Senescence of the Immune System

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### CDDW/CASL Meeting Session: (Faculty Template Slide)

**CanMEDS Roles Covered in this Session:**

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
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<tbody>
<tr>
<td>Medical Expert (as Medical Experts)</td>
<td>Physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.</td>
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<tr>
<td>Communicator (as Communicators)</td>
<td>Physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.</td>
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<td>Collaborator (as Collaborators)</td>
<td>Physicians effectively work within a healthcare team to achieve optimal patient care.</td>
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<td>Manager (as Managers)</td>
<td>Physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.</td>
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<tr>
<td>Health Advocate (as Health Advocates)</td>
<td>Physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.</td>
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<tr>
<td>Scholar (as Scholars)</td>
<td>Physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.</td>
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<tr>
<td>Professional (as Professionals)</td>
<td>Physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.</td>
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The aging population
a world-wide healthcare crisis

Most rapidly growing segment is the “oldest old”
In 2001 = 430,000 = >2X 1981 = 20X 1921

“Oldest old”
- require more health care
- consume ~ 1/3 annual health care dollars
“Inflamm-aging”

- Global reduction in the ability of the elderly to cope with antigenic, chemical, physical and nutritional stressors
- Concomitant progressive increase in proinflammatory markers
- Age-related pathologies share a common inflammatory pathogenesis

The “diseasome” of inflamm-aging

- Cancer
- Cardiovascular diseases
- Atherosclerosis
- Hypertension
- Frailty
- Sarcopenia
- Alzheimer’s disease
- Dementia
- Depression

Adapted from Cevenini et al. 2013
Increasingly pro-inflammatory environment of the aged intestine

- Aging increases the vulnerability to gastrointestinal (GI) disorders
- 35-40% of geriatric patients report at least one GI complaint during routine physical examination (Hall et al., Gastroenterology 2005)

Tran & Greenwood-Van Meerveld, 2013
Intestinal immune system

1) epithelial barrier function
Intestinal permeability increases with age

Tran & Greenwood-Van Meerveld, 2013
2) M cell function
Microfold cell (M-cell) density is reduced in aged mice

- M-cells have an important role in the induction of specific mucosal immune responses in Peyer’s patches
- Efficient M-cell sampling of gut luminal antigens is required for the induction of some mucosal immune responses

Kobayashi et al. Mucosal Immunol, 2013
Uptake of particulate antigen into Peyer’s patches and secretion of IgA is impaired in aged mice

Kobayashi et al. Mucosal Immunol, 2013

Schmucker et al. Mech Age Dev 2001
3) phagocytic cell function

MacDonald and Monteleone, Science 2005
Phagocytic cells in aging

Reduced chemotaxis

Altered localization of Toll-like receptors and signaling components to lipid rafts

Reduced superoxide production

Decrease in TLR4 in lipid rafts but not TLR2
Macrophages fail to efficiently clear alpha-synuclein aggregates in the ENS of aged rats

CD163+ macrophage = black
alpha-synuclein debris = dark brown

Intestinal immune system

4) Dendritic cells
Dendritic cells in Aging

Numbers and morphology of DCs are comparable

Aged DCs display increased basal activation

Agrawal et al. J. Immunol 2009

Dendritic cells in Aging

Reduced phagocytic activity

Impaired ability to phagocytose apoptotic cells

- impaired maintenance of self-tolerance
- increased production of pro-inflammatory cytokines

Mesenteric lymph node DC from older mice are unable to prime young T cells

**in vitro**

**A**

- 8 week DC + EC
- 9 month DC + EC
- 8 week DC - EC
- 9 month DC - EC

* * p≤0.004

**B**

- 8 week T cells + EC
- 9 month T cells + EC

**C**

- IL-12 (pg/ml)
- DC: 8 week, 9 month
- EC: -, +

p=0.003
p=0.015

T cells respond equally well to in vitro priming.  

**in vivo**

**A**

- 8 week spleen DC + EC
- 8 week MLN DC + EC
- 9 month spleen DC + EC
- 9 month MLN DC + EC

* * p≤0.01

**B**

- 8 week spleen DC + EC
- 8 week MLN DC + EC
- 9 month spleen DC + EC
- 9 month MLN DC + EC

* * p≤0.01

Intestinal immune system

5) T and B cells

MacDonald and Monteleone, Science 2005
**Thymic involution**

- Naïve T cell output of thymus
  - infants = $>10^9$ CD4+ cells/day
  - 20 yr old = $6-7 \times 10^7$/day


Lynch et al. Trends in Immunology 2009

78 yr old woman – continuing thymopoiesis into at least the 5th decade of life
Key changes in T cells with age

- Expansion of memory cells
- Decrease and even exhaustion of naïve cells
- Shrinkage of T-cell repertoire
- Global reduction of the "immunological space"

Diagram showing:
- Activation of naïve T cells by dendritic cells
- Differentiation into Th1, Th17, Treg, and Th2 cells
- Production of IFN-γ, IL-22, IL-17, IL-10, TGF-β, IL-4, IL-13, IL-5

Graph illustrating the change in T cell population over time from newborn to adult to elderly, with naïve and memory T cell populations decreasing.
Aged and naïve TCR beta-chain diversity

- Frequency distribution is very well maintained up until the age of 65 yrs, despite marked decrease of thymic output

- severely contracted TCR repertoires after ~75 yrs of age.

Age-related T cell activation deficits with age

- Exhausted T-cells are monoclonal expansions
- lose ability to home to secondary lymphoid organs

Loss of CD28:
- CD4+ cells:
  - resistant to apoptosis
  - produce proinflammatory cytokines
  - perpetuate inflammation
- CD8+ cells:
  - resistant to apoptosis
  - enhanced cytotoxic capacity
  - reduced antibody response to vaccination

- in aged population: 15% of CD4+ and 60% of CD8+ T cells have lost CD28

Moro-Garcia et al. Curr Genomics 2012
Low IL-2 production impairs T cell proliferation

Addition of IL-2 restores the proliferative capacity of aged CD4 cells

Haynes et al. JEM 1999
Aging B-cells

- reduced IL-2 production contributes to impaired humoral (B cell) response in the aged
- decreased output from bone marrow
- peripheral B cell numbers stay constant
- composition changes

Johnson and Cambier Arthritis Research & Therapy 2004
Aging and Tregs

- increased frequency of Tregs in aged humans and mice controversial!


- due to reduced apoptosis rather than increased thymic output, increased peripheral proliferation or enhanced peripheral conversion

Aging and Tregs

• The frequency and absolute number of naturally occurring Tregs (both CD4+ and CD8+) increases with age.

• The inducibility of Tregs from nonregulatory CD4+ and CD8+ precursor cells declines.

• Aged Treg function
Aging and neuromodulation of immunity

Nijhuis et al. 2010
Aging and neuromodulation of immunity

Sympathetic

Rat jejunum 6 moa

Rat jejunum 24 moa

Varicosities / 100μm axon with age

Varicosities / frame area with age

Baker and Santer
Mech Age Dev 1988
Cholinergic anti-inflammatory pathway

Phillips and Powley Auton Neurosci 2007
The gut loses its mind with age

Neuron loss
(up to 40-60% in rat and human colon)

Preferentially affecting cholinergic neurons
[Bernard et al. 2009 (human); Cowen et al. 2000 (rat)]

McClain, Grubišić et al. Gastroenterology 2013

Inflamm-aging as a consequence of macroph-aging

increase in proinflammatory status at an organismal level, caused by chronic age-related stimulation of the macrophage

Microglia derived from aging mice exhibit an altered inflammatory profile

altered morphology with age (decreased branching)

accumulation of lipofuscin deposits
Nlrp3 inflammasome links systemic low-grade inflammation to functional decline in aging

• NLRP3 is strongly expressed in myeloid immune cells, particularly splenic conventional DCs, monocytes, macrophages, and neutrophils

• Unifying activator of the NLRP3 inflammasome is the generation of ROS

Youm et al., Cell Metabolism 2013
Ablation of Nlrp3 inflammasome reduces innate immune activation in CNS

Youm et al., Cell Metabolism 2013
Activation of Nlrp3 inflammasome reduces T cell progenitors in aging

Youm et al., Cell Reports 2011
Ablation of Nlrp3 inflammasome reduces age-related thymic involution

Youn et al., Cell Metabolism 2013

- mechanism is independent of IL-1
Conclusions

- Loss of barrier function
- Impaired phagocytic activity
- Loss of self tolerance
- Loss of suppressive Treg functions
- Autonomic neuropathy

M cell dysfunction

T cells
- Accumulation of effector cells
- Loss of naive T cells

B cells
- Reduced B cell production
- Weak antibody response

MacDonald and Monteleone, Science 2005
Acknowledgements

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