Review Letter

Microvesicular secretion, a mode of cell secretion associated with the presence of an ATP-diphosphohydrolase

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The eukaryotic cell generally releases its secretory products in a soluble form, except in a few cases such as mammary gland cells or lung alveolar cells. In exocrine cells, the products are usually stored in large vesicles which, upon secretagogue stimulation, fuse with the plasmalemma and release their contents by a process known as exocytosis. In the pancreas acinar cell, the digestive enzymes are stored in zymogen granules. We have found that under 'resting' conditions the protein composition of the pancreatic juice was different from that of the zymogen granule content from which it was presumably derived [1–6]. This led us to wonder if in addition to exocytosis there was another secretory activity that would substantially contribute to the protein content of the juice. Using freeze-substitution methods we fortuitously detected microvesicles in the lumen of pancreas acini. We termed this type of secretion 'microvesicular secretion' [7]. Microvesicles were isolated from the rat pancreatic juice collected in vivo under resting conditions, and freeze-fracture studies revealed that both their membrane leaflets were devoid of intramembrane particles. Polyacrylamide gel electrophoresis showed that the vesicles contain only one major glycoprotein, which was identified by a Western-blot technique as GP2, a glycoprotein previously localized within the cell. A second glycoprotein was also detected by the same technique, the ATP-diphosphohydrolase. The latter enzyme has been previously purified and characterized in our laboratory [8–10].

Several years ago Rosenberg et al. [11] isolated some microvesicles from the chicken oviduct. The microvesicles are transferred from the outer surface of the epithelial secretory cells to the surface of the ovulated oocyte forming the vitellin membrane complex. These authors studied the protein composition of these microvesicles and found an ATPase activity among these proteins. More recently in a combined research study, our two groups further characterized the ATPase activity from the chicken oviductal secretion. It was found, by a Western-blot technique, that a rabbit antibody to pancreas ATP-diphosphohydrolase cross-reacted with the purified phosphohydrolase from chicken oviductal secretions (approx. 58 kDa).

In a very recent review Ronquist and Brody [12] described organelles that they termed 'the prostasomes'. These organelles were found both in the prostatic fluid and in prostatic epithelial cells. As a rule, the prostasome was surrounded by a trilaminar membrane but sometimes there was a multilaminar architecture. The diameter of the vesicles was approx. 150 nm, which was comparable to the vesicles found in oviductal secretion. More intriguing was the presence of an Mg^{2+}- and Ca^{2+}-dependent ATPase activity. The latter

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phosphohydrolase exhibited a wide substrate specificity, being very active with triphosphonucleosides and much less active with ADP, whereas AMP and inorganic pyrophosphates were not hydrolysed. According to the classification of Dixon and Webb [13], that description would more likely correspond to an ATP-diphosphohydrolase (EC 3.6.1.5). We have found a protein of 58 kDa which cross-reacts with ATP-diphosphohydrolase antibodies in the rat prostate and in a particulate fraction from prostatic fluid. From these studies on three different systems, it appears that normal exocrine cells release some secretory products wrapped into microvesicles. It also appears that, in these three cases, an ATP-diphosphohydrolase is associated with the microvesicles.

One major question raised by these observations is how are these microvesicles extruded from exocrine cells? A second question is what is the role of the ATP-diphosphohydrolase in these microvesicles? In the case of the prostate epithelial cell, prostasomes are found within the intracellular storage vesicles. Ronquist and Brody [12] provided some evidence that these prostasomes could be released by two different mechanisms: by exocytosis, or by diacytosis. In the latter case, the whole storage vesicle would be extruded with its content into the acinar lumen. As for the pancreas microvesicular secretion, there is no morphological evidence to support the concept of diacytosis or exocytosis as a mode of microvesicle release. Even if microvesicles are extruded by diacytosis there remains the question of how the microvesicles enter the intracellular storage vesicle. Such passage, to our knowledge, has never been clearly demonstrated, although some images obtained by Locke and Sykes, with the insect fat body, would indicate that microvesicles (primary lysosomes) pass intact into microvesicular bodies [14].

It is not known to what extent this type of microvesicular secretion is found in animal cells but the fact that it has already been detected in these three secretory systems suggests that it could be widespread. Secondly, it appears that this type of secretion is associated with an ATP-diphosphohydrolase. Finally, the observation that the same type of vesicles are found in the neighbourhood of the spermatozoa and the oocytes suggests that they could play a common physiological role.

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