Evaluation of Immunomodulatory Mesh for Pelvic Floor Reconstruction in a Rabbit Colpopexy Model

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Statement of Purpose: Approximately 12.6% of women will undergo surgery to repair pelvic organ prolapse (POP) during their lifetime. The use of polypropylene mesh in POP repair has improved anatomical outcomes associated with native tissue repairs. However, it is reported that 11 – 18% of women implanted with mesh experience complications 1 – 6 years after prolapse repair, often requiring surgical revision. While the occurrence of complications is complex and multi-factorial, studies in primates have shown that the degree of mesh integration with vaginal tissue is correlated with individual mesh properties, such as stiffness, porosity and weight. Animals implanted with higher stiffness, higher weight polypropylene prolapse mesh were observed to experience both an increased inflammatory response and more significant tissue degradation post-implantation. Studies analyzing mesh explants of women experiencing either mesh exposure or pain, have also shown evidence of a chronic, proinflammatory macrophage response, even decades post-implantation. This study evaluates differences in the host response to implanted polypropylene mesh in subcutaneous tissue versus vagina, and demonstrates a method for modulating the early host macrophage response with interleukin-4 (IL-4) coated polypropylene mesh to lessen the pro-inflammatory response and promote tissue integration.

Methods: Commercially available polypropylene mesh was used with an adapted radio frequency glow discharge method to create a stable negative charge on the surface of the mesh, followed by the sequential deposition of polycationic and polyanionic polymers to provide a stable, conformal, nanoscale coating. Chitosan served as the polycation, chosen because of its known antimicrobial and biocompatibility properties. Dermatan Sulfate served as the polyanion, chosen for its important role in regulating extracellular matrix components and enhancing the activity of cytokines. It is well known macrophages are characterized on a spectrum ranging from a pro-inflammatory M1 phenotype to an M2 anti-inflammatory phenotype. Interleukin-4 (IL-4), an immunomodulatory cytokine known to promote the M2 phenotype, is incorporated into the coating to be released in a controlled manner upon implantation. In vitro assays confirm the bioactivity and the controlled local release allowing for shifts in immune response to promote implant integration.

Utilizing an adapted lumbar colpopexy in New Zealand white rabbits, we implant mesh analogously to human implantation and evaluate changes in the immunologic response at early (14 days) and tissue remodeling outcomes at late stages (90 days) of implantation. Following a hysterectomy, two 3 x 12 cm2 pieces of mesh are secured along both sides of the vaginal wall. The remaining flaps at the top are then secured to a ligament in the sacral/lumbar space, creating the support to the pelvic organs. Upon closing the abdominal fascia, mesh is implanted subcutaneously. Both of these implantations of mesh allow for the assessment of the immune response in the pelvic area (relevant for prolapse patients) and in the abdominal area (relevant from prior work on host response to implants). The mesh-tissue complex was removed from each rabbit and processed for histological analysis. Histological analysis included hematoxylin and eosin staining to observe tissue organization and Masson's trichrome staining to determine collagen area and distribution surrounding mesh fibers. Further analysis included immunolabeling of macrophages with a pan-macrophage marker (RAM11+) and identification of indicators for angiogenesis (CD31+). Gene expression analysis included a panel for pro-inflammatory (iNOS, IFN-γ, IL-6, IL-1β) and anti-inflammatory (Arg1, IL-10, TGF-β1) markers.

Results: The results of this study show that mesh implanted via lumbar colpopexy elicited an overall increased host inflammatory response as compared mesh materials placed subcutaneously. There were significant differences in macrophages between 14 & 90 days in vaginal implants. Both abdominal and vaginal implants show significant differences in collagen formation between 14 and 90 days. Additionally, increased vascularity surrounding mesh fibers at 90 days was observed in vaginal implants only.

We further present a nanometer thickness, tunable, and uniform coating capable of releasing bioactive IL-4. We evaluated the biological functionality of the coated mesh via in vitro studies and in vivo implantation. In vitro testing demonstrated that the IL-4 coating was bioactive following terminal sterilization of the coated mesh, promoting macrophage transition to an anti-inflammatory phenotype. When implanted, IL-4 coated mesh materials were shown to shift the host macrophage response towards a more anti-inflammatory, M2 macrophage phenotype at 14 days as compared to uncoated polypropylene mesh. This shift resulted in improved mesh integration, decreased tissue degradation, improved tissue mechanical strength, and a reduction in intraabdominal adhesions representing significant improvements in the remodeling outcome.

Conclusion: Modulation of the early host response to polypropylene mesh toward an M2 phenotype has the potential to result in significant improvements in mesh integration, reduction in tissue degradation and associated complications, and overall clinical success.