REVIEW ARTICLE

Targeting P-selectin glycoprotein ligand-1/ P-selectin interactions as a novel therapy for metabolic syndrome

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Obesity-induced insulin resistance and metabolic syndrome continue to pose an important public health challenge worldwide as they significantly increase the risk of type 2 diabetes and atherosclerotic cardiovascular disease. Advances in the pathophysiologic understanding of this process has identified that chronic inflammation plays a pivotal role. In this regard, given that both animal models and human studies have demonstrated that the interaction of P-selectin glycoprotein ligand-1 (PSGL-1) with P-selectin is not only critical for normal immune response but also is upregulated in the setting of metabolic syndrome, PSGL-1/P-selectin interactions provide a novel target for preventing and treating resultant disease. Current approaches of interfering with PSGL-1/P-selectin interactions include targeted antibodies, recombinant immunoglobulins that competitively bind P-selectin, and synthetic molecular therapies. Experimental models as well as clinical trials assessing the role of these modalities in a variety of diseases have continued to contribute to the understanding of PSGL-1/P-selectin interactions and have demonstrated the difficulty in creating clinically relevant therapeutics. Most recently, however, computational simulations have further enhanced our understanding of the structural features of PSGL-1 and related glycomimetics, which are responsible for high-affinity selectin interactions. Leveraging these insights for the design of next generation agents has thus led to development of a promising synthetic method for generating PSGL-1 glycosulfopeptide mimetics for the treatment of metabolic syndrome. (Translational Research 2016;■:1–13)

Abbreviations: PSGL-1 = P-selectin glycoprotein ligand-1; JNK = c-Jun N-terminal kinases; NF-κB = nuclear factor-κB; ACE-I = angiotensin converting enzyme inhibitors; TLR2 = toll-like receptor 2; SPM = specialized pro-resolving mediator; PPAR-α = peroxisome proliferator-activated receptor alpha; MCP-1 = monocyte chemoattractant protein 1; ICAM = intracellular adhesion molecule 1; VCAM = vascular cell adhesion protein 1; GSP = glycosulfopeptide; EGF = epidermal growth factor; SCR = short consensus repeat; EC = endothelial cell; MPO = myeloperoxidase; rPSGL-Ig = recombinant P-selectin glycoprotein immunoglobulin; NO = nitric oxide;

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CHO = Chinese hamster ovary; cDNA = complementary DNA; sLe^X = sialyl Lewis X; PSALM = P-Selectin Antagonist Limiting Myonecrosis; TIMI = thrombolysis in myocardial infarction; sLe^A = sialyl Lewis A; ST = sialyltransferase; PLGA = poly(lactic-co-glycolic acid); C2 = core-2

INTRODUCTION

The metabolic syndrome, characterized as a collection of risk factors for atherosclerotic cardiovascular disease and type 2 diabetes, is driven by excess energy intake and obesity.[1] The five interrelated factors comprising the syndrome are atherogenic dyslipidemia, elevated blood pressure, glucose intolerance and insulin resistance, a pro-thrombotic state, and a pro-inflammatory state.[2] Primarily, management of metabolic syndrome focuses on lifestyle modifications, such as weight reduction and increased physical activity.[3] In patients with persistent risk factors, further treatment with lipid lowering agents, antihypertensives, and antiplatelet agents help reduce the risk of cardiovascular disease, whereas drugs to reduce serum glucose and improve insulin sensitivity can be used to treat resultant diabetes.[2] Currently, despite a prevalence of 20–30%, therapies to prevent the development of cardiovascular disease and diabetes due to obesity-induced metabolic syndrome are lacking.[2]

Mechanistically, a state of chronic inflammation has been suggested to underlie metabolic syndrome.[4] Specifically, obesity-induced immune cell infiltration of adipose tissue has been found to be a significant factor in the development of insulin resistance, type 2 diabetes, hepatosteatosis, and atherosclerosis.[5-11] Broadly, the inflammatory response includes monocytes,[8,12-16] neutrophils,[17,18] T cells,[19-22] B cells,[23,24] mast cells,[25] and eosinophils,[26] with the extent of metabolic dysfunction directly correlating with the activation of pro-inflammatory cytokines and chemokines,[27-29] as well as the modulation of inflammatory pathways such as the c-Jun N-terminal kinases (JNK) and nuclear factor-κB (NF-κB) transcription factor.[30,31]

In view of this, attempts to develop targeted therapies that modulate the inflammatory cascade as it pertains to metabolic syndrome, are ongoing.[4] Examples of such anti-inflammatory agents include statins and angiotensin converting enzyme inhibitors (ACE-I), which suppress the production of the pro-inflammatory Th1 and Th17 cells[32,33]; apolipoprotein C-III inhibitors that prevent toll-like receptor 2 activation (TLR2)[4]; omega-3 fatty acids that can be converted to specialized pro-resolving mediators (SPMs)[34,35]; and peroxisome proliferator-activated receptor alpha (PPAR-α) agonists, which promote suppression of monocyte chemoattractant protein 1 (MCP-1), intracellular adhesion molecule 1 (ICAM), vascular cell adhesion protein 1 (VCAM),[36] and NF-κB.[37] In addition, in randomized clinical trials, the anti-inflammatory drug salsalate has been found to improve insulin sensitivity and inflammatory parameters,[38] as well as glucose and triglyceride levels.[39] In a subsequent multicenter trial, a reduction in blood glucose, diabetes medication, and markers of cardiovascular risk were noted over a 48-week interval in patients with type 2 diabetes.[40] A sustained improvement in insulin sensitivity, along with a reduction in markers of systemic inflammation, has also been reported in response to an IL-1 receptor antagonist.[41] Although the magnitude of glucose lowering has been modest in response to both salsalate and IL-1β blockade, these studies suggest that targeting inflammation is a valid strategy for the prevention and treatment of the adverse metabolic effects of obesity. With the inflammatory pathway continuing to evolve as a focus for the prevention and treatment of obesity-induced insulin resistance, diabetes, and cardiovascular disease, new promising targets have been identified and warrant review.

In this article, targeting the interaction of P-selectin glycoprotein ligand-1 (PSGL-1) with selectin will be discussed as a novel therapeutic strategy for metabolic syndrome. Specifically, PSGL-1 and selectin interactions in inflammation will be reviewed, with a specific emphasis on their role in the pathophysiology of obesity-induced metabolic syndrome. Importantly, current strategies of blocking PSGL-1/P-selectin interactions will be discussed and next generation synthetic approaches of creating PSGL-1 glycosulfopeptide (GSP) mimetics will be considered.

PSGL-1/P-SELECTIN INTERACTIONS AS MEDIATORS OF OBESITY-INDUCED INFLAMMATORY RESPONSES

PSGL-1 is a glycoprotein that is expressed on the surface of all leukocytes and supports leukocyte recruitment as a component of a range of inflammatory responses.[42-46] Structurally, PSGL-1 is a membrane protein with a disulfide-linked homodimer that has a mucin ectodomain with serine, threonine, and proline repeats that are sites for potential O-glycan modification.[46] PSGL-1 is a ligand for endothelium-selectin (E-selectin, CD62L), platelet-selectin (P-selectin, CD62P), and leukocyte-selectin (L-selectin, CD62L), but binds with highest affinity to P-selectin.[47,48]