Collagen's Critical Role in Uterine Structure and Function and Implications in Placenta Accreta Spectrum

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Background

- Properly synthesized and cross-linked collagen fibrils are the principal source of tensile strength in tissues and altered during pregnancy.
- We previously described changes in collagen at the decidual-stromal interface in placenta accreta spectrum (PAS).

Objective

- We aim to describe the histoarchitectural variables of collagen organization to understand the role of collagen in pregnancy and repair as it related to PAS.

Study Design

- We utilized 2 different mutant type I collagen mice:
  - ***Col1a1*$^{Aga2/+}$ (*Aga2/+*)** mice which express modified *Col1a1,* C-terminal frameshift mutation
  - ***Col1a1*$^{+/-}$** which express reduced levels of type I collagen.
- These mice, historically used in the study of skeletal dysplasias, allow us to interrogate the role of type I collagen.
- Uteri and placenta from wildtype (WT), *Col1a1*$^{+/-}$, and *Aga2/+* mice were harvested. Additionally, we utilized a surgical mouse model of PAS.
- We employed quantitative histomorphometry with standard histochemistry as well as label-free 3D spectroscopy to understand collagen fibril orientation and distribution.

Results

- Type I collagen (*Col1a1)* was expressed in WT non-pregnant mice and at postpartum day 1
- In the WT, collagens were organized around smooth muscle and in the basement membranes of luminal and glandular epithelium (see Fig 1). PP type I collagen staining was prominent within the endometrial stroma.
- *Aga2/+* mice demonstrated decreased type I collagen with a compensatory increase in type III collagen but no difference in type I and III collagen PP. *Aga2/+* stromal thickness was decreased.
- Utilizing the surgical PAS mouse, RNA and protein expression of COL1A1 was altered and there was an increase deposition of type III collagen at the decidual-placental interface in PAS (see Fig 2).

Collagens are a main component of the dynamic architecture of the uterus. **Type I collagen remodeling** is a physiologic component of pregnancy and birth and is **altered in PAS.** The **increased abundance and disorganization** of collagen fibers at the site of adherence in PAS provide spatiotemporal clues to the mechanisms of PAS.

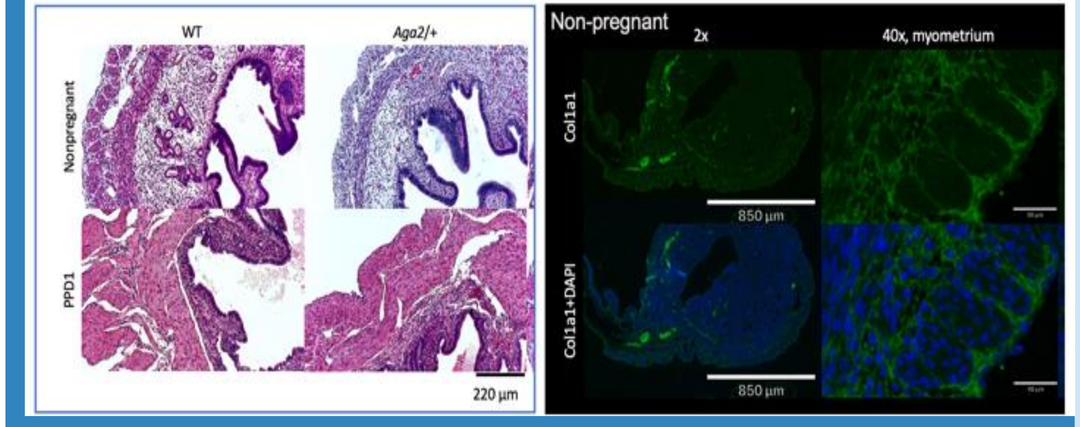

Figure 1. H&E staining of uteri from WT and Col1A1 mutant mice (non-pregnant and postpartum day 1 [PPD1]) without significant gross differences. Immunofluorescence demonstrates visualization of endometrial and myometrial Col1a1 protein (green) relative to nuclear staining (DAPI; blue) in non-pregnant WT mice.

Questions?
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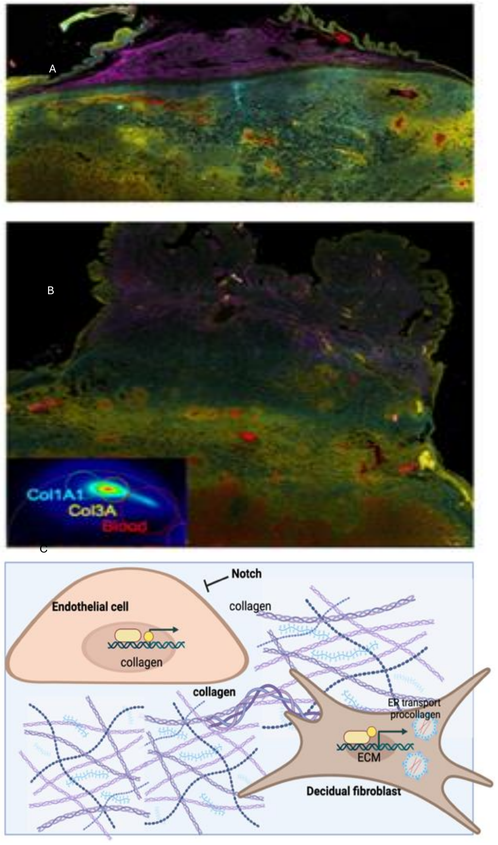

Figure 2. (A) Fluorescence lifetime imaging microscopy of uterine tissues from mouse pregnancies without PAS and without scarring compared to (B) PAS mice. (C) Collagen remodeling is a requirement for endothelial cell migration at the maternal-fetal interface and modulated by decidual fibroblast driven ECM production and regulation through endoplasmic reticulum transport.