



Structure-Based design and synthesis of FGF inhibitors and FGF modulator compounds.

Principal Investigators

Moosa Mohammadi, Ph.D., David Green, MD. Ph.D., Robert J. Linhardt, Ph.D*.

Background

Fibroblast growth factors (FGFs) are essential for physiological angiogenesis and wound healing but are also implicated in the pathobiology of cancer and certain skeletal disorders. Therefore, modulating FGF-induced signaling *in vivo* may have tremendous therapeutic potential for treating the above described diseases. FGFs exert their action via interacting with receptor tyrosine kinases (FGFRs). The success of FGF signaling is determined by FGF-induced FGFR dimerization, which in turn depends on the presence of heparin or heparin sulfate proteoglycans (HSPG) to enhance FGF-FGFR affinity and aid in formation of FGF-FGFR-heparin dimers. The essential role of heparin and HSPGs in FGF-induced dimerization suggests that these compounds could be used as therapeutic agents for modulating FGFR-related activity. At present, however, the large-scale synthesis of homogeneously sulfated heparin oligosaccharides is limited. Therefore, identification of other molecules that can mimic or antagonize the action of heparin would be of tremendous value.

Description

Dr. Mohammadi and coworkers have shown that sucrose octasulfate, (SOS) acts like heparin analog in promoting and stabilizing FGF-dependent FGFR dimerization *in vivo* (Volkin et al., 1993). The authors further described a crystal structure of FGF-FGFR-SOS complexes (Yeh et al., 2002) in order to elucidate a mechanism of SOS action. These findings of heparin-like SOS activity are particularly important in the light of difficulties associated with large-scale heparin synthesis. In contrast, the synthesis of the sulfated sucrose derivatives is considered to be straightforward.

Applications

The work described above will allow for rational design of compounds that modulate FGF - mediated signaling. The compounds designed to augment FGF- induced signaling may prove beneficiary in physiological angiogenesis and wound healing. One example of such compounds is a well-documented pharmaceutical composition, Carafate, used for treatment of stomach ulcers. The structural data described by the authors explains that the above-described composition heals ulcers by promoting FGF-FGFR1-FGFR2 dimerization. By using these structural data as a framework for rational drug design more effective therapeutics for ulcer treatment may be developed in the future.

On the other hand, compounds designed to inhibit FGF-induced signaling may be of great value in treating cancer related angiogenesis and inhibiting growth of FGF-dependent tumors.

Patent Status

A U.S. patent application has been filed covering this novel technology

For further information please contact

New York University
Office of Industrial Liaison
650 First Avenue, New York, N.Y.10016
Tel (212) 2638178 Fax (212) 2638189

*University of Iowa