Cracking the Sulfation Code: Understanding the Binding of Chondroitin Sulfate Tetrasaccharides to the Growth Factor Midkine

Peter M. Clark, Nagarajan Vaidehi, Linda Hsieh-Wilson, William A. Goddard III

Recent work by the Hsieh-Wilson lab has shown that, depending of the sulfation pattern, certain chondroitin sulfate tetrasaccharides can either promote or retard neuronal growth. In this study we report the first solution structures of Chondroitin Sulfate A (CS-A), Chondroitin Sulfate C (CS-C), Chondroitin Sulfate E (CS-E), and Chondroitin Sulfate R (CS-R) tetrasaccharides using explicit water molecular dynamics. Each of these tetrasaccharides contain the same chondroitin sulfate backbone (a repeated disaccharide unit of D-glucuronate and GalNAc) but differ in the placement and number of their sulfate groups. Using DOCK-DIV we docked each chondroitin sulfate to the neuronal growth factor midkine. We then investigated the interactions between the chondroitin sulfate molecules and midkine. These studies show that both the number and the distribution of the sulfate groups on the chondroitin sulfate molecules are critical for their docking to proteins. Future studies will investigate how these chondroitin sulfate molecules interact with other neuronal growth factors.