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Glycosaminoglycans in health and disease

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Glycosaminoglycans (GAGs) are large complexes of negatively charged heteropolysaccharide chains composed of a repeating disaccharide unit [acidic sugar and amino sugar]. The amino sugar is either D-glucosamine or D-galactosamine, the acidic sugar is either D-glucuronic acid or L-iduronic acid. GAGs are located primarily on the surface of cells or in the extracellular matrix (ECM). The specific GAGs of physiological significance are hyaluronic acid, dermatan sulfate, chondroitin sulfate, heparin, heparan sulfate, and keratan sulfate. Hyaluronic acid may be important in permitting tumor cells to migrate through the ECM. Chondroitin sulfate most abundant GAG. Heparan sulfate, extracellular GAG contains higher acetylated glucosamine than heparin and less sulphated groups. Some tumor cells have less heparan sulfate at their surfaces. Heparin is an intracellular GAG, component of intracellular granules of mast cells. Heparin is an important anticoagulant. Its most important interaction is with plasma anti-thrombin III. Dermatan sulfate is a glycosaminoglycan found mostly in skin. Keratan sulfate originally the designations KSI and KSII were based on differences between KS from cornea and that of cartilage. GAGs such as heparin, heparan sulfate (HS) and dermatan sulfate (DS) serve as key biological response modifiers by acting as co-receptors for growth factors, cytokines and chemokines; regulators of enzyme activity; signaling molecules in response to infection, wounding and and targets for viral, bacterial and parasitic virulence factors for attachment and immune system evasion.

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Use of stable isotope tracers and chemical biopsy methods for non-invasive studies of hepatic carbohydrate metabolism in humans

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The liver plays a central role in the maintenance of constant blood glucose levels during the daily feeding-fasting cycle. This is achieved by a coordinated reciprocal regulation of metabolic pathways that generate glucose such as gluconeogenesis and glycogenolysis and pathways that dispose of glucose such as glycolysis, glycogenesis and lipogenesis. In diseases such as diabetes and glycogen storage disease, this regulation is disrupted resulting in unstable blood glucose levels. To more precisely understand how these pathologies disrupt the control of hepatic glucose fluxes in humans, there is a need for practical, safe and non-invasive methods for evaluating hepatic carbohydrate fluxes. To this end, we are developing non-invasive measurements of these fluxes using deuterated water ($2H_2O$) as a relatively inexpensive and easily administered isotopic tracer coupled with "Chemical Biopsy" of UDP-glucose via glucuronidation of Acetaminophen and other xenobiotic compounds whose glucuronides are cleared into urine. Analysis of urinary glucuronide positional 2H -enrichment by high-resolution $2H$ NMR informs the main sources of endogenous glucose and glycogen synthesis. Integration of this information with ^{13}C NMR measurements of glucose and glucuronide ^{13}C -isotopomers from ^{13}C -enriched precursors provides further detail on the metabolism of specific sugars or gluconeogenic substrates. To illustrate the application of NMR and stable isotope tracers in improving our understanding of hepatic carbohydrate metabolism, highlights of our studies will be presented and future perspectives will be briefly discussed.

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