Shang-Cheng Hung

Profile

Shang-Cheng Hung studied at the National Tsing Hua University (Hsinchu, Taiwan) and obtained his Ph.D. in organic chemistry under the supervision of Prof. Biing-Jiun Uang and Prof. Chun-Chen Liao in 1992. After two years of military service, he spent a year with Prof. Andrew Streitwieser at the University of California, Berkeley as a postdoc. In 1995, he moved to the Scripps Research Institute for his second post-doctoral research with Prof. Chi-Huey Wong for three years. He then was recruited back to Taiwan as an Assistant Research Fellow at the Institute of Chemistry, Academia Sinica and was promoted to the rank of Associate Research Fellow in 2002. He moved to the Department of Chemistry, National Tsing Hua University as an Associate Professor (2005) and was promoted as a full professor (2006) and Distinguished Professor (2007). In 2009, he joined the Genomics Research Center, Academia Sinica as a Research Fellow and, in 2012, advanced to the rank of Distinguished Research Fellow. His research interests focus on the synthesis of biologically important sugars, particularly, glycosaminoglycans and mycobacterial cell envelope components, together with their bio-evaluations. He received several awards including the Distinguished Research Award from the National Science Council of Taiwan, the 17th Teco Award from the Teco Technology Foundation, and the Outstanding Scholar Chair from the Foundation for the Advancement of Outstanding Scholarship (FAOS). He is also a member of the Editorial Board of Carbohydrate Research.

Heparanomics : Synthetic approaches for characterization of specific interactions with proteins

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Heparan sulfate (HS) is a linear polysaccharide that is widely distributed in metazoan cell surfaces, extracellular matrices, and basement membranes, where it exists as proteoglycan component. The HS chain is initially assembled as a simple 1→4-linked copolymer of *N*-acetyl-α-D-glucosamine and β-D-glucuronic acid (GlcA), but the seemingly regulated but non-template driven modifications cause extensive microheterogeneity along the sugar backbone comprised of around 50 to 200 disaccharide units. These modifications, which include *N*-deacetylation, *N*-sulfonation, GlcA 5-C epimerization forming α-L-iduronic acid, and multiple O-sulfonations, are implemented by several enzyme isoforms of varying specificities and are always incomplete, accounting to theoretically 48 disaccharide variations. Organisms, tissues, or particular cells, thus, express a range of HS structures that, in its entirety, comprise what is collectively called the heparanome. With such ubiquity and structural complexity, numerous proteins acquired the ability to utilize HS as an accessory in eliciting their bioactivity. Consequently, HS play crucial roles in many physiological and pathophysiological processes such as signaling, development, tumor progression and metastasis, viral and bacterial infections, and inflammatory response.

The myriad of functional group patterns decorating the sugar backbone allowed HS to encode a high density of structural information that rivals proteins and nucleic acids. Such array of modifications is responsible for mediating or modulating protein activity. While some proteins bind non-specifically through ionic interactions with the negatively charged sugar chain, a large number of proteins are believed to require particular modification patterns for optimum activity. It should be noted that the actual binding site represents only a small segment of the HS chain, usually around 2-10 disaccharides. These biologically active domains within the heparanome, the character of their interaction with protein ligands, and the influences they exert in physiology as a whole are the subjects of the emergent heparanomics field. Keen interests are focused in deciphering the molecular level details of the HS-protein interactions because they may present therapeutic opportunities. However, unlike the fully developed methods of protein acquisition, the preparation of structurally defined oligosaccharides based on potential HS binding sites is considered a bottleneck in conducting structure–activity relationship studies.

Chemical synthesis has so far proved reliable in the procurement of well-defined HS oligosaccharides at a considerable scale suitable for biological assays. Synthetic approaches aimed at constructing HS-based compounds are met with challenges concerning the preparation of sugar building blocks particularly the rare L-*ido*-configured derivatives, the regio- and stereoselective formation of glycosidic linkages, and the regioselective functionalization of similarly reactive hydroxyl groups to emulate the complex modification patterns of the naturally occurring materials. To access the L-idose building block, our group developed methodologies starting from the commercially abundant diacetone α-D-glucose with 5-*C*-epimerization, 1,6-anhydro-ring formation, and metal triflate-mediated acetolysis as key steps. We also established protocols for the regioselective one-pot protection and stereoselective one-pot protection-glycosylation that effectively reduced the amount of time and effort in constructing building blocks and sugar backbones. The preparations of D-glucose and D-glucosamine acceptors and donors using this strategy are being routinely carried out in our laboratory. A completely stereoselective glycosylation that generates the α-D-glucosamine unit is usually difficult to accomplish. After a systematic evaluation of protecting groups for the 2-azido-2-deoxy-D-glucosyl donors, we found that the installation of *tert*-butyldiphenylsilyl group at 6-O, 2-naphthylmethyl group at 4-O, and *p*-bromobenzyl group at the 3-O position confer exclusive α-stereoselectivity regardless of leaving group, activator, and sugar acceptor. Even more noteworthy is that these protecting groups are orthogonal and flexible enough to allow functional group manipulations, enabling us to generate several disaccharide building blocks from a single precursor. Complementing the potential disaccharides present in HS, our laboratory prepared 48 disaccharide building blocks that may be assembled and eventually transformed to target any structure that could be found in the natural compound. We have accomplished the total synthesis of several lengths of HS-based oligosaccharides containing identical repeating disaccharide components. The length-dependent interactions of these sugars with eosinophil cationic protein, eosinophil-derived neurotoxin, fibroblast growth factors, and mycobacterial heparin-binding hemagglutinin were examined using either cell-based inhibition or direct binding assays. In one groundbreaking achievement, the chemical preparation of two HS-based 3-*O* sulfonated octasaccharides possessing non-regular disaccharide repeats were completed by us. This effort was also remarkable because the target compounds carry free amino, acetamido, and sulfonatamido functionalities, a difficult feat to realize in HS-based oligosaccharide synthesis. Both oligosaccharides inhibited the herpes simplex virus 1 infection of Vero cells. Identifying the optimal sugar sequence sought by binding proteins require a series of compounds with variable functional group patterns. However, for making such a compound library to be practical, efficient strategies that minimize the number of synthetic steps must be adopted. By this manner, we undertook the procurement of all 48 HS-based disaccharides from only two orthogonally protected disaccharide precursors using different combinations and sequence of functional group transformation steps. Binding assays conducted between the synthesized disaccharides and fibroblast growth factor-1 using isothermal titration calorimetry showed that only four compounds significantly bound the growth factor. The molecular details of the interactions were revealed by the X-ray co-crystal analysis of the identified sugars and the protein. Altogether, our findings illustrate the value of synthetic chemistry in advancing the current understanding of the functions embedded within the heparanome.

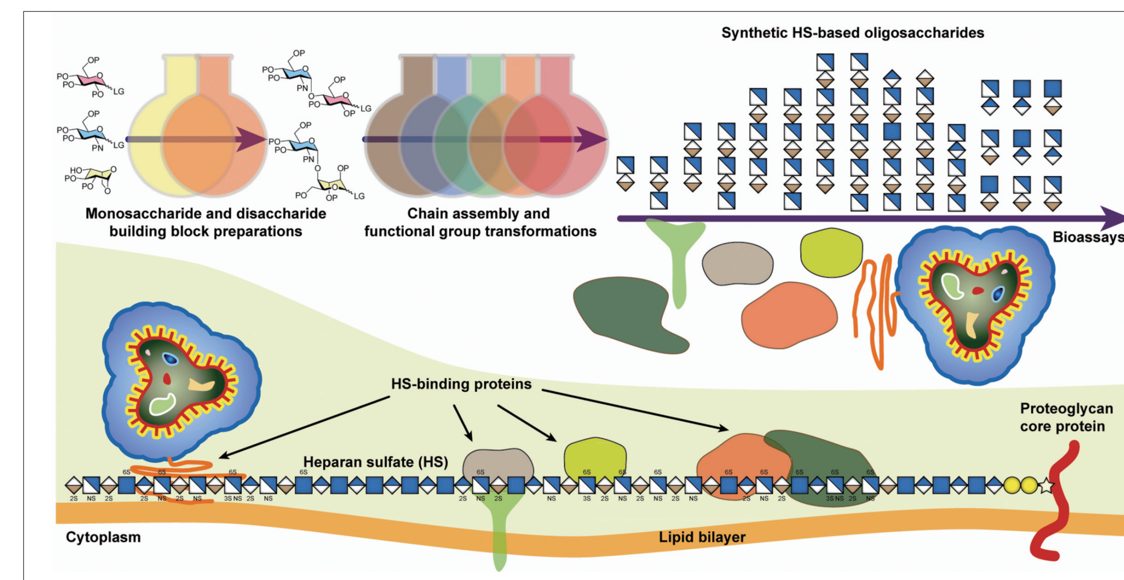

Figure 1. Synthetic HS-based oligosaccharides are important tools in understanding the character of HS-protein interactions.

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