Inflammatory Blues Turns Velvet Skin Into Rawhide
Monocyte Rolling on Modified Endothelial PSGL-1

Rory R. Koenen, Philipp von Hundelshausen, Christian Weber

The directed homing of leukocytes is crucial during immune surveillance or inflammation and is accomplished by a complex cooperation of signaling and adhesion molecules. Its pathophysiologic relevance is exemplified by various inflammatory diseases such as atherosclerosis. At present, the course of leukocyte trafficking is well established through the classical multistep cascade of initial tethering and rolling of leukocytes over vascular endothelium, followed by firm adhesion and their subsequent spreading and transendothelial migration. Leukocyte rolling is mediated by a subgroup of C-type lectins; E-, L-, and P-selectin, through shear-resistant binding to particular cell-surface carbohydrates. E- and L-selectin are expressed on activated endothelial cells and most leukocytes, respectively, while P-selectin is stored in the secretory compartments of platelets and endothelial cells to become rapidly upregulated on cell activation. The best characterized ligand for selectins is P-selectin glycoprotein ligand-1 (PSGL-1), a heavily posttranslationally modified homodimeric transmembrane glycoprotein. PSGL-1 contains functionally essential sialylated and fucosylated carbohydrate moieties, known as sialyl Lewis X (sLex) groups, and is expressed on blood cells such as neutrophils, monocytes, and platelets. The importance of PSGL-1 for cell recruitment is highlighted by studies using transgenic mice deficient in PSGL-1, which revealed a crucial contribution to P-selectin–dependent rolling on inflamed endothelium, indicating a function of PSGL-1 in early inflammatory responses. Presented by endothelium-bound leukocytes, PSGL-1 supports the initial L-selectin–dependent tethering of blood-borne leukocytes to the already adherent leukocytes at the inflamed vessel wall followed by E-selectin-mediated rolling on the endothelium. Besides supporting leukocyte–endothelium interactions, PSGL-1 promotes the P-selectin–dependent initial tethering of platelets to monocytes followed by more stable interactions through integrins expressed on both platelets and monocytes. In addition, the interaction between PSGL-1 and P-selectin also plays an essential role in the delivery of tissue factor to platelet aggregates via PSGL-1–bearing microparticles at sites of vascular injury. Interestingly, engagement of PSGL-1 on monocytes by platelet P-selectin has been shown to induce chemokine synthesis by monocytes, a process that depends on RANTES released by monocyte-adherent platelets. In line with this observation, activated platelets, their secretory products, and platelet-leukocyte aggregates are involved in the development of cardiovascular disease. Of particular interest in this respect is the finding that circulating activated platelets exacerbate atherosclerosis in apolipoprotein E (Apoe)-deficient mice, a process that may be attributable to the formation of platelet-monocyte aggregates, which display increased adherence to atherosclerotic endothelium both by enhanced primary and secondary tethering. In addition, activated platelets have been shown to deposit proinflammatory chemokines onto endothelium leading to increased monocyte arrest and neointima formation after injury in Apoe-deficient mice. A puzzling role in this process is played by platelet P-selectin; platelets deficient of P-selectin neither deposit RANTES nor promote neointima formation and atherosclerosis. Intriguingly, blockade of platelet PSGL-1 or endothelial P-selectin does not affect RANTES deposition, raising the question which counterligand for P-selectin on endothelial cells may be responsible for the proatherogenic effects of platelets. A candidate ligand would be PSGL-1, but so far studies have indicated that endothelial PSGL-1 expression is restricted to certain endothelial cell subtypes or particular (pathologic) conditions.

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A possible explanation for this conundrum is provided by a study from the research group of Zwaginga published in this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, which demonstrates the presence of PSGL-1 on endothelial cells. On human endothelial cells derived from umbilical vein and microvasculature, PSGL-1 was found to be constitutively expressed on the protein level, independent of inflammatory stimuli. Surprisingly, despite similar expression levels of PSGL-1 before and after stimulation with tumor necrosis factor α (TNFα), platelet adhesion and binding of a soluble P-selectin/Fc protein to activated endothelial cells was dramatically enhanced, compared with resting endothelial cells. The accumulation of platelets could be reversed by blockade of either endothelial PSGL-1 or platelet P-selectin with antibodies. These data imply that PSGL-1 on resting endothelial cells exists in a non-functional state only to become active as a cell-recruiting selectin receptor under inflammatory conditions. This notion was further supported by the observation that monocytes and platelet-monocyte aggregates only show rolling and stable interactions with TNFα-activated endothelial cells under flow conditions. Rolling and arrest of platelet-clad monocytes depended on monocyte PSGL-1 and platelet P-selectin, indicating a role for platelet P-selectin in establishing primary interactions with endothelial.
Platelets, monocytes, and platelet-monocyte complexes do not show PSGL-1–dependent rolling on resting endothelial cells under shear flow. Through yet to be identified mechanisms, inflammatory stimuli such as TNFα lead to the expression of sulfated PSGL-1 at the endothelial surface. By binding to platelet P-selectin and monocyte L-selectin, sulfated endothelial PSGL-1 facilitates rolling and stable interactions of monocytes with inflamed endothelium.

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precise characterization of the role of endothelial PSGL-1 in atherosclerosis and other inflammation-related diseases would be desirable.

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**References**
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