MICRODIALYSIS STUDIES OF CYTOKINES INVOLVED IN THE FOREIGN BODY RESPONSE

by

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ABSTRACT

The foreign body response elicited by biomaterial implantation has long been of interest to bioengineers seeking to control its outcome. Cytokines are important signaling proteins directing the cellular response to biomaterial implants. The aim of this dissertation is to create microdialysis methodology that would allow collection and measurement of cytokines directly at the biomaterial/host interface.

Microdialysis sampling is based on passive diffusion of analyte through a semipermeable membrane. Microdialysis calibration procedures and theory for small molecules have been well developed, however few studies have addressed macromolecule calibration. The large molecular weight (MW) of cytokines (8-80 kDa) results in a predominant hindered mass transfer during microdialysis sampling. Fluorescein isothiocyanate (FITC)-dextrans were used to obtain fundamental calibration parameters including membrane mass transport resistance (R_m) using an improved mass transport model. This modeling provides a useful insight towards dextran mass transport through asymmetric membranes. Interleukin-6 (IL-6) was used to understand relative roles of membrane and tissue properties on substantial decreased *in vivo* analyte mass transfer during long-term microdialysis sampling. *In vivo* collection data combined with *in vitro* recovery suggests that the decreased IL-6 mass transfer was caused principally by tissue effects rather than membrane fouling.

Open-ended tubes were implanted into dorsal subcutis of rats to estimate cytokines in interstitial fluid at the biomaterial/tissue interface. IL-6, IL-10, IL-1β, and macrophage chemoattractant protein-1 (MCP-1) were found to be in detectable levels. IL-4 and TNF-α were not detected. This information suggests the feasibility of microdialysis sampling of cytokines.

Microdialysis sampling of cytokines at tissue/biomaterial interface was achieved by co-implanting a probe into a piece of polyethylene tubing into rats, and IL-6 was monitored up to 14 days. Compared to the control probe, the probe at material side shows four times higher IL-6 concentration after 3 days implantation. FITC-dextran (4 kDa) was used to calibrate the probe. In a preliminary study, a multiplex assay with five cytokines IL-6, MCP-1, IL-10, IL-1β, and IL-4 was performed. This study is the first

one that collected multiple cytokines during the foreign body response. This possibility of collecting important cytokine information will be highly valuable for creating materials with improved compatibility.