Clinical Summary

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Yousefzadeh MJ, Flores RR, Zhu Y, et al. An aged immune system drives senescence and ageing of solid organs. Nature 2021;https://doi.org/10.1038/s41586-021-03547-7.

Immune Aging May Drive Overall Aging

This strategic series of laboratory investigations clarifies that senescence of the immune system hastens and may precede systemic aging. Animals genetically modified for accelerated aging of white and red blood cells displayed immunosuppression and a senescence-associated secretory phenotype (SASP), which has been associated with 'inflamm-aging' and disequilibrium between immune offense and defense functions.

Research advances in the past decade have demonstrated that organismic aging occurs as the result of altered metabolism in cells and tissues, leading to heightened oxidative stress and immune imbalance. Because immune cells help regulate tissue and circulatory environments, they can significantly influence biological aging and immunometabolic tone throughout the body. For this reason, aging of immune cells and subsequent changes in the regulation of immunity itself may have disproportionately great influence over whole-body senescence.

The innate immune system must detect pathogens and pathogenic tissue changes, and it is charged with cataloguing an organism's ever-expanding immune memory bank. In an immune response, innate and adaptive arms of immunity coordinate the mobilization of resources to address threats and restore tissue homeostasis. Both of these aspects of immunity undergo aging; while innate immunity tends to become more active as genetic damage, oxidative stress, and epigenetic repatterning progress over a lifetime, adaptive immunity tends to become less targeted and efficient with age. The result of these changes is often an individualized mosaic of reduced immunity to pathogens (immunosuppression) paired with heightened propensity for inflammation.

This study employed an animal model of accelerated hematopoietic cell aging, selectively deleting a DNA-repair gene from these cell populations in mice. These mutant mice were compared over time with normal 'wild-type' and with progeroid (prematurely senescent) mice for

changes in immune cell populations, vital organ function, and lifespan. The team then examined the effects of transplanting spleen cells from young animals into aged ones, and vice versa. Finally, they treated the genetically-altered mice with the senolytic (senescent cell-clearing) agent rapamycin to observe its influence on SASP expression.

According to this research team:

"Senescence in the immune compartment, as occurs with normal ageing, affects innate and adaptive immunity, in particular follicular helper T cells and natural killer cell function, and potently drives senescence and age-related changes in solid organs."

Research Summary

In discovering how senescence of immune cells hastens body-wide aging in mice with a DNA repair gene deletion, this research team found the following:

- As part of their senescence-associated secretory phenotype (SASP), aged and damaged cells may express the key senescence markers p16 and p21. The gene-deleted mice expressed higher levels of these and other SASP markers in their B cells, T cells, natural killer cells, and macrophages, as well as in bone marrow and spleen cells. Naïve (undifferentiated) T cells and immunomodulatory T regulatory cells were also strongly impacted.
- The mutant mice showed minimal immune changes in youth, but in middle age developed leukopenia (reduced white cell counts) that particularly affected T and B cells, while memory T cell counts increased. Over time, they displayed reduced thymic and splenic weight and lymph node atrophy. These signs indicated degeneration of immune capacity and balance.
- Expression of the Nrf2 master antioxidant enzyme was upregulated in young mutant mice, yet its activity was significantly reduced in older gene-deleted animals. Older animals also showed higher levels of lymphoid organ oxidative stress and lower spleen levels of the antioxidant glutathione in its more potent reduced form.
- An especially notable finding was that in mutant mice, the liver, kidneys, lungs, and pancreas variously showed marked increases in tissue damage and SASP expression, along with lower levels of reduced glutathione. These animals also displayed lower grip strength, impaired muscle regeneration, and lower levels of cushioning glycosaminoglycans in their intervertebral discs, all of which are associated with aging.
- The mutant mice showed a significant decrease in the ratio of pro-resolving M2 macrophages to proinflammatory M1 macrophages, demonstrating how senescence impacts the polarization of these crucial tissue-resident immune cells.
- Mutant mice receiving spleen cell transplants from normal young mice displayed reduced tissue damage and SASP expression, while mice receiving senescent spleen cells from

gene-deleted animals soon showed upregulation of SASP expression. This proves that the senescence status of immune cells is transplantable.

- Mutant mice had significantly shortened lifespans along with reduced healthspan, and the researchers concluded that senescence-driven alterations to vital function contributed to these losses.
- Gene-deleted mice given the senolytic drug rapamycin displayed reductions in circulating cytokines, and the treatment also elicited lower SASP expression in these animals' peripheral T cells, demonstrating potential benefits from targeted senolytic agents.

CONCLUSION

Senescent immune cells are key contributors to systemic aging through their impaired function and proinflammatory signaling, with subsequent alterations in the regulation of immunity. Senolytics can aid the elimination of these aged and dysfunctional cells, yet senolytic agents tend to be quite selective in the types of cells they influence. This study identifies immune cells as a pivotal target for senolytic substances. The use of appropriate senolytics may potentially help preserve vital organ function and limit immunosuppression and inflammation during aging.