Getting a G–RRP on regulated exocytosis in the heart

Christopher C. Glembotski

Department of Biology, The SDSU Heart Institute and San Diego State University, San Diego, CA 92182

A study by Rybkin et al. (see p. 527) substantially advances our understanding of regulated exocytosis by specialized secretory cells, such as atrial myocytes. A second member of the Ras-related protein family, RRP17, was identified and shown to participate in regulating the secretion of the cardiac-derived peptide hormone, atrial natriuretic peptide. In addition to the heart, RRP17 was shown to be expressed in neuronal, pancreatic, and skeletal muscle cells, suggesting a widespread role in regulated secretion for this new protein.

Numerous proteins are involved in the docking and fusion of LCDVs with the plasma membrane; some are located on the LDCV membrane, while others are found on the cytosolic face of the target membrane, or in the cytosol. SNAREs (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) facilitate the docking of the LCDVs near the plasma membrane in preparation for the fusion event (Stojilkovic, 2005), while others, such as calcium activated protein for secretion 1, or CAPS1 (Walent et al., 1992) confer calcium dependence to the fusion event. The Ras superfamily of small GTPases, including all Rho family members, Rab, ARF, Gαs, and Ral, are also involved in regulated exocytosis (Pfeffer, 2007).

Rybkin et al. (2007) identified a novel small GTPase in the heart, Ras-related protein on chromosome 17 (RRP17) which is also expressed in brain, pancreas, and skeletal muscle. They also demonstrated that RRP17 can interact with CAPS1, a protein known to mediate LDCV exocytosis, suggesting that RRP17 may also be involved in regulated exocytosis of LCDVs. Consistent with this concept are the similarities in the previously published expression patterns of CAPS1 and RRP17, although CAPS1 expression had not been previously examined in the heart. Rybkin et al. (2007) found that atrial myocytes expressed CAPS1, RRP17, and ANP; however, ventricular myocytes, which do not normally express ANP and are not known to have LCDVs under these conditions, expressed only RRP17 (Table I, Normal heart). This led to the hypothesis that RRP17 might require CAPS1 to participate in regulated exocytosis. The authors used two experimental approaches to examine this hypothesis. In the first, they took advantage of the fact that ANP expression in ventricular myocytes is induced during certain cardiac pathologies, such as pressure overload. In contrast to normal ventricular tissue, they found that CAPS1 and ANP were both expressed in the ventricles of mice subjected to maneuvers that mimic cardiac pathology (Table I, Pathologic heart). The second approach, Rybkin et al. (2007) generated RRP17 knock-out mice and found that, compared with normal mice, the atrial myocytes in the RRP17−/− mice possessed smaller LCDVs. Moreover, the hearts of RRP17−/− mice contained less ANP, and the mice exhibited increased blood pressure, both of which are consistent with roles for RRP17 in the pathway leading to LDCV exocytosis of ANP from the heart.

The study by Rybkin et al. (2007) shows for the first time that a small GTPase, RRP17, can interact with CAPS1, and that RRP17 participates in ANP release from cultured cardiac

Abbreviations used in this paper: ANP, atrial natriuretic peptide; CAPS1, calcium-activated protein for secretion 1; LDCV, large dense-core vesicles.
myocytes, and from the heart, in vivo. But other aspects of RRP17 function are yet to be addressed. For example, recent evidence suggests that CAPS1 plays roles in regulated, as well as constitutive exocytosis (Fujita et al., 2007); thus, as a CAPS1 binding partner, it is possible that RRP17 might participate in both forms of exocytosis. Also, because RRP17 is expressed in ventricular myocytes, even in the absence of CAPS1, perhaps it has CAPS1-independent roles in the release of membrane-bound cargo, or other membrane fusion events. Moreover, as described by Rybkin et al. (2007), the structure of RRP17 is such that it is likely to interact with novel regulators of its GTPase activity, which may reveal new molecular mechanisms of action of this new and growing family of small GTPases. Thus, while much remains to be discovered about RRP17, the study by Rybkin et al. (2007) adds to our understanding of the cell biology of LDCV exocytosis, as well as contributing to the mechanism of peptide hormone release by normal and diseased myocardium, in vivo.

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Table I. Summary of atrial and ventricular myocyte characteristics

|                  | Normal heart | Pathologic heart |
|------------------|--------------|------------------|
|                  | Atria        | Ventricles       | Atria | Ventricles |
| ANP              | +            | –                | +     | –          |
| LDCV             | +            | –                | +     | ?          |
| Reg exocytosis   | +            | –                | +     | +          |
| RRP17            | +            | +                | +     | +          |
| CAPS1            | +            | –                | +     | +          |

This table summarizes the expression of ANP in the atria and ventricles of the normal and pathologic (hypertrophic) adult mouse heart, as well as our current state of knowledge concerning the presence of LDCVs and whether the myocytes in each tissue exhibit regulated exocytosis. Also shown is a summary of the expression of RRP17 and CAPS1 in the two tissues under normal and pathologic conditions, as demonstrated in the study by Rybkin et al. (2007).
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