Interrogating Heparan Sulfate with Small Molecules

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In a search for small molecule antagonists of heparan sulfate, we examined the activity of bis-2-methyl-4-amino-quinolyl-6-carbamide, also known as surfen. Fluorescence-based titrations indicated that surfen bound to heparin and other sulfated compounds. Surfen also neutralized the anti-Factor Xa activity of heparin-antithrombin complexes, composed of unfractionated heparin or low molecular weight derivatives. Addition of surfen to cultured cells blocked binding and signaling mediated by FGF2, which depends on formation of ternary complexes of FGF, FGF receptors and cell surface heparan sulfate. Furthermore, surfen blocked cell adhesion to the heparin-binding Hep-II domain of fibronectin and prevented infection by Herpes simplex virus-1 dependent on glycoprotein D binding to cell surface heparan sulfate. Surfen also blocked both FGF2 and VEGF165-mediated endothelial sprouting in Matrigel. Derivatives of the aminoglycoside antibiotic neomycin, in which all of the ammonium groups of the have been converted into guanidinium groups, also binds to heparan sulfate. Like surfen, guanidinoneomycin will block FGF2 binding to cells. Guanidinoneomycin also has the capacity can carry large (>300 kDa) bioactive molecules across cell membranes by an endocytic mechanism. Conjugation of guanidinoneomycin to the plant toxin saporin, a ribosome-inactivating agent, results in proteoglycan-dependent cell toxicity, indicating that some of the compound can escape the endocytic pathway and enter the cytoplasm. The binding of guanidinoneomycin and surfen to heparan sulfate suggests the possibility of making derivatives that bind to specific sulfated domains in glycosaminoglycans, which may provide small molecules to block specific activities associated with proteoglycans or to exploit them as carriers to modify cell behavior.