Autoregulatory circuit regulating basolateral cargo export from the TGN: role of the orphan receptor GPRC5A in PKD signaling and cell polarity

Rosaria Di Martino¹, Anita Capalbo¹, Lucia Sticco¹, Alessandra Varavallo², Vidya Kunnathully¹, Valentina De Luca¹, Namrata Ravi Iyengar¹, Matteo Lo Monte¹, Petra Henklein², Jorge Cancino³ and Alberto Luini¹*

¹ Institute of Biochemistry and Cell Biology, National Research Council, Via Pietro Castellino 111, 80131 Naples, Italy
² Telethon Institute for Genetics and Medicine (TIGEM), Pozzuoli, Italy.
³ Institut fur Biochemie, Charite Universitätsmedizin, Berlin, Germany.
⁴ Centro de Biología Celular y Biomedicina (CEBICEM), Facultad de Medicina y Ciencia, Universidad San Sebastián, Lota 2465, Santiago 7510157, Chile.

The membrane transport apparatus comprises a series of separate membrane bound compartments, or transport stations, that are responsible for the synthesis, processing, transport, sorting and delivery to their final cellular destinations of most transmembrane and soluble luminal proteins. Over the last decades the membrane transport system has been shown to be extensively regulated both by environmental inputs and by internal homeostatic signalling systems, or control systems, that operate to maintain the homeostasis and optimal functionality of the main transport stations, such as the endoplasmic reticulum and the Golgi, in the face of internal and external perturbations. The trans-Golgi network (TGN) is a major transport and processing station and the main sorting compartment of the transport apparatus. However, the mechanisms that control cargo export and sorting at the TGN have so far remained elusive. Here we focus on the sorting of basolateral cargo proteins and show that these proteins bind to the TGN localized orphan receptor GPRC5A. The cargo-GPRC5A complex triggers the activation of a signaling pathway that involves the Gβγ subunits dependent activation of the phospholipase C beta 3 (PLCβ3), which in turn induces diacylglycerol (DAG) production. DAG recruits and activates protein kinase D (PKD) and the phosphorylation of its substrates. This step results in the formation of basolateral carriers for delivery of these cargoes to the basolateral plasma membrane domain. We term this mechanism “ARTG” (AutoRegulation of TGN export). Remarkably, the impairment of ARTG pathway components, and in particular of GPRC5A, causes defects in the polarized organization of epithelial cells.

References:


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Contacts: rosaria.dimartino@ibbc.cnr.it, alberto.luini@ibbc.cnr.it
Website(s): http://www.ibp.cnr.it/research/alberto-luini
Other: