Research

Protein Trafficking and Cancer Cell Biology

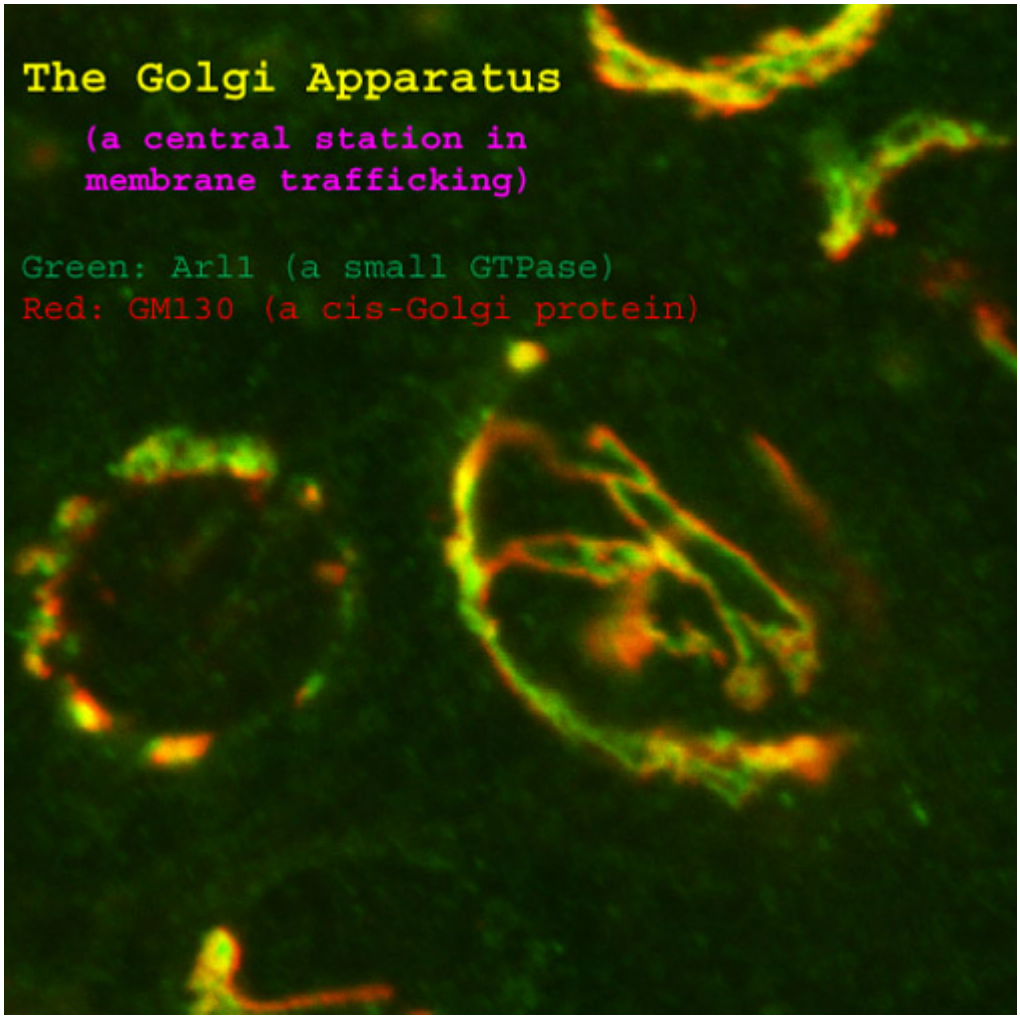
Proteins encoded by the estimated 25,000 human genes must be targeted to the right sites for proper function, and many human diseases arise from defects in the protein trafficking process. Protein traffic in the secretory and endocytic pathways governs many physiological processes such as the synaptic transmission of neurons, regulated exocytosis of the endocrine and exocrine systems, and regulated secretion by many cells in the circulation. Protein trafficking also regulates signalling events and developmental processes. Studying the mechanisms of protein traffic will not only provide new insights into developmental and physiological biology but also offer new strategies to detect and treat human diseases such as diabetes and cancer.

His early works identified the transmembrane domain as the targeting signal for Golgi-localized integral membrane proteins such as β-galactoside α2,6-sialyltransferase and N-acetylglucosaminyltransferase I, as well as the cytoplasmic Tyr-based targeting signal for TGN38. He also revealed that Brefeldin A selectively inhibited apical membrane trafficking in some polarized epithelial cells. His lab cloned the mammalian KDEL receptor and established the functional conservation of the retrograde recycling pathway to retrieve luminal proteins of the endoplasmic reticulum. His lab has contributed significantly to the identification and functional characterization of numerous proteins participating in membrane trafficking in mammalian cells. Half of the 40 or so known mammalian SNAREs, which participate in vesicle fusion events, were independently identified and functionally studied his lab. His collaboration with the Curie Institute has revealed that the VAMP4-Syntaxin6-Syntaxin16-Vti1a SNARE complex mediates retrograde transport from the early endosome to the trans-Golgi network (TGN). Using gene knockout mice, he and his collaborators have established a physiological role for endobrevin/VAMP8 in the regulated secretion by acinar cells of several exocrine organs, and that of several secretory cells in the circulation and kidney collecting duct cells. His lab is among the first few to independently discover that the phox (PX) domain represents a new motif for interacting with phosphoinositides, unveiling a novel mechanism for the cell to integrate diverse cellular processes via a spectrum of about 47 PX domain proteins. His independent and collaborative studies of SNX27 (a PX-domain sorting nexin) using knockout mice suggest that SNX27 may act as part of a general endosomal sorting machinery for membrane proteins (such as GPCRs and ion channels) containing type I PZD-binding motif. Defects in SNX27 impaired the recycling of post-synaptic NMDA receptors. His lab also contributed to the understanding of the molecular mechanisms governing the action of small GTPases such as Arl1, Rab7 and Rab34. His lab was amongst the first few to reveal that Arl1 functions to recruit GRIP-domain Golgin-97 and Golgin-245 on the TGN to regulate endosomal

traffic back to the Golgi apparatus. The collaborative work with Haiwei Song's lab has revealed a novel mode of action of small GTPases in that two Arl1 molecules interact with dimerized effectors. A similar mode of action was also revealed for Rab7 and its effector (RILP). RILP was identified as a common effector for Rab7, Rab34 and Rab36. His works also contributed to the current understanding of COPII in protein export from the ER, COG complex involved in Golgi function and human diseases called congenital disorders of glycosylation (CDG), and Tom1 VHS domain protein family in post-Golgi sorting.

He has also made significant contributions in the field of cancer cell biology. His early works demonstrated that E2F1 is sufficient to confer oncogenic growth. He has identified human Hbrm as a novel interacting protein of the tumor suppressor retinoblastoma protein. His recent work has demonstrated that TAZ is a novel oncogene and is able to promote cell migration, invasion and tumorigenesis. The oncogenic function is dependent on its ability to interact with TEAD transcriptional factors. His lab also uncovered the functional importance of TAZ/YAP interaction with Wbp2, as well as identified Axl receptor tyrosine kinase as a downstream target gene of TAZ/YAP-TEADs in mediating oncogenic events. Angiomotin family proteins were identified as negative regulators of TAZ/YAP. His collaborative works resolved the X-ray structure of YAP-TEAD4 and Vgll1-TEAD4 complexes.

His future studies will focus on the physiological role of two SNAREs (VAMP8 and VAMP5), three PX-domain sorting nexins (SNX3, SNX12 and SNX27) and two small GTPases (Rab34 and Rab36) by analyzing the knockout mice. The mechanism governing the role of TAZ/YAP in promoting invasiveness of breast cancer or other cancers will be studied by focusing on interacting proteins and downstream target genes. This is particularly significant because TAZ and YAP are downstream targets of the Hippo pathway. The objective is to ultimately identify and design novel candidates that will modulate the activity of TAZ/YAP as either anti-cancer drugs or regenerative medicines for tissue repair.


The Golgi Apparatus
(a central station in
membrane trafficking)
Green: Arl1 (a small GTPase)
Red: GM130 (a cis-Golgi protein)