

# RA: A Role for Immunosenescence?

This article discusses the mechanism by which immunosenescence spawns autoimmunity and the evidence that it is involved in the development or progression of RA.

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# Definition

Immunosenescence is a gradual deterioration of the immune system that occurs w/ aging.

This can leave Elderly susceptible to:

1. Infection
2. Cancer
3. Possibly Autoimmune- mounting evidence shows it contributes to the pathogenesis of RA.

# Immune System

1. Innate component which includes the natural killer (NK) cells, macrophages, dendritic cells (DCs), and complement factors
2. Adaptive component including T and B cells

Innate is rapid and nonspecific and Adaptive slow starter but once activated is specific and generates immunological memory. Both work independently and together to mount an effective immune response.

# Effective adaptive immune response

Response that attacks and gets rid of foreign antigens and leaves the body's own cells and tissues unharmed. There are multiple mechanisms that insure self-tolerance which include:

1. Central tolerance mechanisms in the thymus
2. Peripheral tolerance which relies on interaction between T-cells and DCs.

# Two Signal model of activation

- Signal 1 DCs to Naïve T-cell via presentation of antigen using MHC to TCR.
- Signal 2 DC to Naïve T-cell via B7 to CD28
- This signaling leads to differentiation and clonal expansion CD8+ and CD4+ and then memory cell
- In Autoimmunity there is a loss of expression of the CD 28 on the T-Cell. CMV is associated w/ increase numbers of CD28- T-cells. (CMV found 50% of adult population and 90% of elderly individuals)

# Autoimmunity

Convergence of Genetic predisposition and environmental triggers can result in immune system recognizing the body's own cells as foreign.

Given the interaction between the innate and adaptive immune system there is no doubt that both play a role in the initiation and perpetuation of RA.

# T-Cells

RA is associated w/ genes encoding molecules involved in T-Cell activity such as HLA-DR4, CTLA4, and PTPN22

Rheumatoid joints have abnormally high T-cell numbers

T-cells drive the development of arthritis in animal models

# B-Cells involvement in RA

- B cells are present in RA joints
- There are autoantibodies that are specific to RA
- The autoantibodies can be used to exacerbate RA in mice
- Therapeutic efficacy of B-cell depleting agents in pt w/ RA.

# Innate immune cells in RA

- DCs
- Macrophages

Both can lead to the breach of self tolerance in RA by presenting arthritogenic antigens to autoreg T cells, and to the destruction of joint cartilage by producing proinflammatory and degradative mediators.

# Multiple Issues in RA

Characterized by inflammation and cartilage and bone erosion in the synovial joints, RA is also a systemic disorder and can affect multiple organs along w/ joints.

The mechanism by which self tolerance is initially breach remains to be defined but probably involves:

- dysregulation of immune system at the systemic level followed by immune system targeting joints

# Environmental Factors in RA

- Smoking is the only accepted risk factor
- There is also a link between periodontitis

Both involved in not recognizing citrulline as self.

# Immune system factors that change w/ Age and the aging of the immune system

- Aging of T-cells and decline in generation of new T-cells which is associated w/ normal involution of the Thymus and demise of Hematopoietic stem cells that give rise to T-cells
- Loss of T-cell diversity and co-stimulation control – decline in T-cell generation results in reduction of diversity. The decline in generation of new T-cells elicits compensatory increase in prolifer of naïve and memory T-cells in the periphery which is proposed to lean toward recognition of self.
- The question is Cause or Consequence?
  - does premature immunosenescence increase susceptibility to RA or is result of RA.
  - Two theories to CD28- T cells, 1) b/c of accelerated prolifer and through autoregativity, contribute to breach of tolerance that lead to the development of RA and 2) or CD28- is secondary to the development of RA that stem from the chronic immune stimulation associated w/ RA in a manner analogous to the exhaustion of the immune system in older adults by CMV mediated chronic stimulation of immune system.

# Other Immune system Factors

- The changing face of naïve CD4 T-cell subsets – Increase production of IL-17 by TH17 cells are important in certain autoimmune diseases
- Overreacting memory B-cells and increase of autoantibodies w/ increasing age
- DCs, macrophages, neutrophils, and NK cells become dysregulated.
- Increase in proinflammatory cytokines TNF and IL6 w/ aging which could be associated w/ macrophages and the senescence of fibroblast and epithelial cells which can change the secretory profile of these cells, as well as expression of these cytokines in adipose tissue in older individuals.

# Conclusion

- Longer life expectancy = need for research on the aging immune system which can lead to cancer, infection and certain autoimmune disease like RA.
- Pathological features typical of immune dysfunction include: Loss of T-cell diversity, dysregulation of T-cell reactivity, high levels of autoantibodies and proinflammatory cytokines, and perturbation of DC activity. All of these could lead to the development or progression of RA.
- A Clear picture is still needed to explain the relationship of immunosenescence and RA.
- With more research w/ specific immunosenescent parameters could potentially be a screen for predictors of RA; although reliable predictors of the development of RA still need to be found, anti-CCP antibodies are promising and other prognostic biomarkers are in development.
- Understanding the mechanisms underlying immunosenescence should help us understand the pathogenesis, and inform strategies for the tx of RA
- Clinical trials are underway for strategies aimed at reversing T-cell senescence, which could potentially present a novel approach to the tx of RA