European Journal of Medicinal Chemistry 92 (2015) 353–369

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Invited review

Sulfated glycans in inflammation

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ARTICLE INFO

Article history:
Received 18 October 2014
Received in revised form
31 December 2014
Accepted 2 January 2015
Available online 3 January 2015

Keywords:
Carbohydrate-based drug development
Fucoidan
Fucosylated chondroitin sulfate
Glycosaminoglycans
Heparin
Inflammation

ABSTRACT

Sulfated glycans such as glycosaminoglycans on proteoglycans are key players in both molecular and cellular events of inflammation. They participate in leukocyte rolling along the endothelial surface of inflamed sites; chemokine regulation and its consequential functions in leukocyte guidance, migration and activation; leukocyte transendothelial migration; and structural assembly of the subendothelial basement membrane responsible to control tissue entry of cells. Due to these and other functions, exogenous sulfated glycans of various structures and origins can be used to interventionally down-regulate inflammation processes. In this review article, discussion is given primarily on the anti-inflammatory functions of mammalian heparins, heparan sulfate, chondroitin sulfate, dermatan sulfate and related compounds as well as the holothurian fucosylated chondroitin sulfate and the brown algal fucoidans. Understanding the underlying mechanisms of action of these sulfated glycans in inflammation, helps research programs involved in developing new carbohydrate-based drugs aimed to combat acute and chronic inflammatory disorders.

1. Introduction

Inflammation is a reactive response of the body to harmful stimuli. This protective action is primarily achieved by the increased movement of defense cells from the bloodstream into injured or infected tissues. Inflammation is overall regulated by a cascade of many molecular interactions and biochemical reactions responsible to propagate and mature the inflammatory response. It involves the local vascular system, the immune system, and various cell types. The major events of inflammation are intimately regulated by both structure and function of a series of glycoconjugate carbohydrates, especially those coating the endothelial and leukocyte surfaces [1,2]. The carbohydrate moieties with functional roles in inflammation are essentially the *O*-linked tetrasaccharide Sialyl-Lewis^X motif of P-selectin glycoprotein ligand-1 (PSGL1) on the leukocyte surface, and the sulfated glycosaminoglycans (GAGs), such as heparan sulfate (HS), dermatan sulfate (DS) and chondroitin sulfate (CS) heavily distributed as lateral chains of proteoglycans (PGs) at both leukocyte and endothelial cell surfaces.

The PSGL1 in leukocytes is responsible to interact with platelet (P)-selectin molecules displayed at the surface of activated endothelial cells (Fig. 1). The endothelial cells are activated by cytokines released from resident macrophages of the inner tissues after encountering an inflammatory stimulus such as an infectious agent like a bacterium. The PSGL1-P-selectin interaction is a molecular complex in charge to enable the first leukocyte contact and adhesion onto the endothelial layer [3] (Fig. 1). Endothelial-cell (E)-selectin expression may also be induced on the surface of endothelial cells by cytokine activity released in the inner tissue. Although PSGL1 can bind to all members of selectin, P-, E- and leukocyte (L)-selectins, the highest affinity is for P-selectin [1,2]. The interaction of PSGL1 with its ligands (primarily P-selectin) also initiates leukocyte rolling on the endothelial surface of inflamed areas. The leukocyte rolling is thereafter regulated, and further stabilized by leukocyte L-selectin binding to GAGs (mainly HS) of the endothelial-cell PGs. Regulation of the leukocyte rolling on the endothelial surface is one of the first roles of the sulfated GAGs in inflammation [2] (Fig. 1).

Another initial activity of GAGs in inflammation is the transcytosis of chemokines across the endothelial-cell layer. Upon interaction with the inflammatory stimulus, inflamed tissue-resident macrophages release great amounts of chemokines, particularly interleukin (IL)-8, also known as CXC-chemokine ligand (CXCL)-8 [4]. The released chemokines, which express clusters of positively charged amino acid at their tertiary structures,

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http://dx.doi.org/10.1016/j.ejmech.2015.01.002
0223-5234/

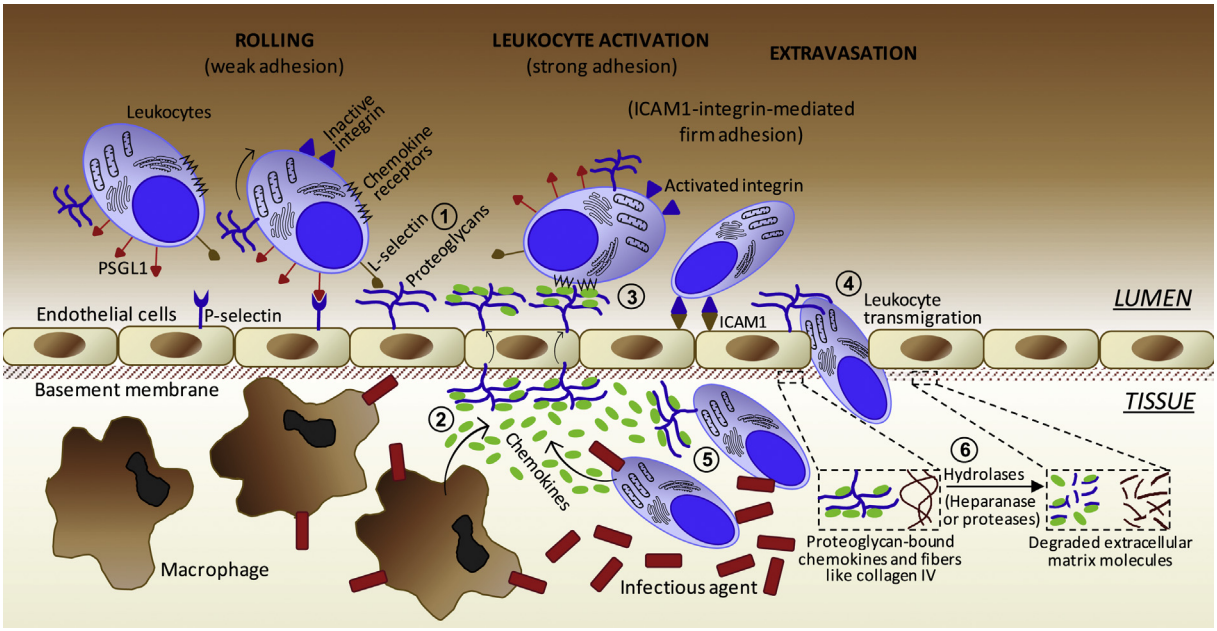

Fig. 1. Schematic representation of the major players and events involved in inflammation. In response to a certain inflammatory stimuli, such as a bacterial infection, resident macrophages in inner tissues produce both chemokines that attract leukocytes into these inflamed tissues, and cytokines (such as tumor necrosis factor, TNF) that trigger, at the early stages, the display of pre-formed P-selectins on the luminal surface of endothelial cells (the cytokine-induced P-selectin exposure pathway is not shown). Cytokines can also induce the expression of E-selectin by endothelial cells (not shown). Glycosaminoglycans at endothelial proteoglycans play essential roles in inflammation such as L-selectin binding (**1**); in chemokine attachment at the inflamed tissue (**2**), transcytosis, and presentation to chemokine receptors on leukocytes on the lumen of the blood vessel (**3**); leukocyte transendothelial migration (**4**); interaction of infiltrated leukocytes with released chemokines at the inner tissue (**5**); and partial degradation of the extracellular matrix molecules of the underlying endothelial basement membrane (**6**). P-selectin glycoprotein ligand-1 (PSGL1), P- and L-selectins, heparan sulfate proteoglycans, integrin, and intercellular adhesion molecule 1 (ICAM1) are important endothelial or leukocyte cell-membrane proteins involved in weak adhesion, rolling and firm adhesion during the processes of leukocyte recruitment and migration.

bind to PG-linked sulfated GAGs located at the endothelial basement membrane [5–7] (Fig. 1). After transcytosis, the chemokine-bound PGs enable leukocyte recruitment and trafficking along the endothelial surface [8–10]. In fact the chemokine released from macrophage are structurally and functionally organized by endothelial surface GAGs in a functional arrangement that facilitates both guidance and proper migration of the leukocytes. This arrangement relies on the process of protein (chemokine) multimerization and gradient formation. Each particular chemokine multimerize within different association levels [8–10]. The GAG-bound chemokines are also responsible to further activate leukocytes via molecular interaction with the G protein-coupled receptors displayed at the leukocyte surfaces [8–11] (Fig. 1). This activates in turn integrin at the surface of the leukocytes. Activated integrin is able to interact with intercellular adhesion molecule-1 (ICAM1) on the endothelial surface [2]. The activated integrin-ICAM1 intermolecular complex leads to a stronger and more stable leukocyte adhesion onto the endothelium [2] (Fig. 1), which consequently slows down the leukocyte rolling. The chemokine-mediated leukocyte activation also triggers the necessary morphological changes on this cell type in order to allow its transmigration through the endothelial barrier (diapedesis). Endothelial-cell GAG PGs, mostly HS, play roles in this migration process (Fig. 1) likely regulating other signaling proteins, such as kininogen, which in turn works on vascular permeability [12]. The strong leukocyte–endothelium interaction driven by the active-integrin-ICAM1 complex helps the success of the transendothelial migration [13]. Once leukocytes have completed transendothelial migration, they become able to interact with more chemokines immobilized at the underlying basement membrane [2] (Fig. 1). These chemokines are presented to the infiltrated cells by basement membrane extracellular matrix (ECM) molecules such as HS PGs. In order to increase infiltration capacity of the activated leukocytes into the inner inflamed tissues, the leukocytes that have gained access to these tissues deploy certain hydrolases such as heparanase and proteases (like collagenase) to further degrade HS and fibers of collagen of the basement membrane [14,15].

Based on the above narration about the major molecular and cellular events of inflammation, the multiple roles played by the sulfated GAGs are notorious. Inasmuch, the interventional application of exogenous sulfated glycans that could compete with or mimetic the structures and functions of the endothelial and leukocyte GAGs, is likely able to produce an anti-inflammatory outcome. In fact, several scientific works have supported this theory demonstrating that sulfated glycans of various types such as mammalian or marine heparin (Hp), HS, CS, DS and derivatives as well as holothurian fucosylated chondroitin sulfate (FucCS) and brown algal fucoidans, are indeed able to be anti-inflammatory. Numerous *in vitro* and *in vivo* models of inflammation have been taken to assess and measure their effects. Structural analyses have also been employed to unravel the chemical requirements involved in the outcome. Below, I discuss some of these models and the major achievements obtained so far from the recent studies concerning the anti-inflammatory actions of the sulfated glycans. It has been noted that these compounds are able to act not only on one or more of the various points of action of the sulfated GAGs in inflammation (Fig. 2), but also at additional points as detailed further. The multiple sites targeted during the anti-inflammatory process of the exogenous sulfated glycans enhance both efficiency and efficacy of their medicinal actions.