Comment on Nimrichter et al, page 3744

E-selectin prefers fatty-sweet receptors on rolling neutrophils

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In this issue of Blood, Nimrichter and colleagues have defined the structure and function of distinct E-selectin ligands on the plasma membrane of neutrophils. They demonstrate that as few as 60 receptors/μm² of these sialylated and fucosylated glycolipids facilitate neutrophil capture and rolling at sites of acute inflammation.

Selectins constitute a highly conserved family of glycoproteins that, as their lectin surname suggests, bind terminal sugars expressed on lipid and protein receptors to mediate adhesive interactions and transmembrane signaling between leukocytes, platelets, and inflamed endothelium. It has long been known that all 3 selectin family members exploit a common biochemical recognition strategy in binding proteins decorated with fucosylated sialyl Lewis sugars. What has remained elusive is the discovery of the E-selectin binding partners on human neutrophils that confer selectivity and affinity and facilitate trafficking at sites of inflammation.

Here, Nimrichter et al have identified a set of protease-resistant sialylated glycosphingolipids with 5 N-acetyllactosamine repeats and 2 to 3 fucose residues that function as major E-selectin receptors on human neutrophils. In order to isolate these so-called myeloycans with E-selectin–binding capacity, plasma membranes were extracted from 10¹⁰ neutrophils, representing a mass purified from nearly 10 liters of whole blood. Glycolipid ligand candidates were resolved by HPLC, adsorbed as membrane monolayers in order to simulate the neutrophil’s outer membrane leaflet, and then, in a reversal of their natural design, their functionality was confirmed based on their capacity to support tethering and rolling of E-selectin expressing cells under fluid shear stress. Using this approach, they found that several glycolipid species supported avid E-selectin–mediated tethering, even when adsorbed at sites densities as low as approximately 60 molecules/μm², whereas P-selectin–expressing cells did not tether or roll at any density. They concluded that very specific classes of sugars decorating lipid moieties can function as high affinity ligands for E-selectin, a major distinction from glycoprotein ligands bound by P-selectin. These data also highlight a fundamental difference in biosynthesis of E-selectin ligands on mouse neutrophils as compared with human neutrophils. Specifically, they found that the fucosyltransferase-7 enzyme, which places fucose on the appropriate sugar for production of functional E-selectin ligands on mouse neutrophils, was not involved in decorating the most active E-selectin binding structures on human neutrophils. This discovery goes a long way toward explaining why major E-selectin receptors on mouse neutrophils are biochemically distinguishable from those on human neutrophils. It also provides insight into the respective function of E-selectin during inflammatory neutrophil recruitment and signaling, which appears to differ between animal species. For example, E-selectin tethering to its ligands during human neutrophil rolling results in the redistribution of L-selectin and PSGL-1 receptors to the cell’s trailing edge. This provides a potent means for inducing the next step of leukocyte recruitment; activation of integrins that facilitate the process of shear resistant arrest and subsequent transmigration across inflamed endothelium under the stress of blood flow. It remains unknown which particular ligands of those that E-selectin recognize are the most important for this outside-in signaling of integrins. However, the study by Nimrichter et al shows unequivocally that sweet lipids represent more than half of the E-selectin receptors on human neutrophils that support trafficking to sites of acute inflammation. Such information may be used to repair fucosylation defects in the immune-deficit disease, Leukocyte Adhesion Deficiency II or to design strategies to tune down inflammation in autoimmune disorders.

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Comment on Steele et al, page 3827

Suppressing the tumor suppressor in CLL?

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In this issue of Blood, Steele and colleagues present a series of elegant experiments that illuminate a p53 transcription-independent mechanism of apoptosis induction in primary CLL cells.

As is the case in most human cancers, loss of function or deletion of the p53 tumor suppressor gene signals bad news in chronic lymphocytic leukemia (CLL). The reasons for this are complex, but clearly the majority of current treatments induce apoptosis via a p53-independent pathway. Although p53 has been traditionally considered a transcription factor, there is growing evidence that it also causes extranuclear effects that can induce powerful cellular responses independent of de novo gene transcription. In this issue of Blood, Steele et al present compelling evidence that CLL cells preferentially employ a transcription-independent mechanism of apoptosis. They demonstrate that treatment-induced p53 is predominantly found in the mitochondrial fraction of cell extracts and is associated with the antiapoptotic protein Bcl-2. Furthermore, they show that the p53 transcription-blocking agent pifithrin α can enhance chlorambucil- and fludarabine-mediated apoptosis. This
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