Editorial

When Flow Goes Slow, von Willebrand Factor Can Bind Red Blood Cells

Scott L. Diamond

"Stasis, hypercoagulability, vessel wall injury": If you repeat Virchow's triad to yourself a few times, it almost sounds like the definition of clotting rather than the cause of clotting. Still, Virchow's triad is a remarkable predictor of where clotting initiates, specifically during venous thrombosis in the valve pocket. In the body, blood is typically clotting under flow conditions unless it has pooled outside of a broken vessel. Within vessels, the prevailing flow dictates the cellular collision frequency, the collision interaction time, as well as the forces on adhering or aggregating cells. However, when venous flows becomes pathologically slow at <100 s^{-1} wall shear rate (or <1 dyne/cm^2 wall shear stress), the collision rate drops, while the interaction times for adhesive bonding increase, and the forces on those bonds also decrease. Unusual adhesion bonding events may reveal themselves at pathologically low flows that would never exist in physiological venous or arterial flows. Also, at low flow, red blood cells (RBC) can form rouleaux to dramatically increase blood viscosity.

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Apart from hemoglobinopathies and malaria, RBCs were generally considered passive bystanders during thrombosis. Arterial clots often lack RBC, while venous clots were thought to merely entrap the RBC during fibrin polymerization. The passive entrapment of RBC during venous thrombosis was called into question when healthy RBC were shown to bond to activated neutrophils, activated platelets, and clotted plasma at low shear rates.[1] More recently, the role of FXIIIa-mediated cross-linking of fibrin was shown to be essential for RBC retention during clot retraction.[2] In this issue, Smeets et al[3] used pathologically low flows to visualize a new bonding interaction between RBCs and VWF (von Willebrand factor). In thrombosis and hemostasis, VWF is an extremely well-studied polymeric protein known for capture of flowing platelets via glycoprotein Ibα.

Smeets et al found that VWF immobilized on a surface led to capture of RBC at 0.75 dyne/cm^2, an adhesion not seen with albumin or other matrix proteins, such as collagen, fibronectin, fibrinogen, or fibrin. This adhesion was even more abundant on VWF at extremely low shear stresses (0.125–0.5 dyne/cm^2) that remained nonpermissive for RBC adhesion to collagen, fibronectin, fibrinogen, or fibrin. To date, the RBC surface receptor(s) that mediate adhesion to VWF are unknown. Also the subdomains in VWF that mediate RBC adhesion at low flow remain unknown. In a novel observation, the treatment of RBCs with the calcium ionophore, ionomycin, led to a substantial increase in adhesion. Ionophore treatment apparently changes the RBC surface in certain respects, one of which is the exposure of phosphatidylserine as detected with Annexin V. While ionophore treatment is a laboratory protocol, it may offer insights into other pathological processes, such as complement activation or RBC aging. For example, lysophosphatidic acid treatment also enhanced RBC binding to VWF at low shear rates, an effect involving calcium influx. In a remarkable set of immunohistochemical sections of human venous thrombus, the clots were strongly staining for VWF, and RBCs were frequently (but not always) colocalized with this VWF.

The stage is set to understand the molecular mediators of RBC–VWF bonding, the relative roles of platelet-released VWF and plasma VWF and endothelial-released ultralarge VWF, and in vivo enhancers of RBC adhesion to VWF. Such information will aid in identifying the most proximal molecular causes of deep vein thrombosis (the ornamentation on Virchow's triad) and physical/biochemical processes that predispose certain venous clots to embolize.

Disclosures

None.

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