Glycoprotein VI: Thrombosis and Collagen Reaction

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Abstract

Platelets normally circulate in the bloodstream in an inactive state. When a blood vessel is damaged and proteins in the extracellular matrix surrounding the blood vessel are exposed, platelets become activated, stick to one another to form a thrombus, and close up the wound. One of the major components of the extracellular matrix is collagen. Glycoprotein VI (GPVI) is a protein that plays a major role in allowing platelets to bind to and become activated by collagen. GPVI is embedded in the membrane of platelets; the extracellular region of GPVI is the section that binds to collagen, whereas the intracellular region is active in sending a signal to the inside of the platelet that enables the platelet to become activated. Activation of platelets by collagen can be beneficial during wound healing but, if platelets are activated and form a thrombus on the inside of a blood vessel, a heart attack or a stroke can result. An example of situation associated with clinical thrombosis complications is the use of coronary angioplasty to open up blocked blood vessels. Patients undergoing coronary angioplasty may have damaged artery walls with exposed collagen, which can cause excessive formation of thrombi that block the blood vessel up again. Researchers in the laboratory of Dr. Debra Newman at BloodCenter of Wisconsin have discovered that individuals who have GPVI deficient platelets exhibit only minor bleeding disorders. They are therefore interested in trying to develop a drug that would shed GPVI molecules from the platelet’s surface so as to treat patients with clinical thrombosis complications, with the expectation that such a drug would not cause major bleeding disorders.

Heart Attack and Stroke Information

- There are about 1.2 million heart attacks in the United States every year.
- There were about 450,000 deaths from heart attacks in the United States in 2004.
- Heart attacks account for about 20% of all deaths in the United States each year.
- There are about 700,000 strokes in the United States every year.
- Strokes account for 1 out of every 15 deaths and ranks third among all causes of death in the United States, behind diseases of the heart and cancer.

Platelets in Thrombus Formation

Figure 1. A schematic diagram of the GPVI/Fcγ chain collagen receptor complex on the surface of a platelet. The extracellular region of GPVI has two immunoglobulin domains (IgD1 and IgD2), which are the only portions of GPVI that are included in the model. The transmembrane and intracellular portions of GPVI interact with the Fcγ chain, which is responsible for transmitting signals into the platelet that activate it upon binding of collagen to IgD1 of GPVI.

GPVI Structure and Function

Figure 2. Effect of thrombus formation on blood flow. When a thrombus forms in an artery, the area for blood flow is lessened. This decreases the amount of blood that flows past the thrombus (reduced blood flow). In addition, rate at which blood flows past the thrombus is increased, which can cause the thrombus to detach from the artery, get carried in the bloodstream to smaller blood vessels, and get stuck (no blood flow). In both cases, the tissue served by the artery is starved for oxygen. When the tissue served is the heart, a heart attack results. When the tissue served is the brain, a stroke occurs.

References

3. Platelet Activation During Thrombosis [http://mail.bris.ac.uk/~pmawp/Thrombus-figure.jpg]

Therapeutic Implications

Exposed collagen in injured blood vessels is a primary stimulus for activation of circulating platelets. Inhibition of platelet responses to exposed collagen, therefore, holds significant promise for prevention and treatment of heart attack and stroke. GPVI is the major activating receptor for collagen on the platelet surface. Therapeutic agents that interfere with the interaction of GPVI with collagen are currently under development. The most well-developed of these agents is an antibody that blocks GPVI-mediated activation of platelets by collagen. Also promising is an antibody that temporarily cleaves GPVI from the platelet surface. Since GPVI deficiency results in only a mild bleeding disorder, this latter type of agent could reduce the risk of myocardial infarction or stroke without creating an intolerable long-term risk of extensive bleeding.

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