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Immunosenescence and Rheumatoid Arthritis: Does Telomere Shortening Predict Impending Disease?

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Abstract

The pathogenesis of RA, a disabling autoimmune disease, is incompletely understood. Early in the development of RA there appears to be loss of immune homeostasis and regulation, and premature immunosenescence. While identification of risk factors and understanding of the phases of RA pathogenesis are advancing, means of accurately predicting an individual's risk of developing RA are currently lacking. Telomere length has been proposed as a potential new biomarker for the development of RA that could enhance prediction of this serious disease. Studies examining telomere length in relation to RA have found that telomere erosion appears to proceed more rapidly in subjects with RA than in healthy controls, and that telomere lengths are shorter in those with the RA-risk *HLA-shared epitope* genes. These studies have been small, however, with retrospective or cross-sectional designs. The potential role of telomere shortening as an independent biomarker for future RA risk, perhaps strongly genetically determined by *HLA-SE* genes, after controlling for known risk factors such as smoking, body mass index and immunosuppressant medication use, as well as systemic inflammation, is an unanswered question.

Keywords

immunosenescence; rheumatoid arthritis; telomere; biomarker; risk factor; aging; autoimmune

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1.1 Pathogenesis of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis that progressively destroys synovial joints and causes systemic complications and early mortality(1). While RA affects approximately 1% of the world's population(2), at present there is no known cure. RA therapies have improved in the past decade, but new immunosuppressive agents are potentially toxic; long-term prognosis remains poor and average life expectancy is reduced by 3 to 18 years(3). The direct costs of treatment, and the indirect costs of disability and lost productivity are high(4).

Active RA is characterized by extensive systemic inflammation, increased levels of circulating inflammatory cytokines, and synovial hyperplasia with infiltration by lymphocytes, monocytes, macrophages, and fibroblasts. Aberrant T cell activation occurs early, with CD4+ T cells stimulating monocytes and macrophages to produce inflammatory cytokines, as well as proteolytic enzymes that destroy synovium, cartilage, and underlying bone(5, 6). T cells infiltrating rheumatoid synovium are oligoclonal, implicating an antigen-driven process(7, 8), but the inciting antigen or antigens are unidentified. Activated T cells signal B cells to increase production of immunoglobulins, including rheumatoid factor (RF). Active RA is characterized by production and release of pro-inflammatory cytokines such as tumor necrosis factor(TNF)-α and IL-6 (9). TNFα is a critical cytokine in RA pathogenesis(10) and TNF-antagonists are remarkably effective treatments for RA(11, 12). IL-6 produced by T cells, monocytes, macrophages and synovial fibroblasts(13) also causes joint destruction and systemic symptoms, and correlates with RA severity(14). IL-6 levels are elevated in subjects with early untreated(15) and preclinical RA(16, 17)

1.2 Oxidative stress in RA

Increased oxidative stress has also been documented in patients with RA compared to controls and is likely due to polymorphonuclear leukocyte and lymphocyte production of reactive oxygen intermediates(18, 19). Levels of lymphocyte 8-oxo-7-hydrodeoxyguanosine (8-oxodG), a promutagenic DNA lesion induced by reactive oxygen intermediates, were significantly higher in 98 RA patients than in 68 healthy controls(18). Lymphocytes from RA patients, but not those with scleroderma, also showed cellular hypersensitivity to the toxic effects of hydrogen peroxide. Increased DNA damage and increased susceptibility to cytotoxic killing by hydrogen peroxide in RA lymphocytes from patients have been explained by defective repair of DNA damage and increased production of reactive oxygen intermediates in inflammation(18).

1.3 "Normal" Immunosenescence

Normal aging of the immune system, or immunosenescence, is characterized by changes in T cell subsets, cellular and molecular alterations and thymic atrophy. It results in a decline of T and B cell function and loss of ability to recognize "self" and "foreign" antigens(20). A specific skewing of the T cell repertoire has been demonstrated with aging, with an increase in memory T cells. A large proportion of these memory T cells have lost normal expression of the surface CD28 receptor, which is involved in dendritic cell-T cell interactions central to the recognition of self vs. foreign antigens, and have acquired expression of other surface markers (including killer immunoglobulin-like receptors, NKG2D receptors and lymphocyte function-associated antigen)(21, 22). These CD28− T cells have a lowered threshold for antigen-specific activation, and more cytotoxic granules, while aging dendritic cells in response secrete higher levels of inflammatory cytokines and can induce T-cell proliferation even in response to self-peptides. Altered apoptosis, increased cytokine secretion, and the altered T cell repertoire is thought to give rise to a chronic inflammatory state, producing an "autoimmune-risk phenotype"(20).

1.4 Telomeres and Telomere Length

Telomeres are composed of proteins complexed to a hexameric nucleotide (TTAGGG)n repeat sequence at the distal ends of eukaryotic chromosomes that are critical in maintaining the structural integrity of the genome. Telomeres prevent fusion of chromosomal ends, nucleolytic decay, and atypical recombination(23). With each mitotic cell division in normal somatic tissue, telomeric repeats shorten by 30 to 200 bp (24). The progressive loss has been likened to a “molecular clock” reflecting the number of divisions a cell has undergone(25, 26). The rate of telomere attrition is not constant, but a function of age(27), oxidative stress, and antioxidative defenses, as well as cell turnover(28). When telomeres reach a critically truncated length, the cell will either undergo replication-mediated senescence or apoptosis(29). Hence, telomere length is considered a biomarker of biological rather than chronological age(30).

Telomerase, a ribonucleoprotein enzyme, maintains telomere length in germline and stem cells. The protein catalytic subunit of telomerase, telomerase reverse transcriptase (TERT), adds telomere repeats to the ends of chromosomes by reverse transcribing an RNA template (TERC) to DNA. Telomerase activity is generally low in replicative somatic tissues, but high in germ cells, in which chromosomal integrity is critical for fecundity(31–33). Telomere erosion associated with advancing age is determined in part by genetics, and in part by the balance of cell turnover, telomere damage and telomerase repair activity(34). Telomeres and telomerase are central to the biology of cancer, stem cells and aging(35).

1.5 Epidemiologic Associations between Telomere Length, Exposures and Disease Risk

Cigarette smoking potentially contributes to accelerated telomere shortening in humans by enhancing oxidative stress(36–38). In a study by Valdes and colleagues, age-adjusted telomere length was approximately 5 bp shorter for every pack-year smoked: 40 pack-years of smoking corresponded to 7.4 years of age-related shortening in telomere length(36). Morla and colleagues also observed a dose-response relationship between cumulative lifetime exposure to tobacco smoking and telomere length(37). In addition, obesity, likely acting via increased systemic inflammation, and oxidative stress has been associated with decreased telomere length in several studies(36, 39). Telomeres have been shown to be significantly longer in women compared to men, after adjusting for age and smoking(38, 40), but the reasons for this are not known.

Telomere length in peripheral blood leukocytes (PBLs) has emerged as a biomarker of aging and risk of age-related diseases such as cancer. In a study by Wu and colleagues, shorter telomere length was significantly correlated with baseline DNA damage as measured by the Comet assay and with mutagen sensitivity in lymphocytes after gamma-irradiation or exposure to benzo[*a*]pyrene diol epoxide, suggesting that telomere length is a marker of DNA damage and of susceptibility to such damage(41). Relationships between PBL telomere length and risk of several different age-related diseases, including bladder, skin and esophageal cancers, Parkinson’s disease and cognitive decline have been investigated(38, 42–47). Interestingly, telomere shortening was significantly associated with the risk of some, but not all, of these disease states, pointing to specific pathways of cellular senescence and disease pathogenesis. These findings suggest that truncated telomeres in PBLs are *specific risk markers for certain diseases*, rather than a generic marker of cellular aging.

2.1 Immunosenescence and Telomere Length in RA

Among patients with RA, loss of normal immune regulation and "premature immunosenescence" have been described(20, 21, 48, 49). T cell repertoires in RA patients are age-inappropriately skewed compared to age-matched controls, with increased proportions of CD28− T cells, possibly reflecting accelerated thymic output (50). Weyand and colleagues have found that multiple cell lines, including lymphocytes and neutrophils, from RA patients have telomere sequences that are significantly shortened compared with those from age-matched controls(51, 52). They studied T cell repertoire diversity and telomere length comparing 51 patients with established RA meeting American College of Rheumatology (ACR) classification criteria, to 47 healthy controls of the same age, and reported that increased self-replication of T cells in RA patients was indicated by age-inappropriate erosion of telomeres in circulating T cells with almost complete attrition of telomeric reserves in patients 20 to 30 years of age. In this small study, the degree of telomere loss among RA patients was not related to disease duration (53). In a related study, they compared telomere maintenance in circulating hematopoietic progenitor cells in RA, comparing 63 patients with established RA to 48 healthy matched controls(52). Telomeres in hematopoietic progenitor cells from RA patients were markedly shortened (Figure. 1). RA patients who were 20–30 years old had progenitor cell telomeres shortened to approximately 9,000 bp, a length equivalent to that observed in the 50–60-year-old controls. RA-derived progenitor cells lost 45 bp of their telomere ends per year of life, emphasizing an abnormal proliferative turnover of the surviving progenitor cells. Using the same sample of RA patients and controls, the Weyand research group has reported that upon stimulation, RA naïve CD4 T cells are defective in up-regulating telomerase activity due to insufficient induction of TERT(54). These defects were present in untreated patients and were independent from disease activity. Thewissen and colleagues in Germany have reported that, among early RA patients with a disease duration of less than one year, TERT mRNA levels were reduced compared to healthy controls; however chronic RA patients, with a disease duration of more than one year, did not show these reduced TERT mRNA levels(55). Thus, it remains unclear at what point (s) in the development of RA telomerase activity may be insufficient, and whether these defects may be seen even prior to disease onset.

2.2. *HLA-shared epitope* and Telomere Length

Using blood, venous cord blood and semen samples from healthy volunteers, and blood samples from patients with well-established RA, the Weyand group tested whether *HLA-shared epitope (SE)* alleles were associated with T cell telomere erosion(51). In healthy individuals, *HLA-SE* alleles were associated with excessive loss of telomeres in CD4+ T cells. Accelerated telomeric erosion occurred before age 20 and reduced homeostatic T cell proliferation was seen in *HLA-SE* positive adults(51).

2.3 Telomere length in other connective tissue diseases

The handful of studies of telomere length and telomerase activity in other connective tissue diseases has recently been reviewed(26). In a case-control studies of patients with existing autoimmune diseases, including systemic lupus erythematosus(56–58), scleroderma(59), Wegener's granulomatosis(60) and sarcoidosis(61), compared to healthy matched controls, premature telomere shortening has been found in peripheral blood mononuclear cells and has been associated with disease activity and/or duration..

2.4 Limitations of past telomere length-RA association studies and need for larger epidemiologic studies

Telomere erosion has thus been posited to reflect premature immunosenescence in RA and has been ascribed to excessive proliferative pressure or inadequate telomeric maintenance (49, 52, 53). The Weyand group hypothesizes that telomerase insufficiency in RA results in excessive T cell loss, leading to the observed “aged” T cell repertoire in RA. The past relatively small studies from this group have not observed correlations between RA disease duration or RA disease activity and telomere shortening. Analysis of a small number of patients with RA who had not been treated with any immunosuppressive medications showed their telomeres were eroded to the same degree as those from patients who had received immunosuppressive treatments. As telomere shortening was observed in these RA patients apparently independently of the duration, severity, and activity of the disease and the treatment, RA itself may be associated with intrinsic telomere shortening and bone marrow-derived hematopoietic progenitor cell dysfunction.

The potential for telomere shortening to be a relatively specific biomarker of RA is exciting. Past studies examining telomere shortening in RA have been small, however, with cross-sectional designs. These intriguing studies did not take patient cigarette smoking, reproductive status, or body mass index into account, and included a paucity of untreated patients. Treatments such as corticosteroids, methotrexate, and other immunosuppressant medications undoubtedly have measurable effects upon telomere length. These factors could be important confounders in the relationship between telomere length and RA, but to date no studies of telomere length *prior to the onset of RA symptoms* have been performed. As inflammation and autoantibodies are present years prior to RA onset, systemic inflammation likely leads to telomere shortening prior to RA. Prior studies have detected abnormalities in subjects affected with RA compared to controls. The retrospective study design used to date cannot address whether abnormalities predate RA onset or whether telomere shortening could be used as a predictive biomarker for RA. The potential role of telomere shortening as an independent biomarker for future RA risk, perhaps strongly genetically determined by *HLA-SE* genes, after controlling for known risk factors and systemic inflammation, is an unanswered question.

3.1 What if we could identify imminent or impending RA?

Early diagnosis and treatment strategies are critical to minimize disability from joint destruction as treatment with biologic therapies such as anti-tumor necrosis factor(TNF)-α inhibitors slow disease progression(62). Anti-citrullinated peptide antibodies and cytokines are elevated prior to clinical onset(63, 64), but means for accurately predicting RA development in those at risk and therefore intervening before the onset of suffering and irreversible damage are currently lacking. The identification of individuals at high risk for disease could lead to prevention during the pre-clinical period when patients are asymptomatic(63–65).

Telomere shortening, associated with genetic factors, aging and systemic inflammation, is present in RA subjects and could be a potential biomarker of immunosenescence associated with subsequent RA risk. If telomere shortening and telomerase activity are affected years prior to the onset of clinical RA, might there be a window one day for intervention with a telomerase-restoring therapy? Understanding whether telomere abnormalities precede RA onset, and how early prior to RA they occur, is crucial in distinguishing inciting from secondary events in RA pathogenesis. Relationships between genetic risk factors for RA, cytokines and biomarkers of systemic inflammation and oxidative stress, telomere

shortening and ultimately RA susceptibility are complex. The potential role of telomere shortening in the development of RA remains an unanswered question.

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Take home messages

- Premature aging of the immune system, known as immunosenescence, has been convincingly demonstrated in patients with RA.
- Telomeres, the distal ends of eukaryotic chromosomes that are critical in maintaining the structural integrity of the genome, function as a “molecular clock”. Premature telomere shortening has been observed in lymphocytes and hematopoietic stem cells from patients with RA compared to those from healthy controls and is likely related to immunosenescence.
- Prospective studies with bloods collected prior to diagnosis of RA are necessary to decipher whether these changes are due to the immune dysregulation of RA itself, or arise prior to the disease, pointing to their involvement in the pathogenesis of disease.

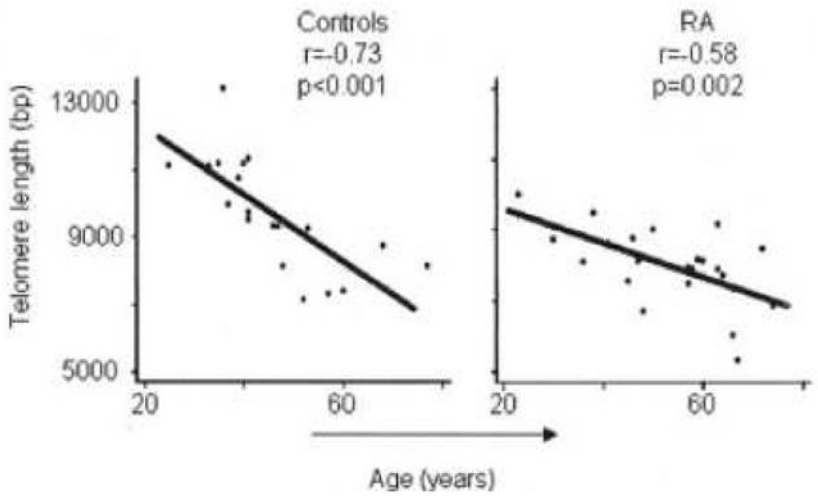

Fig. 1.
Association between age and telomere length in RA subjects and controls, from Colmegna, 2008 [21]