



Heparan sulfate – what will work and what will not?

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Medical training at Uppsala University. Graduate studies at University of Chicago and Uppsala University, Ph.D. 1966 (Thesis: Structure of the heparin–protein linkage region). Professor in Medical and Physiological Chemistry at the Swedish University

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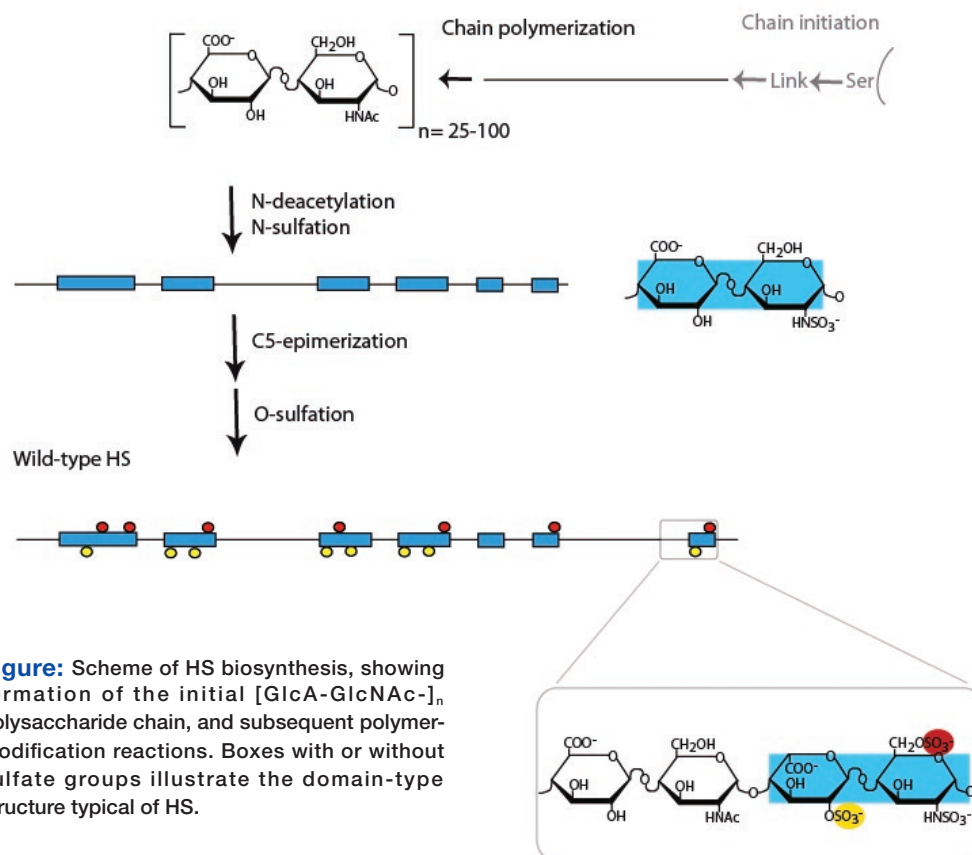


Figure: Scheme of HS biosynthesis, showing formation of the initial $[GlcA-GlcNAc-]_n$ polysaccharide chain, and subsequent polymer-modification reactions. Boxes with or without sulfate groups illustrate the domain-type structure typical of HS.

Heparan sulfate (HS) is a sulfated polysaccharide synthesized in proteoglycan form by most animal cells. It is of vital importance in embryonic development as well as in homeostasis, and influences a multitude of biological processes including inflammatory reactions, angiogenesis and tumor growth and metastasis. The functional roles of HS depend on interactions with a variety of proteins that bind in more-or-less specific fashion to selected domains of the saccharide chain. Such domains are generated through a series of biosynthetic reactions initiated by formation of a [GlcA-GlcNAc]_n chain of the appropriate structure. The resultant polymer is then modified through the concerted action of several enzymes, including GlcNAc *N*-deacetylase/*N*-sulfotransferase(s), a GlcA C5-epimerase [that converts glucuronic acid to iduronic acid (IdoA) units], and finally several *O*-sulfotransferases that catalyze the incorporation of *O*-sulfate groups in various positions. Regulation of the biosynthetic process, through yet poorly understood mechanisms, results in the formation of saccharide domains of different size, that range in structure from essentially unmodified to highly *N*- and *O*-sulfated, IdoA-rich sequences (Fig. 1). The ability of a HS chain to interact with proteins is determined by its domain assembly; it is generally held that the strict regulation of polymer modification serves to generate specific

HS sequences required for selective interactions with various protein ligands. This notion will be reassessed in view of recent studies on transgenic mice with variously modulated HS biosynthesis and metabolism.

Mice defective in various HS biosynthetic enzymes show highly variable phenotypes, ranging from incomplete gastrulation to selective effects on certain cells (1-5). Surprisingly, several developmental signaling processes known to depend on interactions between HS, specific growth factors and their receptors, appear normal in spite of severely deranged HS structures. For instance, mice without functional GlcA C5-epimerase produce a HS devoid of IdoA units, yet show seemingly normal cardiovascular, gastrointestinal and central-nervous systems(5). A tentative conclusion of these findings is that the requirements for specific HS structures in interactions with relevant growth factors/morphogens and their receptors are less stringent than previously assumed. Biochemical studies on the ability of HS-related oligosaccharides to promote formation of ternary complexes with FGF1 or FGF2 and their various receptors support this notion (N. Jastrebova et al., unpublished). The implications of these findings on regulation in HS biosynthesis will be discussed.

References

1. Forsberg E et al. (1999) *Nature* 400, 773-6
2. Lin X et al. (2000) *Dev. Biol.* 224, 299-311
3. Ringvall M et al. (2000) *J. Biol. Chem.* 275, 25926-30
4. Merry CL et al. (2001) *J. Biol. Chem.* 276, 35429-34
5. Li J-p et al. (2003) *J. Biol. Chem.* 278, 28363-6

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