ABSTRACT

With the progression of aging, the immune system and the tendency for abnormal immunological changes are common. Individuals over the age of 50 years are susceptible to infectious diseases as well as inflammation and immune-mediated tissue damage. Aging is the main cause of disease pathology and death, continuously enhancing the risk of cardiovascular disease, malignancy, and infectious diseases. One of the important causes is higher susceptibility to autoimmune diseases like rheumatoid arthritis and other immunodeficiency syndromes. Inflammation is common in age-related pathologies. In immune cells, T lymphocytes have an extensive life cycle and show a robust copying force, constructing them sensitive to ageing-associated pathologies. In dysfunctional ageing of T-cells, protection of T-cell function and cells capable of promoting inflammation are abundant. Rheumatoid arthritis is a long-lasting autoimmune disease that mainly affects the joints. Though RA develops at an early age, the frequency of developing RA increases with the increase in age. It is also seen that RA may develop as a result of premature ageing (immunosenescence) of the immune system. In RA, T-cell ageing occurs prematurely, but the mechanism involved and their role in tissue damage is still uncertain. T-cell ageing and its effects on rheumatoid arthritis are discussed here, as well as how T-cells participate in tissue damage, acute and chronic inflammation, and the ageing process. Also review the DNA damage in response to T-cell aging, telomeric ends shortening during RA and immunosenescence, and T-cells in RA.

**Keywords:** T-cells, Rheumatoid arthritis, Aging, Immunosenescence, Inflammation, Telomere
INTRODUCTION

In the world, thousands of people are getting older with the progression of the human life span and it is becoming a great challenge. Primarily in the world, the overall ratio of people over the age of 65 years leads to a growing interest in the health status of the elderly, diseases that cause rapid mortality, and the financial burden imposed by the care of sick people (1–4). In most countries, getting older is associated with the onset of tumors, cardiovascular disorders, metabolic diseases, and autoimmune diseases (5). The process of immunosenescence is a prevalent and significant component of age-related diseases (6). Immune system ageing lowers the immune system's protective functions against tumor cells and pathogens, but it also increases the probability of autoimmunity and chronic inflammation. Immune ageing, like most other living systems, is a multi-step process that affects both innate and adaptive immunity as well as the tissue context in which immune responses occur (7,8). In the last few years, it has been seen that immunosenescence is also most common in rheumatoid arthritis. In spite of two different mechanisms, patients with RA have the same clinical features as immune compromised patients. RA exhibits irreversible bone and cartilage destruction and results in a short life span due to increased chances of CVS (cardiovascular) diseases. Immune ageing generally affects people after the age of 50 years, but it is faster in rheumatoid arthritis patients. (9,10). Cells devote a significant percentage of their machinery to DNA surveillance and repair to prevent aging or cell death associated with genome variability. In addition, endogenous and exogenous toxins continuously attack the DNA in each of our body's cells, causing damage to the genetic material. Cells trigger a specific extracellular and intercellular response network to recognize, signal, and repair DNA damage in order to prevent nucleotide change, double or single strand breaks, and to maintain DNA reliability (11,12). When the DNA regeneration system's activity declines, damaged DNA accumulates, causing cell death or loss of function. Immune ageing affects the host's defense against pathogen invasion, diminishes wound healing and repair, and increases vulnerability to chronic inflammation and the likelihood of autoimmune disease progression. In RA, the ageing process of immune cells is accelerated, resulting in prematurely aged T cells that lose CD28, have broken telomeres, and produce excessive amounts of cytokines (13) (14).

In this review, we have used the autoimmune disease RA as an example to accelerate T cell ageing and DNA damage in response to T cell aging, telomeric damage related to shortening of
telomeres in T cell aging, mtDNA damage in RA, and immunosenescence and T-cell ageing in RA.

1. Dysfunctional T cells aging in Rheumatoid arthritis

Detection of T cells in RA patients displays features of premature aging, addition of CD28 effector T cells, improper DNA repairing, overproduction of cytokines well matched with senescence-linked secretory functioning. The T cell compartments alter adaptive techniques for the development of new T-cells, the survival of remaining T-cells, and the evaluation of T cell functions in order to maintain immunological homeostasis. Due to the complexity of the thymus throughout the first third of life, humans take a diverse approach to the generation and maintenance of T cell compartments, producing new T cells by exploding previously released T cells (15). Cellular T cell alteration, characterized by cell swelling and TCR (T Cell Receptors) collection, serves as a host for ageing by optimization of anti-viral immunity. Changes in the composition and frequency of regulatory T cells may also be associated with aging (16,17).

In RA patients, the immune system ageing is dysfunctional and improper, which results in the addition of effector cells that induce inflammation and a host predisposition for unchallenged tissue inflammation (18). Unfavorable consequences of immune system ageing include incompetent protection from infection, poor vaccine response, increased susceptibility to cancer, and improper wound healing (19). Generally, studies are conducted on the CD4+ T cells of RA patients who have progressed to the stage of cell differentiation. Also, in previous studies, T cells of RA patients were used as a reference to activate CD4 T cells, which were transformed into effector cells. It is also observed that old RA T-cells remain multiplied and are highly functional (20). Recent studies reveal that functional assurance of RA T cells leads to continuous inflammation of synovial tissues and poor DNA repair (21,22).

2. Destruction of DNA response in T cell aging

DNA damage is considered as inducer of critical cellular aging (23). During cellular aging, multiple forms of DNA damage occur, which include somatic mutations, chromosomal abnormalities, and copy number mutations. These mutations affect the signaling pathway of transcription, which leads to immune cell dysfunction. (24). In old people, damage of DNA occur at blood stem cells, which is an indicator of incompetence of double strand break of DNA repair (9,25). The incidence of double strand breaks in human T cells increases with age,
especially memory T cells, which are more affected. With the passage of time, DNA damage increases the inflammatory responses, acute and chronic disease, and DNA damage results in cellular death, which enhances the higher concentration of cells lacking DNA in the blood plasma. This kind of patient has an increased risk of early death (26).

In patients with autoimmune disease, cells without DNA contribute to tissue damage and cellular inflammation. In eukaryotic cells, DNA replication and repair are associated with the maintenance of genome stability. In CD4 T cells of RA patients, the lack of a DNA damage restoration system results in the addition of telomeric DNA and non-telomeric DNA, which is linked with the ageing of T-cells and chronic inflammation (13,27,28).

3. Telomeric ends shortening in T cell aging

To estimate the age of T cells, telomeres are considered a precarious tool. In mice and other animals, telomeres are considered a biological tool to measure life expectancies. The length of telomeres in memory T cells is constantly shorter than in non-memory T cells. Remarkably, the length of telomeres did not become shorter than 5000 kb, and never attained telomeric disaster. (29). The manifestation of telomerase enzyme in T-cells, which acts as an enzyme (which is involved in transcription reversal) that may add sequence at the ends of telomeres, adds to the complexity of T cells. In RA, premature ageing of T cells may be linked with ageing that results in ultimate shortening of telomeres. (28,30). While the shortening of telomeric sequences clearly confines the capacity for proliferation and clone formation of T cells. In RA patients, the isolation of telomeres in naive CD4 T cells is seen shortened and also damaged, which gives rise to the question of whether a fault in the DNA repair mechanism affects telomeric function (13).

4. Pattern of Telomeres destruction

In RA T cells, basically four damage patterns are identified, which include

- The disparity of telomeric ends,
- Self- binding of both ends of the chromosome,
- Damage of telomeric sequence and
- Telomeres fragility.
Poor emplacement of nuclease MRE11A on telomeres is associated with interpreting T cells which are susceptible to injury. Recent research predicts that telomere repairing activity, which is essentially present on DNA break sites, is continuously expressed to avoid terminal damage of sequences. A composite of six sheltering proteins protects the telomeric ends from binding and the lysis of the nucleus. Loss of this sheltering protein complex leads to uncapping of the telomere and joining of chromosomes.(31,32) The sheltering protein TRF2 specifically interacts with the sensor MRE11A, which is associated with DNA damage in eukaryotes. The mechanism for DNA packing with sheltering proteins in RA T cells is not clearly understood. However, studies in human healthy T cells revealed that poor localization of MRE11A nuclease not only uncaps telomeres but also unties the heterochromatin. However, the precise mechanism by which telomeres convert functions of pro-inflammatory effectors remains unknown. Much more efforts are being made to measure the T cells' age by measuring the length of the telomeres sequence. It is most essential to find the mechanical reliability of telomeres in place of finding nucleotide sequences (33).

5. Mitochondrial DNA damage in Aging

Metabolic changes, DNA integrity protection, and energy production occur in the mitochondria, which is referred to as a powerhouse for energy production because significant energy is produced to perform normal cell functions. Mitochondria contain electron transport chains that act as their own systems, which act against oxidation systems, and two membranes are present that maintain a membrane gradient within the mitochondria itself. Mitochondria are also involved in signal transduction and oxidative phosphorylation. Maintaining mtDNA integrity is important to avoid cell ageing (34). mtDNA is present in the cytoplasm as well as outside the cell, and the amount of circulating mtDNA is involved in anti-inflammatory function. Mutation in mtDNA results in a disturbance of balance between production and consumption of reactive oxygen species, which leads to disturbances in metabolic function and also chronic inflammation(35). In the TLR9-Myd88 signalling pathway, circulating mtDNA is found to be associated with the prevalence of many inflammatory diseases like rheumatoid arthritis (36). mtDNA is considered an immune regulator and also provides communication during cell stress in a microenvironment. It is still not clearly understood how mtDNA is linked with ageing and how it activates cellular aging.
6. Immunosenescence and T cells in Rheumatoid arthritis

Aging effects the whole immune system, but T-cells are considered more sensitive. Aging of T-cells causes an increase in CD4+ and a deficiency of CD8+ manifestation in the CD28 molecule. Initiation and propagation of T-cells continuously decrease with age (37). The outcomes of CD28 loss are different in both CD4+ and CD8+ T-cells. In CD8+ T-cells, it results in decreased function, while in CD4+ T-cells, it results in overproduction of inflammatory cytokines and cytotoxicity. Chronic autoimmune diseases, including rheumatoid arthritis, are seen in patients suffering from chronic autoimmune diseases. Extension is also seen in patients having acute and chronic RA, and they are highly susceptible to RA having HLA-DRB1’04 alleles (38). It is proposed that genetics is involved in immunosenescence acceleration that may result in the progression of RA. The prominent function of CD28 T-cells is thought to be associated with functional changes such as full expression of natural killer receptor, immunoglobulin killer cell stimulating and inhibiting receptors, and lectin like superfamily receptors (39) (40). The function of T-cells in joints is also remain unknown. Some studies demonstrate that the frequency of CD4+CD28 T-cells is less in the synovial fluid of RA patients than in peripheral blood (41). A study shows that CD28 manifestation occur by IL-12 which is widely present in RA joints. This example show some connections between peripheral blood CD28 and synovial fluid CD28+CD4+ T-cells. It is also believed that in RA, CD4+CD28 T-cells react automatically (42,43).

CONCLUSIONS

Aging is a risk factor for diseases associated with the loss of organ functions and immune system failure. Immune ageing results in deterioration of innate as well as adaptive immunity, less regulated immune response, and impaired wound healing. With the increase in age, susceptibility to infectious diseases as well as inflammatory processes also increases. Autoimmune diseases also result in consequences of immune cell aging. For example, rheumatoid arthritis and other immune deficiency syndromes. RA is an autoimmune disease in which the joints are affected due to the abnormal functioning of T-cells and other immune cells. It is seen that premature T-cell ageing of the immune system occurs in RA. In immune cells, T-cells are considered to have a long life span and show strong duplication pressure. Although RA can develop in young people, its incidence increases with age. Aging of dysfunctional T-cells includes loss of simple T-cells,
dysfunction of metabolism, accretion of broken DNA and telomeric ends. This altogether promotes soft tissue damage and inflammatory responses. Dysfunctional T-cell ageing is demonstrated in immune compromised patients like RA, who have impaired telomeric ends displaying cell cycle abnormalities. However, the exact mechanism of T-cell ageing and how they are involved in tissue damage is still unclear.

Authors’ contributions

MO contributed to study concept; BT, TS, JP, IK, and ET contributed to study design, data collection, data analysis and interpretation, literature review, write and critically review the manuscript. All the authors read and approved the final manuscript.

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REFERENCES

4. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia


