (EE) and Stage I premelanosomes.Tyrosinase and TYRP1 traffic through recycling endosomes to be targeted to the maturing melanosome. Fusion of MVBs with the plasma membrane and exosome secretion is also represented. Adapted from Delevoye et al., Med.Sciences, 2011 and Raposo and Stoorvogel, JCB 2013

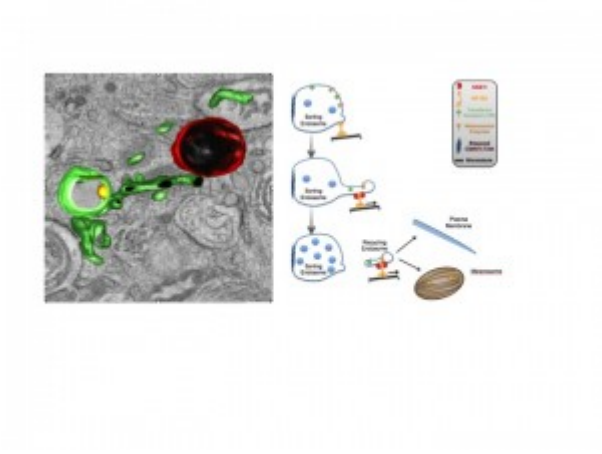

Figure 2: Melanosome maturation requires a close dialogue with specialized Recycling Endosomes Left panel: electron tomography of the endosomal-melanosomal system (endosomes in green, melanosomes in red). Right panel: Representative model of the molecular mechanisms involved in protein sorting and endosome positioning in melanocytes. Delevoye et al., J Cell Biology 2009; Delevoye et al. Cell Rep. 2014.siRNAs and small peptides were developed to inhibit these molecular interactions, which open a path to modulate skin pigmentation in pigmentary disorders.

Our studies are carried out using a variety of human and mouse cell types in culture by combining electron microscopy with light microscopy, biochemistry and siRNA. Melanosomes are cell type-specific membrane-bound organelles within ocular pigment epithelial cells and ocular and epidermal melanocytes in which melanin pigments are synthesized and stored. They are considered “lysosome-related organelles” that have unique morphological and functional features. Among lysosome-related organelles, melanosomes are part of a subclass that coexists with bona fide late endosomes and lysosomes. Over the past years we have addressed the cellular and molecular mechanisms regulating the formation of melanosomes in epidermal melanocytes. Through a fruitful combination of light and electron microscopy, molecular biology and biochemistry, our studies have provided a conceptual framework to decipher novel trafficking pathways that underlie melanosome formation and to understand how different cellular machineries cooperate to control these pathways. Our studies have shed light on the complexity of the endosomal system of melanocytes, the pathogenesis of Hermansky-Pudlak Syndrome (HPS) and related disorders of lysosome-related organelles, the formation of amyloid fibrils in neurodegenerative diseases, and alterations of intracellular trafficking that occur during progression to melanoma. We anticipate that new insights will contribute to the development of novel therapeutic strategies for pigment and neurodegenerative diseases and melanoma.

Key publications

Year of publication 2018

Philip D Stahl, Graça Raposo (2018 May 17)
Exosomes and extracellular vesicles: the path forward.
Essays in biochemistry : 119-124 : DOI : 10.1042/EBC20170088

Guillaume van Niel, Gisela D'Angelo, Graça Raposo (2018 Jan 18)
Shedding light on the cell biology of extracellular vesicles.
Nature reviews. Molecular cell biology : 213-228 : DOI : 10.1038/nrm.2017.125

Frederik Johannes Verweij, Maarten P Bebelman, Connie R Jimenez, Juan J Garcia-Vallejo, Hans Janssen, Jacques Neefjes, Jaco C Knol, Richard de Goeij-de Haas, Sander R Piersma, S Rubina Baglio, Matthijs Verhage, Jaap M Middeldorp, Anoek Zomer, Jacco van Rheenen, Marc G Coppolino, Ilse Hurbain, Graça Raposo, Martine J Smit, Ruud F G Toonen, Guillaume van Niel, D Michiel Pegtel (2018 Jan 18)
Quantifying exosome secretion from single cells reveals a modulatory role for GPCR signaling.
The Journal of cell biology : 1129-1142 : DOI : 10.1083/jcb.201703206

Year of publication 2017

Christin Bissig, Ilse Hurbain, Graça Raposo, Guillaume van Niel (2017 Sep 1)
PIKfyve activity regulates reformation of terminal storage lysosomes from endolysosomes.
Traffic (Copenhagen, Denmark) : 747-757 : DOI : 10.1111/tra.12525

Anand Patwardhan, Sabine Bardin, Stéphanie Miserey-Lenkei, Lionel Larue, Bruno Goud, Graça Raposo, Cédric Delevoye (2017 Jun 14)
Routing of the RAB6 secretory pathway towards the lysosome related organelle of melanocytes.
Nature communications : 15835 : DOI : 10.1038/ncomms15835

Ilse Hurbain, Maryse Romao, Ptissam Bergam, Xavier Heiligenstein, Graça Raposo (2017 May 1)
Analyzing Lysosome-Related Organelles by Electron Microscopy.
Methods in molecular biology (Clifton, N.J.) : 43-71 : DOI : 10.1007/978-1-4939-6934-0_4