



CAIRIBU URO-AGING RESEARCH INTEREST GROUP (UroAging RIG)

CAIRIBU URO-AGING KNOWLEDGE EXCHANGES

EXECUTIVE SUMMARY 4/27/2026

URO-AGING RESEARCH INTEREST GROUP

FEAT: MARIA FLORIÁN-RODRIGUEZ, MD

4/27/26 [3-4PM ET]

(2PM CT | 12PM PT)



Goal: Facilitate knowledge exchange and spur collaborations in uro-aging research and adjacent fields

Summary

When Cells Age and Support Fails: Cellular Senescence and ECM Remodeling in Pelvic Organ Prolapse

Introduction to Pelvic Organ Prolapse and Aging

- [Dr. Florian-Rodriguez](#) provided background on pelvic organ prolapse (POP), which occurs when pelvic organs descend from their normal anatomical position.
- An estimated 30-50% of women will develop POP in their lifetime and experience a range of symptoms; surgical correction is a common treatment worldwide.
- Her lab's work seeks to understand the cellular mechanisms driving POP - particularly, if it is fundamentally an age-related disorder, as POP prevalence increases with age.

The Role of Cellular Senescence

- Dr. Florian-Rodriguez explained that **cellular senescence is the stable, irreversible arrest of the cellular cycle in response to stressors** such as DNA damage, oxidative stress, or mechanical injury. It can be protective in the short term in that it serves roles in wound healing and tumor suppression and prevents damaged cells from proliferating.
- Senescent cells secrete a complex mixture of pro inflammatory mediators and matrix degrading enzymes, known as **senescence associated secretory phenotype (SASP)**.
- The SASP process creates a pro-inflammatory local environment and can induce senescence in neighboring healthy cells through paracrine signaling – this is known as **paracrine senescence**.
- With aging, the clearance of senescent cells becomes less effective, leading to their accumulation in tissues like the pelvic floor. Several conditions related to aging have been shown to have elevated burdens of senescent cells, with experimental clearance leading to functional improvement.

Mechanistic Model of POP

- Dr. Florian-Rodriguez presented a mechanistic model linking pelvic floor injury (from childbirth, chronic straining, menopausal hormonal shifts), cellular senescence, and POP.
- Pelvic floor injury induces DNA damage, activating the cyclic GMP-AMP synthase (cGAS) signaling axis, leading to cellular senescence and the secretion of matrix metalloproteinases and pro-inflammatory cytokines.
- Matrix metalloproteinases degrade elastic fibers and fragment fibulin-5, leading to a self-perpetuating cycle of matrix degradation, weakened supportive tissue, and impaired structural architecture.
- The model suggests that **intervening at multiple points in this cascade could offer opportunities to modify the course of POP**.

Senolytics and Their Potential in Treating Pelvic Organ Prolapse

- Senolytics are drugs designed to selectively target senescent cells for apoptosis and decrease senescent cell burden to, ideally, restore normal tissue function.

- **Combination dasatinib and quercetin (DQ) is highlighted as a promising senolytic regimen**; it has been associated with improved intervertebral disc disease, pulmonary fibrosis, and diabetic kidney disease, as well as improved survival in mice.
- The theoretical framework for using senolytics in pelvic floor disease involves reducing inflammation, improving tissue architecture, and, ideally, preventing or ameliorating prolapse.

In Vitro and In Vivo Data on Senolytics

- ***In vitro* data showed that etoposide reliably induces senescence in vaginal fibroblasts** and that DQ treatment reduces senescence markers.
- Gene expression data confirmed that DQ treatment attenuates inflammatory gene expression and clears senescence cells.
- *In vivo* data using the fibulin-5 knockout mouse model showed that DQ treatment did not rescue the prolapse phenotype but that DQ modified p53 expression, a key mediator of senescence signaling.
 - Dr. Florian-Rodriguez used a systemic oral administration of DQ, but given that prolapse is a localized condition affecting specific pelvic tissues, perhaps a local delivery strategy would achieve more targeted tissue concentrations.
- **Dosage and timing likely matter enormously**; perhaps senolytics are more effective later in the disease or at higher senescence burden.

cGAS Inhibition and Its Impact on POP

- Dr. Florian-Rodriguez discussed the impact of cGAS inhibition on POP using a double knockout mouse model.
- Genetic deletion of cGAS ameliorated the prolapse phenotype, validating cGAS as a mechanistic driver of prolapse and not simply a correlate. **cGAS is a highly promising therapeutic target, warranting further investigation.**
- Immunofluorescence data showed reduced expression of senescence markers in the double knockout mouse model.

Summary and Future Directions

- **Key points:** Cellular senescence contributes to POP, there is a need for gene-specific senolytics, and more studies are needed to optimize timing, dosage, and route of administration.
- Future work includes determining the specific cell population responsible for prolapse and evaluating other tissues like pelvic floor muscles and uterosacral ligaments.

María E. Florián-Rodríguez, MD, is an Associate Professor in the Department of Obstetrics and Gynecology and a UT Southwestern Dedman Family Scholar in Clinical Care. She is a urogynecologist and specializes in the treatment of pelvic floor disorders. Dr. Florián-Rodríguez's clinical interests include the surgical treatment of pelvic organ prolapse, urinary incontinence, mesh complications, and fistulas. Her research focuses on the molecular and cellular mechanisms underlying pelvic floor disorders, with particular interest in tissue regeneration, cellular senescence, fibrosis, and the impact of injury and repair pathways on surgical outcomes. include studying the relationship between the vaginal extracellular matrix, cellular senescence, and prolapse. As a physician-scientist, she is driven by a deep commitment to improving long-term outcomes for women through science-informed care, and her research bridges the gap between bench and bedside in the field of urogynecology.