

Cells in our bodies respond to their environment via cell surface receptors. These receptors bind to hormones, growth factors and nutrients to either initiate a signaling cascade or to internalize their ligand for intracellular use. Dr. Suzanne Pfeffer, the recently appointed Emma Pfeiffer Merner Professor of Biochemistry at Stanford University School of Medicine, is studying how human cells deliver receptors to the correct compartments and transport them from one intracellular compartment to another. This process of “membrane traffic” underlies the secretion of all proteins, synaptic transmission, growth control by receptor signaling and the removal of cholesterol-bearing lipoproteins from the plasma. Pfeffer is an internationally recognized expert in this field.

Pfeffer's research aims to elucidate the precise molecular events responsible for membrane traffic, with focus on the master regulators of these events: the Ras-related, Rab GTPases. The human genome encodes more than 60 different Rab proteins that localize to distinct membrane compartments and catalyze the formation of function-specifying membrane microdomains that confer distinct functions to each membrane compartment. In early work, Pfeffer showed that complexes of prenylated Rabs bound to a protein named GDI contain all the information needed for their accurate membrane delivery to a specific membrane compartment (1). Because her work showed that Rabs bind very tightly to GDI, she postulated and demonstrated the existence of a new class of enzymes she named "GDI displacement factors" that displace prenylated Rab GTPases from GDI on specific membrane compartments to accomplish their specific delivery (2). Her work has provided fundamental information regarding the mechanism by which Rab GTPases are localized and function.

Pfeffer studies the transport of mannose 6-phosphate receptors (MPRs) that deliver newly made lysosomal enzymes to lysosomes. After delivering enzymes from the Golgi to pre-lysosomes, these receptors recycle back to the Golgi. Pfeffer was the first to reconstitute the transport of MPRs from endosomes to the Golgi complex in the test tube (3) and her subsequent work led to the discovery of a discrete set of proteins that make this transport possible. She showed that transport requires Rab9 GTPase; Rab9 recruits a cargo selection protein, TIP47, onto endosomes where it binds the cytoplasmic domains of MPRs and likely packages them into transport carriers (4). Her finding that Rab9 increases the affinity of TIP47 for MPR cytoplasmic domains was the first molecular characterization of how a Rab can facilitate cargo selection during transport vesicle formation (5). More recently she has discovered that the AP-1 clathrin adaptor also decorates these vesicles (6).

Pfeffer and her coworkers identified a transport vesicle tethering protein (GCC185; 7) that is needed to capture the vesicles prior to their fusion at the Golgi complex, and the specific SNARE proteins responsible for their subsequent fusion (8). She showed that both Rab and Arl GTPases cooperate to localize this tether to the Golgi and to regulate interactions with SNAREs; together with Axel Brunger's lab, she solved the crystal structure of a portion of GCC185 in complex with two Rab6 molecules (9). She also discovered that the Rho GTPase-related RhoBTB3 protein is actually an ATPase that may uncoat vesicles upon arrival at the Golgi to enable fusion (10).

Pfeffer recently contributed an important new model that resolves long-standing controversies regarding Golgi function (11). This model posits that Rab GTPases control the formation of distinct Golgi compartments. At least 30% of the proteins encoded by the human genome pass through the Golgi, yet we still do not understand how it is formed or how it functions. The predictions of this new model will be important and exciting to test.

Finally, Pfeffer is studying how cells obtain cholesterol from low density lipoprotein (LDL). Cholesterol is released from LDL particles in pre-lysosomes and its transport into the cytoplasm requires two proteins: NPC1 and NPC2. Patients with mutations in either of these proteins develop Niemann Pick Type C disease, a fatal neurodegenerative disorder. Pfeffer recently showed that cholesterol is likely transferred from NPC2 onto NPC1 proteins for its export from lysosomes (12); disease causing mutations interfere with this process. She was able to generate a distinct domain of NPC1 that binds NPC2-cholesterol complexes. With Dr. Kartik Chandran at Albert Einstein she has recently shown that this domain serves as an intracellular receptor required for Ebola Virus entry.

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