The activation of fibroblast growth factors by glycosaminoglycans

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Fibroblast growth factors (FGFs) constitute a family of signalling polypeptides which are involved in key biological events including cell proliferation, differentiation and angiogenesis. The FGFs exert their biological functions by interacting with specific receptors at the cell surface (FGFRs). In humans twenty two *fgf* genes encode the ligands (FGFs) and five *fgfr* genes encode the cognate membrane receptors (FGFRs). FGFRs consist of two or three extracellular immunoglobulin domains linked to a cytoplasmic domain which contains a tyrosine kinase. The latter becomes phosphorylated, leading to downstream signalling events, following binding of an FGF to an FGFR together with the obligatory co-receptor heparan sulphate (HS). HS is the carbohydrate moiety of cell surface HS proteoglycans (HSPGs). The stimulation of cell proliferation requires, therefore, the formation of a ternary complex of the FGF, the FGFR and the HS co-receptor.

This lecture intends to give an overview of work performed in Madrid (Centro de Investigaciones Biológicas), Seville (Instituto de Investigaciones Químicas) and San Sebastián (CIC biomaGUNE) aimed at elucidating the molecular basis of this complex biological process from a carbohydrate chemistry perspective. The presentation will include: a) the development of strategies for the synthesis of HS-like oligosaccharides, both in solution and in solid phase; b) the investigation of the three dimensional structure of these oligosaccharides in solution; c) a study of the influence of oligosaccharide size and charge distribution on the binding to and on the stimulation of the mitogenic activity of FGF 1; d) the determination of the three dimensional structure of a FGF1-hexasaccharide binary complex and of a FGF1-octasaccharide-FGFR2 ternary complex in solution.

The obtained results which, in conjunction with other biophysical evidences, shed some new light on the specificity of FGF-HS-FGFR interaction, the geometry of the biologically active FGF-HS-FGFR ternary complex and the molecular mechanism of the process will be discussed.