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TITLE

THE BIOAVAILABILITY OF HEPARIN-BINDING MOLECULES ON VASCULAR WALLS IS REGULATED BY HEPARAN SULFATE AND FLOW RATE

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We have been studying the bioavailability of heparin-binding molecules to vascular surfaces using a bioreactor that employs three-dimensional vessel architecture and pulsatile flow. This approach has been conducted in tandem with the design of a computer model to conduct simulations and make predictions of molecular interactions at the cell surface. We used a single pass experimental design to better measure the interactions in the microenvironment and used heparin-binding molecules as our model of binding to vascular surfaces. Heparan sulfate is on the cell surfaces of blood vessels and is involved in the capture and internalization of scores of molecules from angiogenic promoters, such as vascular endothelial growth factor (VEGF) to cholesterol-associated molecules such as low-density lipoprotein(LDL). Our experimental results, which were in close agreement with our simulations showed that expression of heparan sulfate is a crucial factor in the bioavailability of these molecules to cell surfaces. Substantial binding of molecules was measured with intact heparan sulfate. Enzymatic removal of heparan sulfate from the endothelial walls resulted in significantly decreased retention of all heparin-binding growth factors tested as well as LDL. Flow rates slightly above average capillary flow (0.6-3.0 ml/min) exercised strong regulation of capture. In all molecules tested, at any but the lowest flow rates, capture in a single pass was virtually ablated, suggesting that without a reasonable half-life there is little chance of capture on vascular surfaces with flow rates higher than capillary rates.