HEPARIN AND ENDOTHELIAL CELLS: CELL SIGNALING PATHWAYS INVOLVED IN THE INCREASED SYNTHESIS OF HEPARAN SULFATE

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Endothelial cells (EC) exposed to heparin (Hep) increase the synthesis and modify the sulfation pattern of heparan sulfate proteoglycan (PGHS). Previously, we have shown that Hep binds to extracellular matrix (ECM) and triggers cellular signaling pathways increasing PGHS synthesis. In this work we investigated cellular signalling pathways involvement, such as Ras Raf MAP kinase, in the synthesis of the PGHS. Glycosaminoglycan synthesis was undertaken using EC: wild type, lacking Ras (*Ras*17N-EC) and with constant activated Ras (EJ-*ras*-EC) both in presence or not of Hep. Comparative study of PGHS synthesis on EC, EJ-ras-EC and Ras17N-EC cells and study with inhibitors showed that PGHS in EC is dependent of Ras Raf MAP kinase pathway. However, the stimulus of PGHS synthesis in presence of Hep may not be related with this pathway. Using RT-PCR, we observed increased levels of syndecan-4 and no effect on the expression of perlecan, suggesting that syndecan-4 is possibly the PGHS that is being stimulated by Hep. On the other hand a dramatic increase in the expression of tenascin-C, a small increase vitronectin, and no effect on the expression of thrombospondin-1 were observed. The changes in the expression of these proteins could be related with the angiogenic activity promoted by Hep, since they are present in neovascularization (CNPq, FAPESP, CAPES).