Heparin and HS are linear polysaccharides characterized by repeating disaccharide units of alternating N-substituted glucosamine and hexuronic acid residues subject to selective modification including sulfation of the N-position as well as the C-6 and C-3 O-positions of the glucosamine and the C-2 O-position of the uronic acid [1-3] (Fig. 1). Thus, the 32 (or more) potential unique disaccharide units and their grouping into structural motifs make this class of compounds one of the most information dense in all of biology [4-6]. Unlike proteins, the sequence and overall structure of these complex molecules are not defined by a template. Instead, the specific structure is the result of the action of at least 18 biosynthetic enzymes as well as the postsynthetic processing by 6-O-sulfatases and heparanase [7] (Fig. 1). While the structure of HS expressed by cells can rapidly change in response to specific conditions, the specific mechanisms controlling HS biosynthesis and postsynthetic modification remain to be defined.

HS chains are found attached to core proteins in proteoglycans on cell surfaces and within the extracellular matrix (ECM) of nearly all mammalian cells and tissues [2, 6]. On cell surfaces, HS is mainly found attached to two classes of core proteins, the syndecans and glypicans. The syndecans (1 through 4) are characterized by a transmembrane core protein with HS and sometimes chondroitin sulfate chains attached to the region of the core protein extending from the cell surface into the pericellular matrix [8]. Glypicans (1 through 6), on the other hand, are anchored to the plasma membrane via glycosylphosphatidylinositol attached to a hydrophobic domain within the C-terminal region with the HS chains restricted to the last 50 amino acids such that they are held close to the membrane [9]. There are several heparan sulfate proteoglycans (HSPGs) found within the ECM including perlecan, agrin, and collagen XVIII [10, 11]. It is generally believed that the biological function of HSPGs is dependent on HS structure and localization of the HSPG, with cell surface HSPGs being implicated in controlling ligand–receptor interactions and ECM HSPGs being considered important modulators of intercellular molecular traffic [12, 13] (Fig. 2).

In contrast to HS, the highly sulfated and more structurally uniform heparin is stored almost exclusively in the granules of cells of hematopoietic lineage, including connective tissue mast cells, as part of large heparin-proteoglycans that function to package inflammatory proteases [14-17]. In addition, a highly sulfated form of
HS is present in leukocytes [18]. Heparin has been used clinically as an anti-coagulant for ~80 years and has also been shown to have anti-inflammatory activity and both anti- and pro-angiogenic activities [19-22]. The wide range of activities attributed to heparin and HS probably reflects the large number of proteins that these glycosaminoglycans bind and modulate [23-25]. While the majority of disaccharides within heparin contain 2-O, 6-O, and N-sulfate groups, HS is more structurally diverse with protein-binding sites more selectively expressed [23, 25]. Because of this structural diversity, it is thought that changes in HS as a function of environmental stimuli (e.g. tissue injury, ischemia) may lead to regulation of cellular responses to important extracellular proteins through alterations in HS–protein binding.

HS is essential for embryonic development [26] and required for the function of all adult physiological systems. HS structure and expression can change rapidly during development [26-28], indicating that alterations in HS might be a key signal of functional changes in cells and tissues. While the complete mechanisms remain unknown, it is generally believed that HS function is mediated by the ability of HS to bind and regulate proteins. A recent bioinformatics analysis of the HS interactome identified 435 human proteins that interact with HS or the structurally related heparin [29].

Fig. 1. Biosynthesis of heparin and heparan sulfate. The biosynthesis involves initial chain polymerization within the endoplasmic reticulum by Ext1 and 2. Deacetylation, epimerization, and sulfation of specific saccharide units occur in the Golgi apparatus through the action of four N-deacetylase/N-sulfotransferases, one C5-epimerase, one 2-O-sulfotransferase, three 6-O-sulfotransferases, and seven 3-O-sulfotransferases. S domain, sulfate-rich domain; A domain, under-sulfated domain.