Cystitis cystica and recurrent UTIs in postmenopausal women

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The Urinary Bladder and Urothelium

Stores urine until a socially appropriate time to void

- Highly impermeable
- Changes shape
- Slow turnover
- Rapid response to damage
Urinary tract conditions and diseases worsen with age

- Recurrent urinary tract infection (rUTI)
- Interstitial cystitis/bladder pain syndrome (IC/BPS)
  - Sterile inflammation
  - Barrier dysfunction
  - Most often diagnosed in 40s
- 50% of women over 65 have incontinence
- Overactive bladder/urge incontinence (OAB)
  - “Non-inflammatory”
  - Leakage with urge
  - Overactive detrusor muscle
- Stress incontinence
  - Leakage with coughing, laughing, sneezing, etc.
  - Weakness or spasm of pelvic floor muscles

Urinary tract infections (UTIs)

- Most common infectious disease in women (>50% lifetime risk)
- Economic burden >$2 billion annually in US
- Most common reason for outpatient antibiotic prescription
- 20-50% become recurrent UTIs (rUTI)
  - Repeat infection within 6 months of initial infection
  - Despite appropriate antibiotic treatment
  - Women 55+ have ~50% recurrence

Number of recurrent infections within 1 year

![Graph showing recurrence rates]

- 53% recurrence in 55+
- 36% recurrence in <55

“Inflamm-aging”

**Protective**
- Protection from pathogens
- Response to vaccines
- Control of chronic/latent infections
- Removal of mutated cells

**Pathogenic**
- Chronic inflammation
- Autoimmune/inflammatory disease
- Tissue degeneration
- Pro-tumorigenic

Immune System
“Inflamm-aging”

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Mouse model of aging

Young mice – 2-4 months
Aged mice – 18-22 months
Aged mice have frequent UTI recurrences and enhanced QIR formation

Aged mice have spontaneous rUTI phenotype

Large QIR in aged mice

Fashemi et al., in prep
RNA-sequencing reveals highly altered aged bladders

417 genes

>2-fold change, FDR-adjusted p<0.05

Enrichment of Bladder Immune Cells for scRNA-seq

Mince and digest

Immune cell enrichment

Lymphocytes displace macrophages as the predominant immune cell in the aging bladder

Lymphocyte accumulation in aged bladders

Lymphocytes localize to distinct aggregates in bladders from aged mice

Structure suggests bladder tertiary lymphoid tissues (BTLT)

Tertiary Lymphoid Tissues (TLTs)

- Resemble structure & organization of SLOs
- Form ectopically in chronically inflamed tissues
- Play a role in local immune responses
  - Autoimmunity, cancers, chronic infections, atherosclerosis
  - Pathogenic vs. protective?

Aloisi and Pujol-Borrell (2006) Nat Rev Imm
Lymphoid follicle formation increases with age

Cystoscopy in rUTI patients

Normal bladder
Cystitis cystica (CC)

- Small red, yellow, to gray nodules observed on cystoscopy
- Incidental, non-specific chronic inflammation, non-malignant
- Lack of sufficient literature on CC
  - Unknown epidemiology, pathogenesis, or significance (other than “chronic inflammation”)

Are CC nodules are similar to bTLT seen in aged mice?
CC biopsies contain bTLT

Representative images from n=15 patients
CC biopsies resemble mouse bTLTs

Cystoscopic appearance

Classic, well-formed germinal center

B and T cells

Follicular dendritic cell (FDC) network

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