Encapsulated Mesenchymal Stem Cells Alter the Expression of TNF-α and IL-6 by Macrophages

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Statement of Purpose: The host tissue response is a common cause of implant failure because the local reaction creates an environment directed towards destroying the implant. In addition, a chronically inflamed environment develops which is extremely cytotoxic and a major cause of secondary cell death in the surrounding tissue. One of the key cell types in this process is the macrophage, which invades the site shortly after implantation. Macrophages release numerous pro- and anti-inflammatory cytokines as part of their normal role in regulating inflammation[1]. However, in the case of implanted materials, macrophages create a chronically inflamed environment at the implant site by expressing elevated levels of pro-inflammatory cytokines, including TNF-α and IL-6. The aim of this study was to evaluate the expression of TNF-α and IL-6 by LPS-stimulated macrophages in presence of encapsulated mesenchymal stem cells (MSCs). MSCs have shown the ability to alter wound healing and immune responses[2-4]. Our lab has developed a cell encapsulation device for easy delivery of MSCs (Figure 1). Encapsulating MSCs within a hollow fiber membrane creates an engineered space within the body that allows for the transport of solutes across the membrane, while physically isolating the cells. We hypothesize that MSCs encapsulated within a hollow fiber membrane decreases the expression of TNF-α and IL-6 in LPS-stimulated macrophages.

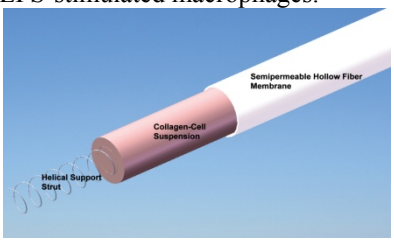

Figure 1 - Schematic of Hollow Fiber Encapsulation Device

Methods: Encapsulation device were constructed from a PAN-PVC hollow fiber membrane. Inside each membrane is a nylon coil that provides structural support to the device. Devices were filled with a collagen-hMSC suspension (MSC group), collagen (Collagen group), or serum-containing media (Naïve group). Encapsulation devices were introduced into cultures of IC-21 macrophages grown in lipopolysaccahride (LPS) conditioned media. IC-21s grown alone in either unconditioned (No LPS) or conditioned media (LPS) served as controls. Media was sampled after 24 and 48 hours. The samples were analyzed using Cytometric Bead Assay (CBA) for concentrations of TNF-α and IL-6.

Results: In comparison to LPS controls, hMSC-collagen filled devices significantly reduced the concentration of expressed TNF-α after 24 hours (630.9 pg/ml, SEM=88.9) and 48 hours (128.5 pg/ml, SEM=36.1) (Figure 2). Similarly, hMSC-collagen filled device significantly reduced IL-6 at both timepoints, 41.6 pg/ml (SEM=7.6) at 24 hours and 18.4 pg/ml (SEM=3.7) at 48 hours (Figure 3). Collagen filled devices significantly reduced expression of TNF-α after 48 hours (114.9 pg/mL, SEM=17.2) but not after 24 hours (Figure 2). Collagen filled device significantly reduced IL-6 expression at both 24 hours (65.8 pg/mL, SEM=7.9) and 48 hours (34.6 pg/mL, SEM=5.3) (Figure 3). Naïve devices did not significantly reduce cytokine expression.

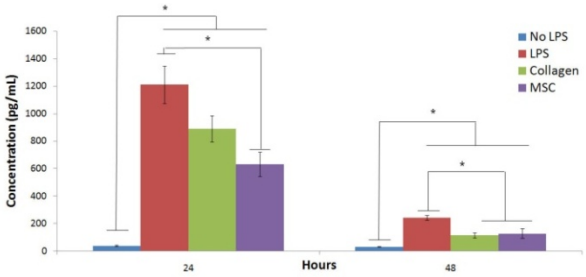

Figure 2 - TNF-α Expression

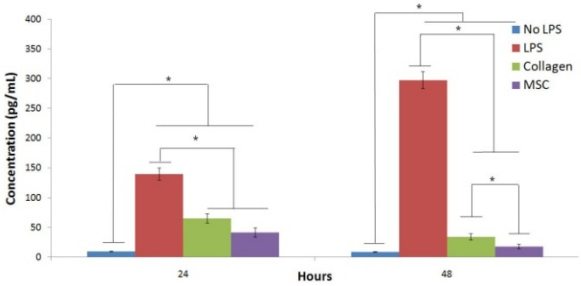

Figure 3 - IL-6 Expression

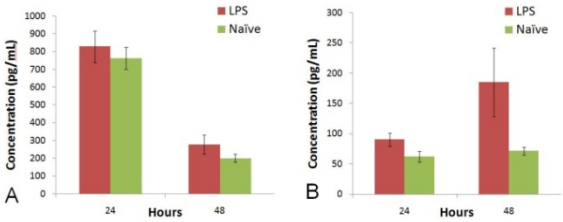

Figure 4 - Cytokine Expression in Response to Naive Device. A) TNF-α, B) IL-6.

Conclusions: The results of this study show that hMSCs when encapsulated in our hollow fiber device significantly reduce the expression of TNF-α and IL-6 by LPS-stimulated macrophages. However, these results also indicate that collagen alone produces a similar effect. These results provide an excellent foundation for future studies using encapsulated MSCs to alter cytokine expression. Future studies will examine the role that encapsulated MSC and collagen play in altering the host response. Ultimately, these cells in conjunction with our encapsulation device offer the possibility of favorably altering the host response *in- vivo* and thus may be used to improve long-term device functionality.

References: (Fujiwara, N. Curr Drug Targets Inflamm Allergy, 2005. 4(3): p. 281–286.); (Falanga, VTissue Eng, 2007. 13(6): p. 1299 312.); (Li, H., et al. Cell Tissue Res, 2006. 326(3): p. 725-736.); (Aggarwal, S. Blood, 2005. 105(4): p. 1815-22.)