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Porosome: The Universal Secretary Portal in Cells

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In the past 50 years it was believed that during cell secretion, membrane-bound secretory vesicles completely merge at the cell plasma membrane resulting in the diffusion of intra-vesicular contents to the cell exterior and the compensatory retrieval of the excess membrane by endocytosis. This explanation made no sense or logic, since following cell secretion partially empty vesicles accumulate as demonstrated in electron micrographs. Furthermore, with the “all or none” mechanism of cell secretion by complete merger of secretory vesicle membrane at the cell plasma membrane, the cell is left with little regulation and control of the amount of content release. Moreover, it makes no sense for mammalian cells to possess such ‘all or none’ mechanism of cell secretion, when even single-cell organisms have developed specialized and sophisticated secretory machinery, such as the secretion apparatus of *Toxoplasma gondii*, the contractile vacuoles in paramecium, or the various types of secretory structures in bacteria. Therefore, in 1993 in a News and Views article in *Nature*, E. Neher wrote “It seems terribly wasteful that, during the release of hormones and neurotransmitters from a cell, the membrane of a vesicle should merge with the plasma membrane to be retrieved for recycling only seconds or minutes later.” This conundrum in the molecular mechanism of cell secretion was finally resolved in 1997 following discovery of the “Porosome,” the universal secretory machinery in cells. Porosomes are supramolecular lipoprotein structures at the cell plasma membrane, where membrane-bound secretory vesicles transiently dock and fuse to release intravesicular contents to the outside during cell secretion. In the past decade, the composition of the porosome, its structure and dynamics at nm resolution and in real time, and its functional reconstitution into artificial lipid membrane, have all been elucidated. Since porosomes in exocrine and neuroendocrine cells measure 100-180 nm, and only 20-45% increase in porosome diameter is demonstrated following the docking and fusion of 0.2-1.2 μm in diameter secretory vesicles, it is concluded that secretory vesicles “transiently” dock and fuse, rather than completely merge at the base of the porosome complex to release their contents to the outside. In agreement, it has been demonstrated that “secretory granules are recaptured largely intact after stimulated exocytosis in cultured endocrine cells”; that “single synaptic vesicles fuse transiently and successively without loss of identity”; and that “zymogen granule (the secretory vesicle in exocrine pancreas) exocytosis is characterized by long fusion pore openings and preservation of vesicle lipid identity.” In this presentation, the discovery of the porosome, resulting in a paradigm shift in our understanding of cell secretion will be briefly discussed.