ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Weibel-Palade Bodies

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H&O What are Weibel-Palade bodies?

JS Weibel-Palade bodies are specialized secretory vesicles that are found in the endothelial cells that line blood vessels throughout the body. They store von Willebrand factor and several other proteins that participate in inflammation, angiogenesis, and tissue repair. George Palade and Ewald Weibel discovered the bodies in 1964, when they performed electron microscopy on endothelial cells from a variety of animals. In 1982, Denisa Wagner and colleagues first showed that Weibel-Palade bodies contain von Willebrand factor, thereby establishing a link between these organelles and hemostasis.

Weibel-Palade bodies have a remarkable shape and structure. They are often described as "cigar-shaped," with a diameter of 0.1–0.3 µm and a length of 1–5 µm. They are surrounded by a standard lipid bilayer membrane. They are quite striking little rods in the cytoplasm of endothelial cells. In cross-section, they appear to be full of loosely packed hollow tubes. In longitudinal section, they appear to have small striations, but in cross-section, they are tubes. These tubules consist almost entirely of von Willebrand factor, which is a large, multimeric protein that can be secreted in response to a number of agonists. The von Willebrand factor propeptide acts as a small, pH-dependent clamp to keep von Willebrand factor packed into tight helical tubules within Weibel-Palade bodies. Whether the propeptide has a biologically important function after secretion into the blood is unknown. The membrane that surrounds the von Willebrand factor and other contents contains a membrane protein called P-selectin—named for "platelet," where it was first identified—that binds to white blood cells.

H&O How do Weibel-Palade bodies affect hemostasis and inflammation?

JS When Weibel-Palade body exocytosis is induced by injury or by treatment with thrombin or other agonists, von Willebrand factor is secreted, and it then binds to endothelial cell surfaces, where it forms long strings that can attract platelets. When the Weibel-Palade body is fused with the plasma membrane, P-selectin concentration there is increased. The P-selectin can mediate the rolling adhesion of leukocytes, which is one component of the inflammatory response to injury.

The number or density per cell of Weibel-Palade bodies varies considerably among different vascular beds. The physiologic significance of these differences is not established, but it may affect the local propensity for thrombosis or the recruitment of leukocytes.

There is another aspect to Weibel-Palade bodies that is relevant to other bleeding disorders. In some endothelial cells, including those in the lungs, factor VIII is stored in Weibel-Palade bodies along with von Willebrand factor and secreted with it. As physicians, we exploit this response therapeutically to treat bleeding in patients with mild hemophilia or von Willebrand disease by administering desmopressin, which causes the secretion of von Willebrand factor, together with factor VIII, from these storage sites and increases the level of these proteins in the blood. The increase in these factors is often enough to stop bleeding in patients with mild to moderate hemophilia or von Willebrand disease.

H&O What is the role of Weibel-Palade bodies in von Willebrand disease?

JS Von Willebrand factor is made in endothelial cells and is targeted to Weibel-Palade bodies. Defects in the assembly and packing of the von Willebrand factor multimer within Weibel-Palade bodies can cause von Willebrand

Table 1. Proteins in Weibel-Palade Bodies

von Willebrand factor	Calcitonin gene-related peptide
Eotaxin-3	Endothelin converting enzyme
Endothelin	α1,3-fucosyltransferase VI
Angiopoietin 2	Tissue-type plasminogen activator
Rab3D	Osteoprotegerin
Rab-27A	P-selectin

Data from Rondaij MG et al. *Arterioscler Thromb Vasc Biol.* 2006;26:1002-1007 and Metcalf DJ et al. *J Cell Sci*. 2008;121:19-27.

disease. In those cases, the secretion of functional von Willebrand factor is impaired, even if the total amount of von Willebrand factor synthesized is not significantly reduced. In severe von Willebrand disease—the kind that affected the children who were discovered by Erik von Willebrand in the 1920s—no von Willebrand factor is synthesized at all, and Weibel-Palade bodies are absent. These patients also do not respond to desmopressin by increasing their factor VIII. So they have a rather severe bleeding disorder: they lack von Willebrand factor and they have relatively low concentrations of factor VIII.

H&O Do Weibel-Palade bodies have any other clinical significance?

JS The contents of Weibel-Palade bodies may also be important for inflammation and tissue healing. Although approximately 95% or more of the proteins in Weibel-Palade bodies are von Willebrand factor, there are other proteins stored there (Table 1). Angiopoietin 2 and a number of cytokines are stored along with von Willebrand factor and released when von Willebrand factor is secreted. These proteins could influence angiogenesis and inflammation after vascular injury. The clinical significance of these molecules in human disease is still under study. However, it is conceivable that inhibitors of Weibel-Palade body exocytosis could be used to treat some inflammatory or thrombotic conditions. Some data in animal models support this notion.

H&O Have there been any recent discoveries in this field?

JS The most exciting recent findings have been made by a combination of cell biology and microscopy methods, which have shown in some detail how von Willebrand factor is packed into Weibel-Palade bodies and some of the ways that it can be secreted. As I mentioned, von Willebrand factor is a long, fibrillar protein—individual molecules may be several tens of micrometers in length—and it is compressed into the Weibel-Palade body in a helical array. An enormously long molecule can be packed into a Weibel-Palade body, with a compression ratio of approximately 50:1 in terms of length. Weibel-Palade bodies can almost be considered little springs stuffed with von Willebrand factor, which—when they fuse with the membrane—spool out to try to catch platelets. This mode of packing has been examined by electron microscopy using purified proteins and in whole cells. These studies, conducted over the past 3 years, have provided very interesting details regarding the internal structure of Weibel-Palade bodies that have important implications for how von Willebrand factor works in hemostasis.

Weibel-Palade bodies can secrete their contents in at least 3 ways. These modes of exocytosis are known as "normal," "a lingering kiss," and "multigranular exocytosis." In normal exocytosis, the protein—the Weibel-Palade body—fuses with the plasma membrane, and the von Willebrand factor, along with everything else, is secreted all at once. Interestingly, simple fusion with the plasma membrane is not enough to expel von Willebrand factor. After fusion, a circumferential ring of actin filaments and myosin II contracts around the Weibel-Palade body and squeezes out the contents. That is the conventional process of exocytosis that dominates when cells are treated with a strong agonist. The "lingering kiss" style of exocytosis involves a transient small pore that forms between the Weibel-Palade body and the plasma membrane; this pore is 10–12 nm in diameter, which is large enough to allow the exit of cytokines, but not of von Willebrand factor or P-selectin. In principle, this process would provide a way to selectively discharge small molecules and perhaps promote inflammation or angiogenesis without involving von Willebrand factor or P-selectin. In the third mode of exocytosis, "multigranular," several Weibel-Palade bodies coalesce inside a large pod, and they then secrete their contents in a very large amount all at once. Why these different modes of exocytosis exist is unknown at the present time, but at least their description provides a substrate for future research.

Suggested Readings

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