Effects of Diabetes Associated Epigenetic Modifications on Wound Healing and Tissue Remodeling leading to Urogynecologic Mesh Complications

Eric Shaker; Rui Liang, MD
University of Pittsburgh, UPMC Magee Women's Research Institute

ABSTRACT

Recent controversies in the efficacy of vaginally implanted urogynecologic meshes by the FDA have reduced their usage and demand. However, new mechanisms regarding the source of failure associated with mesh implantation are being readily discovered.

In diabetic women who receive urogynecologic meshes for the treatment of stress urinary incontinence and/or prolapse, the rate of mesh complication is significantly higher than the general population. In this study, we aim to identify the biological mechanisms behind the delayed healing and slower mesh integration rate, stemming from the immunological systems of the patient. We explore fibrotic pathways, epigenetic factors, the effects of senescence, alternative macrophage activation and pro-inflammatory factors to understand the causes and methods for mitigation.

CONTACT

Eric Shaker
UPMC Magee Women's Research Institute
Email: ers183@pitt.edu
Phone: 848-213-5000
PI Website:
https://www.obgyn.pitt.edu/people/rui-liang-md

INTRODUCTION

- In diabetic women who receive implantation of urogynecologic meshes, mesh exposure into vaginal cavity occurs more frequently
  - ~ 5 fold relative to non-diabetic women
  - This leads to surgical failure with significantly increased healthcare cost
- Diabetic wounds exhibit a resistance to healing and sustain chronic inflammation due to an alteration in the immune response

HYPOTHESIS

Diabetes induces immunological differences affecting fibrotic pathways and inflammatory mechanisms to ultimately impair wound healing and mesh incorporation. These changes cause an increased complication rate of urogynecologic meshes in diabetic women.

AIM

To identify the mechanism behind the sustained inflammation and impaired wound healing that diabetic wounds exhibit.

BACKGROUND LITERATURE

- Mirza et al. identified sustained inflammasome activity in macrophages as impairing wound healing in type 2 diabetic humans and mice
- Chen et al. found that HDAC deficient macrophages were unable to activate almost half of inflammatory gene expression processes
- Mullican et al. illustrated the effect of HDAC-3 on alternative activation and macrophage polarization in regards to inflammatory alterations

METHODS AND MATERIALS

- Vaginal tissue mesh specimens obtained from 20 diagnosed with type 2 diabetes mellitus (DM) and age-matched 28 non-diabetic participants (NDM) who underwent mesh removal due to complication
- RNAs extracted with TRIzol™ (Thermo Fisher)
- Nanostring multiplex assay performed, mRNA of 166 analytes tested
- Housekeeping genes including ABL1, RPL13a and TBP were used for normalization references
  - Background thresholding and a positive control linearity test was conducted to measure the efficiency of the hybridization reaction
- Log2 fold changes calculate
  - Overexpressed genes represented as value > 1 and under expressed values as < -1
- Student t-tests and multiple logistic model utilized to determine differential gene expression
- Pearson correlation test for associations conducted, as well as pathway analysis through the PathView system embedded in Nanostring

RESULTS

- Duration of mesh implantation identified as confounder and adjusted for multiple logistic model
- For samples with DM:
  - Levels of histone deacetylases (HDACs) -3, -5, and -7 strongly correlated with proinflammatory (p65, AKT) and profibrotic (TGFβ1, STAT6, JAK1 and IRS2) pathways (Figure 1)
  - Matrix Metalloprotinease 9 (MMPs) was upregulated in DM by 85% ($p<0.05$)

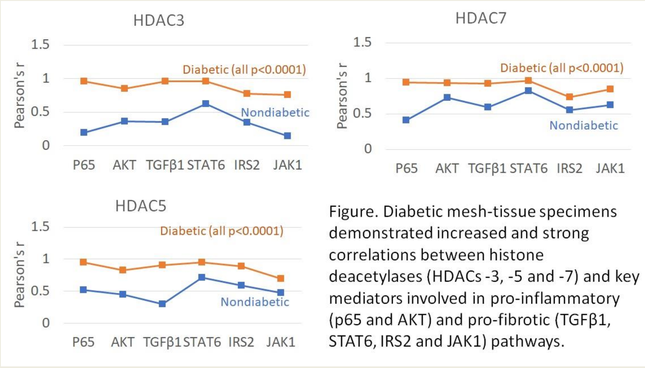

Figure. Diabetic mesh-tissue specimens demonstrated increased and strong correlations between histone deacetylases (HDACs -3, -5 and -7) and key mediators involved in pro-inflammatory (p65 and AKT) and pro-fibrotic (TGFβ1, STAT6, IRS2 and JAK1) pathways.

CONCLUSIONS

Diabetes induced epigenetic modifications may serve as a primary mechanism negatively impacting inflammation resolution and mesh incorporation into tissue, leading to the increased risk of diabetic women in developing mesh complications.

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