Evaluation of Host Response to Polypropylene Mesh in Primate Model of Abdominal Sacrocolpopexy

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Statement of Purpose: As many as one third of premenopausal and half of postmenopausal women are affected by pelvic floor disorders, with an increased occurrence in women over the age of 50. More than 250,000 women per year in the United States alone will undergo surgery for pelvic organ prolapse, with direct costs totaling more than $1 billion. Native tissue repair has a recurrence rate exceeding 30%; therefore, mechanical reinforcement of tissues using synthetic mesh materials is widespread. While mesh implantation has been shown to produce improved outcomes as compared to native tissue repair, high morbidity rates are observed, especially with transvaginal placement. Complications resulting from mesh implantation include shrinkage, erosion, exposure, and pain. These complications have resulted in FDA warnings in 2008 and 2011 and requests for post-market surveillance for all previously and currently approved vaginal mesh implants for pelvic organ prolapse. It has been suggested that the observed complications following mesh implantation are directly attributable to the inflammatory processes associated with the foreign body reaction mounted by the host following implantation of synthetic materials. However, there are a lack of rigorous studies scientific studies characterizing the host response to synthetic mesh materials in the vagina and the design of mesh materials largely relies on data generated in abdominal hernia repair The objectives of the present study were two-fold: (1) to determine the predominant cell type (macrophage, T-lymphocyte, B-lymphocyte, mast cell) present within the area of implantation associated with three separate mesh materials following abdominal sacrocolpopexy in rhesus macaque; and (2) to determine the phenotypic profile (M1 proinflammatory, M2 anti-inflammatory) of the macrophage population participating in the host response.

Methods: 43 female, middle aged, parous, BMI matched rhesus macaques underwent supracervical hysterectomy followed by abdominal sacrocolpopexy with implantation of 1 of 3 different polypropylene mesh materials. Implanted mesh materials included a heavier weight, lower porous Gynemesh PS (Ethicon) and two lighter weight, highly porous Restorelle (Coloplast) and Ultrapro (Prolift+M, Ethicon). Sham-operated animals were used as a control. Three months post-surgery, the vagina-mesh-complex was harvested and a portion was frozen in OCT for histologic sectioning and another portion snap frozen on liquid nitrogen for ELISA assay.

Histologic sections (7 µm) were cut and labeled with antibodies specific for leukocyte common antigen (CD45), macrophages (CD68), T-lymphocytes (CD3), B-lymphocytes (CD20), and mast cells (CD117). Additional labeling was performed using markers specific for M1 (CD86) and M2 (CD206) macrophage phenotypes. All slides were then incubated with appropriate immunofluorescent secondary antibodies and visualized on a fluorescent microscope. Three representative mesh areas were imaged using a 40X objective on each slide and quantification of positively labeled cell populations was done using Cell Profiler Analysis Software (Broad Institute, Harvard University).

Snap frozen tissues were mechanically pulverized and homogenized in a high salt buffer containing protease inhibitors. Samples were centrifuged and supernatants collected. ELISA assays for both pro-(IL-12p70, and TNF-α) and anti-inflammatory (IL-4, IL-10) cytokines were performed.

Similar immunofluorescent and biochemical evaluation was performed on selected explants from human patients.

Results: Immunofluorescent labeling showed a dense cellular response in the area surrounding each individual mesh fiber. This response became more diffuse with increasing distance from the fiber surface. The cellular response was predominated by macrophages, although the presence of T-lymphocytes was observed. Few B-lymphocytes were observed and little to no presence of mast cells was observed. This response was characteristic of the host response regardless of the type of mesh implanted. Few positive cells were observed in the surgical site of sham-operated animals. Further labeling revealed polarization of the macrophage response towards the M1 phenotype in all mesh groups; however the degree of M1 polarization was observed to be less in the groups implanted with light weight, higher porosity mesh materials. Analysis of cytokine levels showed a shift towards an increased expression of anti-inflammatory cytokines in groups implanted with light weight, higher porosity mesh materials as compared to heavier weight, low porosity mesh groups. Evaluation of explants from human patients demonstrated that this response can persist in the long term (5+) years.

Conclusions: The results of this study demonstrate that the host response to polypropylene mesh used for pelvic organ prolapse consists predominantly of macrophages polarized to a pro-inflammatory M1 phenotype at three months post-implantation. However, implantation of lighter weight, higher porosity mesh, appeared to be associated with an attenuated pro-inflammatory M1 response. These mesh materials are also associated with improved clinical outcomes both in primates and humans. While additional work is required to establish a causal relationship, these results suggest a link between macrophage polarization profile during the host response and downstream clinical outcomes. An improved scientific understanding of the mechanisms of the host response to synthetic mesh materials placed in the vagina has the potential to significantly affect the design of next generation mesh materials, inform clinical practices and improve outcomes in pelvic floor repair.

Abstract #853
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