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Targeting P-selectin ligands: ushering in a new treatment paradigm for Sickle Cell Disease

Abstract

Sickle cell disease (SCD) is a debilitating systemic disease with limited treatment options for disease-related complications. Microvascular vaso-occlusion is the hallmark of the disease with profound morbidity and increased mortality. Vaso-occlusion underlies intricate pattern of complications related to hyper-adhesiveness of circulating blood cells and endothelium. Over-expression of P-selectin is central to initiation of the vaso-occlusive cascade by downstream engagement of multiple adhesion receptor/ligand pairs. Blocking P-selectin has been shown to effectively prevent vaso-occlusion by blocking these adhesive interactions. However, the model of the E-selectin inhibitor uproleselan in acute myeloid leukemia (AML) should instigate the development of similar agents that target selectin-ligand adhesive interactions in order to attenuate the clinical effects of vaso-occlusion. Interestingly, the sialylated and fucosylated tetrasaccharide sialyl Lewis(X) (sLeX) was found to be the glycan (carbohydrate) determinant for selectin binding. Therefore, novel synthetic lectins that target glycan determinants on P-selectin-ligands could prove more precise and efficient drugs, not only for prevention, but also for treating patients with vaso-occlusion crises (VOCs).

Keywords: vaso-occlusion, p-selectin, crizanlizumab, psgl-1, slex, artificial lectins

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The key role of P-selectin in vaso-occlusion

The sickle hemoglobin molecule, designated HbS (α2 βs 2), results from substitution of the neutral amino acid valine for glutamic acid by a single missense mutation (Glu6Val) in the β-globin gene. In the deoxygenated state, the substituted β6 valine leads to HbS polymerization into a rope-like structure of inter-twined fibre-pairs causing chronic hemolytic anemia. The second pathobiological manifestation of SCD is endothelial dysfunction resulting in a constant proinflammatory, procoagulant, and prothrombotic state. Chronic hemolytic anemia and endothelial dysfunction/chronic inflammation ultimately result in microvascular occlusion.[1] Microvascular occlusion is the principal indicator of increased severity of SCD. Microvascular occlusion is implicated in the development of VOCs including acute painful crisis, acute chest syndrome and acute ischemic stroke.[2] VOCs are among the most common causes of death in patients with SCD.[3] Perpetuating cycles of intermittent microvascular occlusions eventually leads to microvascular dysfunction attributable to ischemia-reperfusion injury, and finally tissue damage.[4,5]

Adhesion of sickle red blood cells (RBCs) and leukocytes to the endothelium is the harbinger of vaso-occlusion, which ultimately lead to vascular obstruction and tissue ischemia.[6] The severity of vaso-occlusion is directly proportional to the degree of sickle RBC adhesion. Deformed sickle RBC membrane becomes sticky and more prone to adhere to the endothelium through the RBC adhesion molecules, such as CD36 and integrin α4β1. Both adherent sickle RBCs and scavenged nitric oxide driven by hemolysis provoke endothelial activation that causes up-regulation of adhesion molecules including vascular cell adhesion molecule (VCAM)-1 and selectins (eg, P-selectin) that initiates the adhesion of leukocytes (most notably neutrophils) to the endothelium. Translocation of endothelial P-selectin stored in Weibel-Palade bodies of endothelial cells that line blood vessels to the cell membrane results in the prompt adhesion of sickle RBCs to vessels and the development of vascular occlusion. Moreover, translocation of P-selectin stored in α-granules in platelets to the cell surface leads to platelet activation. The activated platelets bind to neutrophils to form arteriolar neutrophil-platelet microemboli that induce pulmonary vaso-occlusion.[7]

P-selectin inhibition in patients with SCD

The idea that blockade of P-selectin could reduce the risk of vaso-occlusion was conceptualized on observations in transgenic mice with SCD who were protected from VOCs when they are deficient in P-selectin and E-selectin with resultant defective leukocyte recruitment to the vessel wall.[8] P-selectin blockade was also shown to significantly reduce the sickle RBCs and leukocytes adherence to the endothelium in transgenic mice with SCD.[9,10] Moreover, P-selectin blockade by heparin was sufficient to improve microvascular blood flow in patients with SCD.[11] The rationale of P-selectin blockade led to the development of crizanlizumab, a humanized monoclonal antibody (mAb) that binds to and inhibits P-selectin by blocking its interaction with its ligand, P-selectin Glycoprotein Ligand-1 (PSGL-1). Its efficacy was evaluated in SUSTAIN trial (NCT01895361), which found that crizanlizumab therapy resulted in a significantly lower rate of vaso-occlusive pain crises than placebo and was associated with a low incidence of adverse events in 198 patients with SCD.[12] On November 15, 2019, crizanlizumab was granted approval by the Food and Drug Administration (FDA) for reducing the frequency of VOCs in adults and pediatric patients with SCD (aged 16 years and older). Although crizanlizumab seems very promising, several important caveats should be considered. First, crizanlizumab can only be administered intravenously once every 3–4 weeks which might not be convenient for many patient and/or their families. Second, several postmarketing cases of infusion-related reactions (IRRs) mimicking severe vaso-occlusive pain crises that required hospitalization has been reported during or within 24 hours of the infusion.[13,14] Third, although crizanlizumab might be effective at preventing vaso-occlusive pain crises in SCD, it may not be useful as a treatment. The effect of crizanlizumab in reducing the risk of thromboses and preventing the development of acute chest syndrome were not adequately addressed in SUSTAIN trial.[15]

The P-selectin/PSGL-1 axis in SCD

Activated endothelial cells have P-selectin being exposed at the lumen of the vessel which initiates endothelial P-selectin interaction with its ligand P-selectin Glycoprotein Ligand-1 (PSGL-1) on leukocytes. Despite its name, PSGL-1 also binds L- and E-selectins with similar affinity as with P-selectin. PSGL-1 (sialomucin, CD162), a disulfide-bonded homodimeric type I transmembrane mucin-like glycoprotein, is the most important selectin ligand on leukocytes. The dimerization of PSGL-1 facilitates tethering to P-selectin under shear stress. The repetitive process of binding and release between endothelial P-selectin and leukocyte PSGL-1 being propelled by flowing blood constitutes the first step of leukocyte migration (leukocyte rolling). P-selectin-PSGL-1 interaction is also important for the GPCR-independent activation of integrins (adhesion molecules expressed on leukocytes that mediate firm adhesion to the endothelium prior to extravasation). Almost all leukocytes express PSGL-1 on their cell surface, but not all PSGL-1 on leukocytes cell surface can bind selectins. High affinity binding of the lectin domain of P-selectin to PSGL-1 requires sLeX-capped *O*-glycans to make PSGL-1 a functional selectin ligand.[16] This is regulated by a series of glycosyltransferases and sulfotransferases required for the biosynthesis of the selectin-binding sLeX structure.[17]

Selectins are vascular cell adhesion molecules (VCAMs) belonging to the C-type (calcium-dependent) transmembrane lectin family with well-characterized roles in homing and tissue recruitment of leukocytes. They mediate adhesive interactions between leukocytes and the endothelium to facilitate entry to secondary lymphoid organs and sites of inflammation during normal and abnormal inflammatory episodes. The three members of selectins are expressed on platelets (P-selectins), leukocytes (L-selectins) and endothelial cells (E- and P-selectins). Selectins share the ability to recognize sLeX and its isomer sialyl Lewis(A) (sLeA). sLeX is a terminal component of glycoconjugates on most circulating leukocytes and sLeA is restricted to some tumor cells but does not occur on normal leukocytes.[18]**.** Both sLeX and sLeA are sialylated Lewis glycan antigens, that mediate the adhesion between tumor cells and the endothelium[19] and their expression was shown to facilitate the arrest of circulating tumor cells on endothelial cells and is strongly associated with increased metastatic potential.[20] Hence, therapies targeting the P-selectin/PSGL-1 axis have been investigated in SCD, cancer cell metastasis and BM transplantation. P-selectin has also been considered a risk factor for recurrent thromboembolism and cardiovascular disorders and P-selectin inhibition using a recombinant P- selectin ligand decreased thrombosis in non-human primate animal models.[21,22]

Targeting glycan determinants on P-selectin-ligands

The success of crizanlizumab should evoke development of different biological agents that intercept the interactions between leukocytes and endothelial cells/platelets. PSGL-1 is a basically a glycoconjugate where the glycan sLeX is covalently linked to protein (sialoglycoprotein). In order to bind selectins efficiently, selectin-reactive carbohydrates must be presented on protein scaffolds of PSGL-1. It is now evident that sLeX is a key determinant of PSGL-1/P-selectin interactions. Therefore, these glycan structures are appealing targets for development of novel targeted therapies. This had led to the development of a new class of small molecular weight lectin antagonists; known as glycomimetics which are pharmaceutical drugs mimicking glycan structures. For example, uproleselan (GMI-1271), a novel E-selectin antagonist, showed promise in a phase I/II trial of uproleselan in combination with chemotherapy for AML, leading to the initiation of a phase III trial (NCT03616470).[23] E-selectin inhibition prevents leukemic stem cells from adhering to hematopoietic stem cells (HSCs) niche before coming quiescent and resistant to conventional chemotherapy giving rise to residual disease which is the most prominent cause of disease relapse.[24,25] Noteworthy, crizanlizumab was created on the wrecks of a previous glycomimetic drug: the pan-selectin inhibitor, rivipansel, which despite demonstrating a decrease in the time to resolution of vaso-occlusion and reduced opioid use in patients with acute sickling crises at phase II trial (NCT01119833)[26], failed to meet its primary end points in mid-2019 at the phase III trial (NCT02187003). However, a post hoc analysis proved that selectin inhibitors may still be useful for vascular disease as patients who received the drug early after the start of pain from vaso-occlusion (within 26 hours) had pain relieved.[27] his delineates the utmost importance of precise selectin inhibition in order to mount a clinically-significant response. Within this context, it is likely that the vast expression of PSGL-1 (not only on leukocytes but also on human hematopoietic progenitor cells), may indicate that targeting PSGL-1 by mAbs could result in many off-target side effects.

More precise (and potent) selectin antagonism can be achieved by creating artificial lectins that target the sLeX-capped *O*-glycans in PSGL-1. Lectins are glycan-binding immunoglobulin-like proteins that can be generated through the current state-of-the-art lectin engineering (protein engineering technology aiming at producing artificial lectins) technologiesis where various methods by which lectin specificity and/or stability of a known lectin scaffold can be improved.[28] In addition, recombinant DNA technology can also be employed as a means of producing pure and sequence-defined anti-sLeX-capped PSGL-1 lectins.[29] In summary, by targeting selectin-ligands, engineered lectins would conceivably be efficient targeted therapies where inhibiting selectins is crucial in the management. This includes diseases like SCD, inflammatory skin disorders, acute myocardial infarction, atherosclerosis, glomerulonephritis, systemic lupus erythematosus, stroke and malignancies.[30]

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Conflicts of interest

The authors declare no conflicts of interest.

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