Journal of Molecular Science

Journal of Molecular Science
Volume 34 Issue 1, Year of Publication 2024, Page 6-8
DoI-17.4687/1000-9035.2024.003

Journal of Molecular Science
www.jmolecularsci.com ISSN:1000-9035

Deciphering Age-Associated Dysregulation in Innate Immune Signaling and Its Role in Heightened Susceptibility to Infectious Diseases

Olivia May Jenkins, George William Harris, Daisy Elizabeth Morris, Jack Edward Palmer

Article Information
Received: 02-02-2024
Revised: 12-02-2024
Accepted: 28-02-2024
Published: 20-03-2024

Keywords
Pattern Recognition Receptor (Prr)

ABSTRACT
Aging is associated with significant alterations in immune function, collectively termed "immunosenescence." These changes compromise the innate immune system, leading to increased susceptibility to infectious diseases. This study explores the molecular and cellular mechanisms underlying age-associated alterations in innate immune signaling, emphasizing pattern recognition receptor (PRR) dysfunction, inflammasome activation, cytokine dysregulation, and myeloid cell functional impairments. We analyze how these changes affect pathogen recognition, inflammatory responses, and resolution of infections. This article further discusses potential therapeutic strategies targeting age-induced immune dysfunction. Understanding these mechanisms is crucial for developing interventions to mitigate infection risks in the elderly.

1. INTRODUCTION

Aging induces profound modifications in the immune system, increasing susceptibility to infections, autoimmune diseases, and impaired vaccine responses. The innate immune system serves as the first line of defense against pathogens; however, with aging, it undergoes structural and functional changes that compromise host defense mechanisms. This review provides an in-depth analysis of age-associated changes in innate immune signaling and their implications for infectious disease susceptibility.

2. Age-Associated Changes in Pattern Recognition Receptor (PRR) Signaling

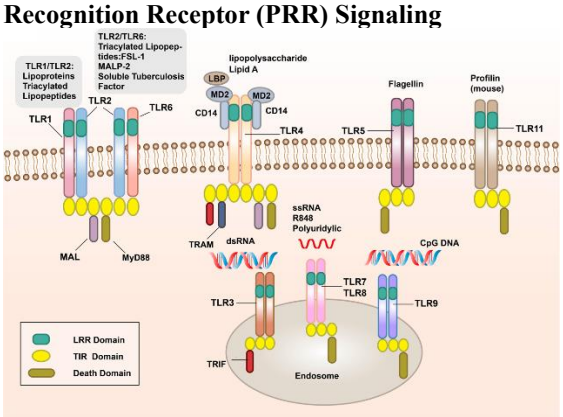

Fig.Pattern Recognition Receptor (PRR) Signaling

Journal of Molecular Science
Volume 34 Issue 1, Year of Publication 2024, Page 6-8
DoI-17.4687/1000-9035.2024.003

PRRs, including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain-like receptors (NLRs), and C-type lectin receptors (CLRs), play a pivotal role in pathogen recognition. Aging results in reduced expression and altered signaling pathways of PRRs, impairing pathogen detection and immune activation. Studies show diminished TLR4 expression on macrophages and dendritic cells in aged individuals, leading to reduced NF-κB activation and impaired cytokine responses.

Table 1 illustrates the age-related decline in PRR function across different cell types.

PRR Type	Young Immune Cells	Aged Immune Cells	Functional Consequence
TLR4	High expression	Reduced expression	Impaired bacterial recognition
NLRP3	Efficient inflammasome activation	Hyperactivation	Chronic inflammation
RIG-I	Robust antiviral response	Decreased IFN production	Higher viral susceptibility

3. Dysregulation of Inflammasome Activation and Chronic Inflammation

The inflammasome is crucial for cytokine production and immune regulation. Aging leads to chronic, low-grade inflammation termed "inflammaging," characterized by persistent activation of the NLRP3 inflammasome. While this response is beneficial for acute infections, prolonged inflammasome activation contributes to tissue damage and immune exhaustion. Elevated IL-1β and IL-18 levels have been correlated with increased mortality in elderly patients with infections. This section delves into the molecular triggers driving persistent inflammasome activation in aging and its implications for disease progression.

4. Cytokine Imbalance and Its Impact on Infection Susceptibility

Aging disrupts cytokine homeostasis, with increased pro-inflammatory cytokines (IL-6, TNF-α) and decreased anti-inflammatory cytokines (IL-10). These alterations lead to ineffective pathogen clearance and prolonged inflammatory responses. Figure 1 depicts the cytokine profile differences between young and aged immune systems. The imbalance in cytokine signaling affects monocyte and macrophage function, reducing phagocytic activity and antigen presentation capabilities.

5. Age-Related Myeloid Cell Dysfunction and Impaired Phagocytosis

Monocytes and neutrophils are critical in innate immunity, but aging impairs their recruitment, chemotaxis, and phagocytic activity. Aged neutrophils exhibit delayed apoptosis and reduced NETosis, leading to inadequate pathogen clearance. Furthermore, macrophages in aged individuals show decreased M1 polarization, resulting in suboptimal pro-inflammatory responses necessary for pathogen elimination.

Table 2 outlines functional differences in myeloid cells with aging.

Cell Type	Young Immune Cells	Aged Immune Cells	Functional Defect
Neutrophils	High NETosis activity	Reduced NETosis	Impaired bacterial clearance
Monocytes	Effective phagocytosis	Decreased phagocytosis	Increased pathogen burden
Macrophages	Strong M1 polarization	Skewed towards M2 phenotype	Weak antimicrobial response

6. Implications for Infectious Disease Susceptibility in the Elderly

Age-related innate immune dysregulation significantly increases vulnerability to bacterial, viral, and fungal infections. Influenza, pneumonia, and COVID-19 have shown higher morbidity and mortality rates among elderly individuals due to compromised innate immune defenses. This section explores clinical data correlating innate immune decline with infection severity, emphasizing the importance of personalized immunomodulatory strategies.

7. Therapeutic Interventions and Future Perspectives

Targeting age-associated immune dysfunction holds promise for improving infection outcomes in older adults. Potential strategies include:

- Pharmacological modulation of PRR signaling to enhance pathogen recognition.
- Inflammasome inhibitors to mitigate chronic inflammation.
- Cytokine-based therapies to restore immune balance.
- Enhancing myeloid cell function through metabolic and epigenetic reprogramming. Future research should focus on translating these strategies into clinical applications to reduce infection-related mortality in aging populations.

8. CONCLUSION

Aging-induced alterations in innate immune signaling contribute significantly to increased infectious disease susceptibility. Understanding the molecular pathways driving these changes is crucial for developing targeted therapies. This review highlights the need for age-specific interventions to restore innate immune competence and improve health outcomes in elderly individuals.

9. REFERENCES

1. Akbar, A. N., & Gilroy, D. W. (2020). Aging immunity

Journal of Molecular Science
Volume 34 Issue 1, Year of Publication 2024, Page 6-8
DoI-17.4687/1000-9035.2024.003

and COVID-19: how to risk-stratify patients. *The Lancet*, *395*(10231), 1088-1090.
2. Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., & Santoro, A. (2018). Inflammaging: a new immune–metabolic viewpoint for age-related diseases. *Nature Reviews Endocrinology*, *14*(10), 576-590.
3. Fulop, T., Dupuis, G., Witkowski, J. M., & Larbi, A. (2016). The role of immunosenescence in the pathogenesis of COVID-19 and aging-related diseases. *Cells*, *9*(4), 730.
4. Goronzy, J. J., & Weyand, C. M. (2019). Mechanisms underlying T cell aging. *Nature Reviews Immunology*, *19*(9), 573-583.
5. Nikolich-Žugich, J. (2018). The twilight of immunity: emerging concepts in aging of the immune system. *Nature Immunology*, *19*(1), 10-19.
6. Oishi, K., & Uchida, T. (2016). Role of innate immune cells in aging and aging-related diseases. *Frontiers in Immunology*, *7*, 152.
7. Shaw, A. C., Goldstein, D. R., & Montgomery, R. R. (2013). Age-dependent dysregulation of innate immunity. *Nature Reviews Immunology*, *13*(12), 875-887.
8. Simon, A. K., Hollander, G. A., & McMichael, A. (2015). Evolution of the immune system in humans from infancy to old age. *Proceedings of the Royal Society B: Biological Sciences*, *282*(1821), 20143085.
9. Zhang, H., Ryu, D., Wu, Y., Gariani, K., Wang, X., Luan, P., ... & Auwerx, J. (2016). NAD+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science*, *352*(6292), 1436-1443.