The role of glycosaminoglycan supramolecular concentrated masses (fractones) in the extracellular matrix in health and disease

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Glycosaminoglycans (GAG) are essentially located in the extracellular matrix, forming basement membranes, fractones and glycocalyx. GAG are initially produced in the Golgi apparatus, then are expulsed outside the cells, in locations where they anchor and interact with signaling proteins (growth factors, cytokines and chemokines). The signaling proteins are diffusible, positively charged whereas GAG do not diffuse and are negatively charged. Multiple studies demonstrated that growth factors require binding to GAG (essentially heparan sulfate proteoglycans) to themselves bind and activate their cognate receptors at the cell surface, ultimately activating and regulating cell proliferation, differentiation, migration and apoptosis (PDMA). PDMA regulation underlies processes of morphogenesis, wound healing, regeneration but also inflammation and pathological progression. GAG are dynamic molecules in the sense that the glycosylated motives are constantly changing according to the challenges of the environment. We have characterized accumulated supramolecular forms of GAG in invertebrate and vertebrate animals, humans, and plants in the extracellular matrix, next to dynamic morphological changes, zones of inflammation, and cytogenic zones. We have named these structures fractones in reference to the concept of Mandelbrot fractal structures. Fractones have characteristics distinct from basement membranes and glycocalyx. Fractones appear as puncta in light microscopy after immunolabeling for GAG. Fractones are located in zones of construction, next to stem cells and their immediate progeny. We demonstrated that fractones bind growth factors and that disruption of this binding results in loss of growth factor activity, consequently loss of PDMA regulation. Moreover, we have demonstrated a high amount of fractones in multiple forms of cancer, and a loss of fractones in the brain of BTBR mice, a model for autism. We have found fractones in all organisms investigated, i.e. humans, rodents, insects, sponges, plants and cyanobacteria. In addition, we have characterized fractones throughout mouse development, starting from the earliest stages of morphogenesis. Through development, the location of fractones correlates with morphogenic events such as blastulation, formation of the inner cell mass (pluripotent stem cell zone), gastrulation, neurulation and further brain morphogenesis. We anticipate that fractones are ubiquitous regulators of signaling proteins, binding, storing, dispatching and activating the signaling proteins to orderly control the regulatory processes of PDMA, themselves underlying morphogenesis, wound healing, regeneration, degeneration, inflammation and pathological progression. Further understanding of fractone function and the role of their GAG components will allow us to reveal mechanisms of cell fate decision and to design innovative strategies to boost wound healing, or stop the processes of inflammation and disease progression. Of particular interest is that fractone GAG are highly conserved through evolution, the motives of interest being always O- and N-sulfations on chains of disaccharides. This provides insights into the possible use of invertebrate or algae GAG extracts for the treatment of human pathologies.