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SYMPOSIUM

A Review of the Foreign-body Response to Subcutaneously-implanted Devices: The Role of Macrophages and Cytokines in Biofouling and Fibrosis

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Abstract

The biological response to implanted biomaterials in mammals is a complex series of events that involves many biochemical pathways. Shortly after implantation, fibrinogen and other proteins bind to the device surface, a process known as biofouling. Macrophages then bind to receptors on the proteins, join into multinucleated giant cells, and release transforming growth factor β and other inflammatory cytokines. In response to these signals, quiescent fibroblasts are transformed into myofibroblasts, which synthesize procollagen via activation of Smad mediators. The procollagen becomes crosslinked after secretion into the extracellular space. Mature crosslinked collagen and other extracellular matrix proteins gradually contribute to formation of a hypocellular dense fibrous capsule that becomes impermeable or hypopermeable to many compounds. Porous substrates and angiogenic growth factors can stimulate formation of microvessels, which to some extent can maintain analyte delivery to implanted sensors. However, stimulation by vascular endothelial growth factor alone may lead to formation of leaky, thin-walled, immature vessels. Other growth factors are most probably needed to act upon these immature structures to create more robust vessels.

During implantation of foreign bodies, the foreign-body response is difficult to overcome, and thousands of biomaterials have been tested. Biomimicry (i.e., creating membranes whose chemical structure mimics natural cellular compounds) may diminish the response, but as of this writing, it has not been possible to create a stealth material that circumvents the ability of the mammalian surveillance systems to distinguish foreign from self.

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Abbreviations: (CTGF) connective tissue growth factor, (FGF) fibroblast growth factor, (FBC) foreign-body capsule, (IL) interleukin, (PC) phosphorylcholine, (PDGF) platelet-derived growth factor, (PLGA) poly lactide-glycolic acid, (TGFβ) transforming growth factor β, (TNFα) tumor necrosis factor α, (VEGF) vascular endothelial growth factor

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