The Porosome Secretory Nanomachine: Discovery to Therapy

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Secretion is a highly regulated fundamental cellular process in living organisms, from yeast to cells in humans. Cellular cargoes such as neurotransmitters in neurons, insulin in beta cells of the endocrine pancreas, or digestive enzymes in the exocrine pancreas are all packaged and stored in membrane-bound secretory vesicles that dock and fuse at the cell plasma membrane to release their contents during secretion. Cup-shaped plasma membrane-embedded lipoprotein structure called **porosomes** were first discovered in 1996 in live pancreatic acinar cells using atomic force microscopy (AFM) and subsequently confirmed in all cells examined including neurons using AFM, electron microscopy (EM), and solution X-ray. The porosome exhibits dynamics and its chemical composition demonstrates the utilization of energy in the form of both adenosine and guanosine triphosphate (ATP & GTP), the participation of molecular motors, ion channels, and soluble *N*-ethylmaleimide-sensitive factor activating protein receptor (SNARE) membrane fusion proteins, among others. Porosomes are composed of nearly 30 proteins, and the nanomachine ranges in size from 15 nm in neurons and astrocytes to 100–180 nm in endocrine and exocrine cells. Porosome has been functionally reconstituted into artificial lipid membrane and in live cells. During secretion, secretory vesicles dock at the base of the porosome complex via v-SNARE proteins at the secretory vesicle membrane and t-SNARE proteins at the porosome base. In the presence of calcium, the v-SNARE and t-SNARE proteins in the opposing bilayers interact in a circular array to establish continuity or fusion pores. An increase in volume of the docked secretory vesicle via the rapid entry of ions and aquaporin-mediated rapid entry of water molecules results in increased intra-vesicular pressure, enabling the measured fractional release of vesicular contents from the cell with great precision. Defects in one or more proteins within the porosome complex, have measurable, often highly potent effects on the regulation of secretion, establishing links between secretory defects and disease. With the molecular understanding of porosome-mediated secretion, secretory disease states such as diabetes, cystic fibrosis, cancers and neurological disorders, can now be better managed and novel drugs and therapies developed for treatment.

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