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Telomeres: New Players In Immune-Mediated Inflammatory Diseases?

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Abstract
Telomeres are repetitive DNA sequences located at the ends of linear chromosomes that preserve the integrity and stability of the genome. Telomere dysfunctions due to short telomeres or altered telomere structures can ultimately lead to replicative cellular senescence and chromosomal instability, both mechanisms being hallmarks of ageing. Chronic inflammation, oxidative stress and finally telomere length (TL) dynamics have been shown to be involved in various age-related non-communicable diseases (NCDs). Immune-mediated inflammatory diseases (IMIDs), including affections such as inflammatory bowel disease, psoriasis, rheumatoid arthritis, spondyloarthritis and uveitis belong to this group of age-related NCDs. Although in recent years, we have witnessed the emergence of studies in the literature linking these IMIDs to TL dynamics, the causality between these diseases and telomere attrition is still unclear and controversial. In this review, we provide an overview of available studies on telomere dynamics and discuss the utility of TL measurements in immune-mediated inflammatory diseases.

Keywords: Telomere, Dynamics, Immune-Mediated Inflammatory Diseases

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1 Introduction

Telomeres are complex heterochromatin structures at the natural ends of linear chromosomes dedicated to the preservation and stability of the genome [1,2]. Telomere length (TL) has been associated to the pace of ageing and to the onset/severity of ageing-related diseases [3].

At the time of birth, TL is highly variable in mammals, specifically humans [3–5], and appears to be associated with parental TL [6–19], gender [16,17,20–29] and ethnicity [25,26,29–32]. From this starting point, telomere attrition accompanies normal ageing. It is rapid during the first 20 years of life, then substantially slowed down [33–35] until telomeres reach a critical length and a DNA damage response is initiated, committing the cell to senescence or apoptosis [36–38]. The secretome associated with telomere-induced cell senescence impacts surrounding cells and can limit the regenerative capacity of affected tissues by compromising the function of tissue-specific stem and progenitor cells [39–41]. Thereby, the accumulation of senescent cells, in addition to inflammation, leads to a loss of tissue function and ultimately to organismal ageing [42].

Telomeres shortening rate can be accelerated by inflammation and oxidative stress in vitro and these phenomena participate in the ageing process [43]. Moreover, chronic inflammation, oxidative stress and lastly TL dynamics have been shown to be involved in various ageing-related non-communicable diseases (NCDs) such as cardiovascular diseases [44–47], cancer [48–50] and immune-associated diseases [51].

Immune-mediated inflammatory diseases (IMIDs) also belong to this group of NCDs which are the leading causes of morbidity and mortality worldwide and represent a burden on national economies whether in low, middle- or high-income countries [52,53].

IMID is a concept used to collectively describe a group of prima facie unrelated disorders that share common inflammatory pathways [54]. They include conditions such as inflammatory bowel disease (IBD), psoriasis (PS), rheumatoid arthritis (RA), spondyloarthritis, and uveitis [51,55] and are characterized by an immune dysregulation that may affect any organ system and result in significant morbidity, reduced quality of life and premature death [56]. Although the aetiology of these conditions is unknown, advances in molecular research have revealed that an imbalance in inflammatory cytokines which accelerated cellular ageing is central to their pathogenesis [56]. In past years, we have seen the emergence in the literature of studies relating these pathologies to TL dynamics [57–73] but nowhere near to the scientific production dedicated to other NCDs.

In this review we briefly cover mechanisms involved in TL dynamics and then focus on the results of telomeres studies on IMIDs available and their methodological implications.

2 Telomere/telomerase biology

The natural ends of linear chromosomes require unique genetic and structural adaptations to facilitate the protection of genetic material [1]. This is made possible by the sequestration of the telomeric sequence into a protective nucleoprotein cap that masks the double strand ends from constitutive exposure to the DNA damage response machinery [2]. The relationship between capping requirements with telomere replication and the enzymatic processing steps obligatory for telomere function is complex [2]. Telomeric proteins and their interacting factors create an environment at chromosome ends that inhibits DNA repair there, however, the repair machinery is essential for proper telomere function [74].
2.1 Biology

Telomeres are composed of hundreds to thousands of tandem DNA repeat sequences associated with specific proteins. In humans, the hexameric sequence of the repeat is TTAGGG in one strand and CCCTAA in the other [2,75]. The 3′ end of telomere terminates with a single-stranded overhang, which folds back and invades the double-stranded telomeric helix, forming a specific structure called T loop [76]. Six protective proteins associated with telomere DNA (TRF1, TRF2, TIN2, POT1, TPP1, and RAP1), collectively termed shelterin complex, stabilize the T-Loop and prevent telomeres from inadvertently activating DNA damage signalling and double-strand break repair pathways [75]. Shelterin must prevent hyper-resection under most conditions. Sfeir et de Lange speculate that the mechanism by which shelterin fulfils this task is related to how it governs the formation of the correct telomeric overhangs after DNA replication [77] (fig. 1.A).

However, each normal cell division results in the loss of small parts of chromosomes’ far-end sequences because of the phenomenon known as the end replication problem [78–81], causing telomere length shortening. Once a telomere reaches a critical length, the cell enters a state of permanent cell cycle arrest i.e., intrinsic replicative senescence potentially leading to its programmed death i.e., apoptosis. Exposure to external factors, such as oxidative stress or ultraviolet light can induce premature stress-related senescence. Senescent cells display senescence-associated secretory phenotype (SASP) as long as they remain metabolically active [82] and their accumulation in tissues and resulting SASP-induced proinflammatory state combined with a progressively dysfunctional immune system – dubbed inflamaging – ends up impacting the whole organism.

Maintenance of the integrity of telomeres requires telomerase – a specific RNA-dependent DNA polymerase enzyme complex that carries its own integral RNA template (TERC) and adds telomeric repeats to the ends of chromosomes using a telomerase reverse transcriptase (TERT) [83–86]. TERT sub-unit uses TERC as a template to extend the 3′ end of the chromosome [83–85] (fig. 1.A). This enzyme responsible for generating de novo telomere sequences is active during gestation and in immature undifferentiated cells but predominantly inactive in human somatic cells (except in lymphocytes) [83]. Its activation is a key component of rapid cell division in many cancer cells and occurs in 85-90% of all human cancers [87,88] although it is not a dominantly acting oncogene that can induce physiological transformation by itself [89].

The progressive attrition of telomeres, which is believed to be an initial proliferative barrier to tumour formation in humans and other long-lived animals [90–92], is directly involved in ageing whether it is a natural or pathological process [36,37] and accelerated ageing-associated diseases are characterized by increased cellular senescence.

The clocking mechanism of telomere/telomerase biology can thus be put in parallel with the countdown initiated by chronic inflammatory disorders. Indeed, telomere/telomerase biology impairment has been previously connected to chronic inflammation and to the subsequent immune system disruption of affected patients [43,93].

2.2 Telomeres and lifestyle

As mentioned previously, telomere attrition during the highly proliferative early years of life – during intrauterine life even – is rapid [8,9,33–35,94–100]. Benetos et al. reported an average TL attrition of 40.7 base pairs (bp) per year in leukocytes of children under 14 from the STANISLAS Study, twice the attrition rate of their parents [35]. Children can thus be greatly impacted by external factors altering cellular replication pacing, especially in utero. Maternal exposures during pregnancy for
instance can reflect on fetal TL [13,99,101–109] and maternal nutrition [110,111], weight [99,101,112], mental health [102–104,107] and smoking [103,105,106,108] can exert a ‘programming’ effect on their offspring’s TL.

During adulthood on the contrary, telomere attrition is relatively low [33–35] – between 23.6 and 31.2 bp per year in leukocytes – and has little effect on TL ranking in population [33]. Lifestyle is thus unlikely to exert a major impact on TL. However, the effect of many lifestyle factors which are involved in IMIDs pathophysiology on telomere dynamics have been reported in the literature, but the study designs rarely make it possible to decide on causality.

For instance, studies about the effect of smoking on TL are contradictory even if it seems logical at first that the oxidative stress resulting from this behaviour could cause accelerated telomere attrition and faster ageing [113–116]. It is important to note that many cross-sectional studies found association between short TL and smoking habits [113–115,117–122] while longitudinal studies never found any association between smoking and increased telomere attrition [114,123–129]. This observation also applies to findings on the cross-sectional associations between short telomeres and diet [130–136], physical activity [135–148] and body mass index [117,129,130,136,149–151] which are not corroborated in longitudinal studies [135,152–154]. Recently, it was suggested that short telomeres could influence behaviour and that it is in fact this characteristic that could lead to disadvantageous behaviours such as smoking [125]. One explanation may be that children tend to replicate their parents’ lifestyle, diet, and physical activity well into adulthood [155–161]. Similarly they often share socio-economic status [157,160,162–167]. As a result, people with shorter telomeres are more likely to develop metabolic disorders [168–178] or fall into categories of populations presenting disadvantageous behaviours [113–126,130–136].

3 IMIDS and telomere

3.1 Inflammatory bowel diseases

Inflammatory bowel diseases, mainly Crohn's disease (CD) and ulcerative colitis (UC), have emerged as a major public health concern of industrialized countries in the past years [179,180]. IBD imposes health and economic burdens on communities worldwide, and substantially reduces patients’ quality of life [181]. It can affect people of all ages, including children and geriatric populations, and can impact all aspects of life [180]. It is estimated that more than 3 million people in the USA and Europe have IBD [181].

CD is a chronic inflammatory disease potentially affecting the entire gastrointestinal tract while UC is a chronic, recurrent inflammation localized in the colon. UC patients can be characterized as progressors when they present a dysplasia elsewhere in the colon, usually with genomic instability and mitochondrial dysfunction. The term non progressors is used for dysplasia-free patients [182–184].

In 2020, the study of 3 IBD families with 11 affected members over three successive generations concluded that short telomeres, measured in leukocytes, was unlikely to be involved in mechanisms of possible genetic anticipation of the disease [57]. Indeed, TL was not associated with earlier age at onset or severity of IBD in members of successive generations affected by the disease [57]. However, it was demonstrated that TL was shorter in the colonic mucosa of UC subjects compared to age-matched controls [185,186] and associated with more severe clinical phenotypes of UC [185]. A study of TL in colonocytes and leukocytes from UC patients showed shorter telomeres in both cell types in UC patients than in matched controls [58]. Interestingly, the difference in TL in colonocytes
was more pronounced in early-onset UC patients (aged less than 39 years) [58]. The short TL in colonocytes could explain the increased and early cancer risk in this disease. An increase in γH2AX foci, which are early cellular response to DNA double-strand breaks through rapid phosphorylation at Ser-139 of H2AX – the minor variant of histone H2A –, was also found in colonocytes and may reflect oxidative damage secondary to inflammation [58]. In a study with 14 UC patients, an increased load of ultra-short telomeres, as well as a shorter mean TL, were found associated with dysplasia in longstanding UC. Furthermore, the load of ultra-short telomeres was also increased in progressors compared to non-progressors [187]. Another study of 9 UC patients with high-grade dysplasia compared to 4 UC patients without dysplasia supports a model in which inflammation, short telomeres and senescence are the background to tumour progression in progressive UC [59]. Senescence acts as a tumour suppressor mechanism, preventing colons from progressing beyond low-grade dysplasia [59]. However, it has been demonstrated that in colonic mucosa, short telomeres are correlated with chromosomal instability [184]. Eventually some colonocytes bypass senescence and transform, coinciding with the lengthening of telomeres through activation of telomerase and the loss of p53 tumor suppression function [59]. This allows colonocytes with genetic damage to proliferate and progress to high-grade dysplasia and cancer [59]. In contrast to these results, another study with 18 controls, 19 UC and 17 CD concluded that there was no difference in telomere length in peripheral blood mononuclear cells (PBMCs) between these three groups [60]. (Table 1; Fig. 1.B).

Another study, with 18 UC,13 CD patients and 13 controls, observed the downregulation of TRF2 and RAP1 mRNA expression in CD25+ T-lymphocytes in IBD. This could lead to the destabilisation of the T-loop structure in these cells and may contribute to the telomeric fusions and chromosomal abnormalities observed in UC [61]. These findings may also indicate a systemic process of telomere uncapping that could represent a putative biomarker for IBD associated colon cancer risk [61]. (Table 1; Fig. 1.B).

Overall, these studies concur on the presence of short telomeres in colon mucosa of IBD patients. Short TL and telomere dysfunction are also found in leukocytes from these patients. Short telomeres could be the result of higher telomere attrition due to chronic inflammation and higher cell turn-over or partially due to the effect of lifestyle factors such as diet and smoking [113,123,135,188] that are also involved in the aetiology of IBD [189]. However, shorter telomeres could precede IBD and play a role in the pathogenesis. Indeed, in a study on 33 patients with UC, 14 progressors and 19 non-progressors, shorter telomeres were found associated with clonal expansions in nondysplastic biopsies from UC progressors with early-onset of disease (younger than 50 years of age) [62]. Short TL in leukocyte has already been associated with clonal expansion, known as clonal haematopoiesis of indeterminate potential (CHIP) [190,191]. Short telomeres and telomere dysfunction may also play a role in initiating inflammation. Short LTL has been recently linked to the upregulation of NLRP3 inflammasome [192,193], a system that may contribute to IBD susceptibility [194–196]. Moreover, a recent study showed that telomere dysfunction-induced activation of the ATM-YAP1-pro-IL-18 pathway in intestinal epithelium is a primary initiator and driver of colon inflammation [197]. (Table 1; Fig. 1.B).

### 3.2 Psoriasis

Psoriasis is a chronic inflammatory disease of uncertain aetiology characterised by scaly erythematous plaques that can lead to significant physical and psychological distress, affecting approximately 125 million people worldwide [198–200].
Wu et al demonstrated for the first time that increased telomerase activity can be detected in freshly obtained non-stimulated PBMCs from patients with atopic dermatitis (AD), indicating the lymphocytes have already been activated *in vivo* or that a subpopulation of ‘immature’ lymphocytes may be present [65]. The relative reduced telomerase activity of PBMCs to multiple stimulators in patients with AD seemed to be associated with their excessive stimulation *in vivo* and their decreased functional capacity *in vitro* [65]. The authors have published a second study showcasing similar results in T lymphocytes from blood of patients with AD and psoriasis: increased telomerase activity was found together with reduced TL as compared to healthy controls, also indicating an *in vivo* activation of T lymphocytes [64] (table 1; Fig. 1.B). A third study focusing on patients with psoriasis confirmed the higher telomerase activity in PBMCs from patients [63]. In addition, telomerase activity of PBMC in psoriatic patients correlated positively with disease severity [63].

These three studies observe short telomeres and an increase in telomerase activity in circulating cells from patients with psoriasis. Short telomeres may reflect increased TL attrition due to cell proliferation, which would support the view that the affected T cells have gone through a large number of cell divisions because of chronic stimulation *in vivo* [64] (Table 1; Fig. 1.B).

### 3.3 Spondyloarthritis

**Spondyloarthritis** is a group of inflammatory disorders affecting the spine (spondylitis) and joints (arthritis) including ankylosing spondylitis, axial spondyloarthritis, enteropathic spondyloarthritis or IBD-associated spondyloarthritis, peripheral spondyloarthritis, psoriatic arthritis and reactive arthritis which is a subgroup of juvenile idiopathic arthritis [201]. These rheumatic diseases have common features, which may be clinical - inflammation of the axial skeleton (sacroiliac joint and spine) or possibly of the peripheral skeleton - and genetic – association with the *HLA-B27* gene [202–204].

Ankylosing spondylitis, the most common spondyloarthritis, is a chronic inflammatory disease of the axial spine that can manifest with various clinical signs and symptoms [205]. Chronic back pain and progressive spinal stiffness are the most common features of the disease [205]. Involvement of the spine and sacroiliac joints, peripheral joints, digits, entheses are characteristic of the disease [205]. Impaired spinal mobility, postural abnormalities, buttock pain, hip pain, peripheral arthritis, enthesitis, and dactylitis are all associated with ankylosing spondylitis [205]. This chronic inflammatory rheumatic disease has an estimated prevalence per 10,000 to 23.8 in Europe, 16.7 in Asia, 31.9 in North America, 10.2 in Latin America and 7.4 in Africa [206].

In 2010, Tamayo et al. observed in a cross-sectional study that patients with several rheumatic disorders – notably rheumatoid arthritis (n=86) which will be outlined in the following paragraph, psoriatic arthritis (n=56) and ankylosing spondylitis (n=59) – showed longer telomeres in PBMCs when compared with 130 controls [207]. Four years later, the same team continued its investigations on spondyloarthritis and reported that the presence of chronic inflammatory components in psoriatic arthritis could be associated with a higher telomere size in peripheral blood leukocytes (PBL), unlike in cutaneous psoriasis [66]. According to the authors, the rate of telomere loss in PBL was higher in psoriatic arthritis patients (n=42) than in ankylosing spondylitis patients (n=44), revealing a difference in telomere physiology from PBL between both spondylarthritides. [66]. However, reported TL attrition was extremely high in comparison to what could be expected in adults [35] and these results should thus be considered with caution.

Regarding axial spondylarthritis (aSpA) – a group that includes ankylosing spondylitis (radiographic axial spondylarthritis) [204,208]—shorter telomeres were found in CD4+ and CD8+ T cell subsets in
young patients (under 35 years), as well as impaired telomerase in aSpA patients with rheumatoid arthritis [209] (Table 1; Fig. 1.B).

3.4 Rheumatoid arthritis

Rheumatoid arthritis is a systemic inflammatory condition that primarily affects the synovial membrane of affected joints [210]. Extra-articular manifestations are common and may involve any organ system. Rheumatoid arthritis (RA) affects approximately 1% of the adult population and is associated with chronic pain, disability and increased mortality [56].

Telomere length has been studied in the context of RA and first results were contradictory, some studies finding shorter TL in leukocytes from patients than in those from healthy controls [67,211] and other finding rather longer TL in patients [207]. Recently, two meta-analyses confirmed the presence of short TL in patients suffering from RA [212,213]. Formerly, this was suspected to be a consequence of chronic inflammatory activity on TL attrition. However, a Mendelian randomization analysis found that genetically predicted longer TL was associated with a reduced risk of RA [213] excluding reverse causality. This is in concordance with the finding that TL in RA patients do not correlate with disease duration as it should if the disease was driving the association [67]. Interestingly, RA patients present short TL in hematopoietic progenitor cells (HPC) [68]. Short telomere-related defective HPC proliferative function may be a potential pathogenic factor in RA. Telomerase expression and activity have also been observed in RA and are deregulated [70,214] (Table 1; Fig. 1.B).

3.5 Uveitis

Uveitis is a term used to describe inflammatory processes of the portion of the eye known as the uvea, which is composed of the iris, ciliary body, and the choroid. Symptoms and consequences can range from pain and conjunctival injection to complete vision loss [215]. Uveitis occurs with an incidence of approximately 20 individuals per 100,000 per year, resulting in overall population-based prevalence estimates ranging from approximately 40 to 400 individuals per 100,000 [216].

One study involving 91 Birdshot Uveitis patients and 150 unrelated healthy controls showed longer telomeres compared to healthy controls which implies sophisticated telomere biology in chronic inflammation [73]. (Table 1; Fig. 1.B). This study alone does not allow to conclude on the impact of telomeres in uveitis.

As it is the case in most NCDs, telomere dynamics is unquestionably involved in IMIDs whether it be through the deleterious lifestyle leading to their onset, through increased telomere attrition in response high cellular turnover due to chronic inflammation or through a determinant role in the disease onset and progression. Mechanics in play remain to be elucidated, as for pathologies sharing common inflammatory pathways [54], contradictory phenomena are observed: short telomeres and increased telomerase activity in IBD, psoriasis and RA, and potentially longer telomeres in spondyloarthritis and uveitis that must be further investigated.

4 Perspectives

Unlike studies focused on telomere dynamics and other NCDs, those focused on IMIDs tend to gather relatively narrow populations with great difficulty to find healthy controls. This is partly due to the nature of the biological material required for comparison which is difficult to obtain in healthy subjects and questions the statistical power of the majority of results. In addition, most of these
studies used a telomere length measurement methodology based on qPCR that is not the most suitable method for such narrow populations [217,218].

Many studies support the hypothesis that the rate of telomere attrition in adulthood can be substantially affected by different exposures to environmental factors and/or diseases. However, the majority of these studies report a cross-sectional association, without being able to exclude potential confounders, which does not necessarily prove a causal association between exposures and subsequent telomere attrition [219,220]. This causal association could be established in longitudinal studies, where so far the moment, the results differ from cross-sectional studies. Furthermore, the discrepancies in sizes and characteristics of study populations (gender, age, racial/ethnic background), as well as the different measurements (blood, saliva, …) and analysis methods (qPCR, Q-FISH, statistical adjustments…) of TL may partly contribute to the inconsistency of the results. This also applies to the recurrent conflation of telomere length and telomere shortening in the literature [220–223].

Drawing conclusions about telomere shortening without substantial prospective data is challenging and must be further supported with appropriate methodologies. Table 1 illustrates this gap between proper methodologies and adequate conclusions as cross-sectional studies often lead authors to a conclusion on impaired attrition (highlighted in red in table 1).

Furthermore, telomere length measured only during adulthood provides merely partial information about telomere dynamics. Repeated measurements covering the entire lifespan of individuals, considering additionally genetic factors and early childhood exposures could provide better insight on adulthood telomere dynamics even though such longitudinal data would be extremely difficult to gather [114].

A better understanding of suitable telomeres analyses, resulting in a better understanding of telomeres dynamics, may allow their therapeutic use [224]. Anti-aging or regenerative applications require telomeres up-regulation, which is often associated with telomere attrition [225]. In contrast, anti-cancer applications require suppression of various genes integral to telomere maintenance such as telomerase, telomerase RNA components and the shelterin complex, thereby counteracting the immortality process of cancer cells [50,226–229].

Several questions remain unanswered: is the telomere length at birth highly predictive of IMIDs onset? Why is telomere attrition, which seems to be a common trait in IMIDs, efficiently compensated by telomerase activation in some of these disorders while insufficient in others? And in the same way, what mechanism makes it possible to observe a difference between patients with the same pathology? Of course, the specificity of tissues impacted is to consider, but is that the only difference? Can telomere modulation represent a new therapeutic approach in IMIDs?

5 Conflict of Interest

Prof. Peyrin-Biroulet reports personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots, Pharmacosmos, Celltrion, Takeda, Boehringer Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Alma, Sterna, Nestle, Enterome, Allergan, MSD, Roche, Arena, Gilead, Hikma, Amgen, BMS, Vifor, Norgine; Mylan, Lilly, Fresenius Kabi, Oppilan Pharma,
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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

6 Author Contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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9 Captions figure.

**Fig.1:** (A) Telomere maintenance components, (B) Telomere length reported in IMID’s. (A) Telomeres are composed of hundreds or thousands of repeated DNA sequences of TTAGGG in one strand and CCCTAA in the other. The shelterin complex consist of six proteins (TRF1, TRF2, RAP1, POT1, TPP1 and TTIN2) and provides protection of the telomere end, facilitates telomeric DNA replication and recruitment of telomerase to the telomere. The telomerase complex consists of the enzyme telomerase-transcriptase (TERT), the RNA component (TERC) and the protein complex dyskerin (dyskerin, NOP10, NHP2 and GAR1). This complex allows telomere elongation via TERT by adding TTAGGG repeats and has extratelomeric functions.
Table 1: Overview of recent studies investigating the relationship between telomere dynamics and IMIDs. AD = atopic dermatitis; aSpA = axial spondyloarthritis; CD = Crohn’s disease; IBDs = inflammatory bowel diseases; IMIDs = Immune-mediated inflammatory diseases; PBMCs = peripheral blood mononuclear cells; UC = ulcerative colitis. Consistency between methodology and conclusion are highlighted in blue.

<table>
<thead>
<tr>
<th>IMID Study reference</th>
<th>Populations / design</th>
<th>Results</th>
<th>Authors’ conclusion</th>
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<tr>
<td><strong>IMILD</strong></td>
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<tr>
<td>Tutra et al. [57]</td>
<td>11 patients (5 UC, 4 CD, 2 IBD-U) 8 parent-child pairs from 3 families Johns Hopkins IBD Family Study</td>
<td>Median age at diagnosis of children 16.5 younger</td>
<td>Telomere shortening appears unlikely to be involved in mechanisms of possible genetic anticipation in IBD.</td>
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<tr>
<td>Da-Silva et al. [61]</td>
<td>18 UC / 13 CD patients 49 / 44 years Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry UK</td>
<td>13 non-IBD controls 56 years TRF2 / RAP1 / TRF1</td>
<td>The downregulation of TRF2 and RAP1 mRNA expression in CD25+ T-lymphocytes in IBD suggests that these telomere binding proteins play a role in telomere regulation and may contribute to the telomeric fusions and chromosomal abnormalities observed in UC. These findings may also indicate a systemic process of telomere uncapping which could represent a biomarker for IBD associated cancer risk.</td>
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<tr>
<td>Usselmann et al. [230]</td>
<td>25 UC 11 colorectal cancer 9 adenomatous polyps Department of Gastroenterology, University Hospitals Coventry and Warwickshire NHS Trust UK</td>
<td>21 normal colons</td>
<td>Colonic mucosal expression of telomerase is reduced in UC. Levels are low even in microscopically normal mucosa, suggesting that telomerase deficiency may contribute to the pathogenesis of the disease.</td>
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<tr>
<td>Tahara et al. [185]</td>
<td>86 UC / 37.3 years ± 11.4 median clinical duration = 6.9 years ± 5.8 Department of Gastroenterology, Fujita Health University School of Medicine Japan</td>
<td>normal appearing proximal colon of same individuals + severe clinical phenotypes</td>
<td>Telomere shortening is associated with more severe clinical phenotypes of UC, reflecting severe inflammatory state in the colonic mucosa.</td>
</tr>
<tr>
<td>Risques et al. [58]</td>
<td>85 UC (biopsies) / 14-79 years 102 UC (leukocyte DNA) / 31-80 years 43 UC (paraffin-embedded colon) / 31-78 years Department of Pathology, University of Washington, Seattle USA</td>
<td>59 normal colon controls / 2.79 years 45 controls / 3-79 years 53 controls / 31-79 years colonocytes / leukocytes</td>
<td>Colonicocytes of UC patients show premature shortening of telomeres, which might explain the increased and earlier risk of cancer in this disease. Shorter leukocyte telomeres and increased γH2AX in colonocytes might reflect oxidative damage secondary to inflammation.</td>
</tr>
<tr>
<td>Getliffe et al. [60]</td>
<td>19 UC / 45 years 17 CD / 48 years Department of Biological Sciences, University of Warwick, Coventry UK</td>
<td>18 controls / 56 years + azathioprine / + smoking</td>
<td>Telomere shortening is not accelerated and therefore cannot be the cause of the chromosome instability observed in UC peripheral blood lymphocytes. Azathioprine and cigarette smoking modify telomerase expression in these cells.</td>
</tr>
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<td>Salk et al. [62]</td>
<td>14 Progressors UC patients Cleveland Clinic USA</td>
<td>19 Non-Progressors UC patients non-dysplastic biopsies &amp; early onset + clonal expansion in non-dysplastic biopsies</td>
<td>Early-onset progressors develop cancer in a field of clonally expanded epithelium with shorter telomeres. The detection of these clones in a few random nondysplastic colon biopsies is a promising cancer biomarker in early-onset UC. Curiously, patients with late-onset UC seem to develop cancer without the involvement of such fields.</td>
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<td>Disorder</td>
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<td>UC-associated colorectal cancer</td>
<td>Risques et al. [59]</td>
<td>9 UC patients with high-grade dysplasia (biopsies located less than 10 cm from HGD) Department of Pathology, University of Washington, Seattle USA</td>
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<td>4 UC patients without dysplasia</td>
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<td>Dysplasia arises in a preneoplastic field of chronic inflammation, which leads to telomere shortening, DNA damage, and senescence. Senescence acts as a tumor suppressor mechanism that is abrogated during the transition from LGD to HGD in UC.</td>
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<tr>
<td>CD</td>
<td>Mereesse et al. [231]</td>
<td>Surgical samples from 27 patients undergoing ileocolonic resection for CD 19-52 years Service d’Immunologie, EA 2686, Lille France</td>
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<td>Non inflammatory mucosa collected in the healthy mucosa of resected ileum from 10 patients with colonic cancers / 53-82 years</td>
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<td>In the uninvolved ileal mucosa, IEL from CD patients had shorter telomeric lengths than IEL from control patients, suggesting that they have been chronically stimulated. Such perturbation of the IEL population within the ileal mucosa could contribute to the inflammation in CD</td>
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<td>Rheumatoid arthritis</td>
<td>Colmegna et al. [68]</td>
<td>63 patients with diagnosis of seropositive RA according to the American College of Rheumatology 1987 revised criteria 55 years ± 14</td>
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<td>48 age-, sex- and ethnically-frequency matched healthy subjects without history of chronic inflammatory diseases or immunosuppressive/chemotherapeutic therapy 52 years ± 14</td>
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<td>Increase of circulating bone marrow-derived progenitor cells. Concentrations stagnated at levels typical of those in old control subjects. Hematopoietic precursor cells displayed growth factor nonresponsiveness and sluggish cell cycle progression; marked telomere shortening indicated proliferative stress-induced senescence. Defective HPC function independent of disease activity markers suggests bone marrow failure as a potential pathogenic factor in RA.</td>
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<tr>
<td>RA</td>
<td>Fuji et al. [70]</td>
<td>69 patients / 50.5 years ± 14 Department of Medicine, Lowsance Center for Human Immunology and Rheumatology, Emory University School of Medicine Atlanta, USA</td>
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<td>60 healthy control / 47.6 years ± 12</td>
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<td>Telomerase insufficiency in RA results in excessive T cell loss, undermining homeostatic control of the naive T cell compartment and setting the stage for lymphopenia-induced T cell repertoire remodeling. Restoring defective telomerase activity emerges as a therapeutic target in resetting immune abnormalities in RA.</td>
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<td>RA</td>
<td>Steer et al. [67]</td>
<td>176 RA patients / 63.8 years Gay’s, St Thomas’ and Lewisham hospitals in London, UK</td>
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<td>1151 controls / 8.2 years</td>
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<td>Reduced terminal restriction fragment length in a large group of patients with RA, apparently independent of disease duration and markers of disease severity, but is influenced by HLA-DRB1 genotype.</td>
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<tr>
<td>RA</td>
<td>Koetz et al. [211]</td>
<td>51 rheumatoid arthritis / 63.80 years</td>
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<td>47 healthy controls / 18-77 years</td>
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<td>Increased self-replication of CD4+CD5ROnull T cells is thought to lead to premature erosion of telomeres. This reduced terminal restriction fragment length has functional consequences that may explain the increased susceptibility of RA patients to contract infection.</td>
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<td>Spondyloarthritis</td>
<td>Tamayo et al. [207]</td>
<td>86 rheumatoid arthritis / 31-82 years 56 psoriatic arthritis / 26-79 years 59 ankylosing spondylitis / 21-75 years Hospital Universitario de A Coruña Spain</td>
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<td>130 healthy controls / 3–94 years</td>
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<td>The presence of chronic inflammatory component in rheumatologic diseases could be associated to higher telomere size in PBL, unlike in healthy controls.</td>
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<tr>
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<td>Tamayo et al. [66]</td>
<td>42 psoriatic arthritis patients / 55.02 years ± 14.33 44 ankylosing spondylitis patients / 59.07 years ± 14.58 Hospital Universitario de A Coruña Spain</td>
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<td>53 psoriatic at baseline / 53.75 years ± 16.37</td>
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<td>The presence of chronic inflammatory component in PsA could be associated to a higher telomere size in PBL, unlike in cutaneous Ps. The rate of telomere loss in PBL is higher in PsA patients than in AS patients, revealing a difference in telomere physiology from PBL between both spondyloarthritis. The qPCR methodology is sensitive enough to evidence a significant telomere length shortening in specific subjects in a few years, so it could be useful for follow-up in patients.</td>
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### Increased Homeostatic Proliferation of T-cells Leads to Premature Shortening of Telomeres That Is Not Restored by Telomerase Enzyme

**Chronic Inflammatory Skin Diseases**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Study Authors</th>
<th>Patients Details</th>
<th>Controls Details</th>
<th>Notes</th>
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<tbody>
<tr>
<td>Psoriasis</td>
<td>Liu et al. [63]</td>
<td>30 psoriatic patients / 34.03 years ± 7.38 psoriatic patients / 34.03 years ± 7.38 Department of Dermatology Affiliated Hospital of Dalian Medical University China</td>
<td>13 healthy donors / 29.61 years ± 5.14</td>
<td>Positive correlation between telomerase activity in PBMC and disease severity of psoriasis, but not duration. Telomerase activity in PBMC may serve as an objective indicator of psoriasis severity, and inhibiting telomerase activity may become a new target for psoriasis therapy.</td>
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<tr>
<td>Atopic dermatitis</td>
<td>Wu et al. [65]</td>
<td>15 patients with moderate to severe disease activity / 23-47 years Department of Dermatology Morselshorg Hospital, University of Aarhus Denmark</td>
<td>13 healthy donors / 24-40 years</td>
<td>Increased telomerase activity detected in freshly obtained PBMC from patients with AD, indicating the lymphocytes have already been activated in vivo or that a subpopulation of ‘immature’ lymphocytes may be present. No difference between normal and AD patients in the DNA synthesis of their PBMC. Relative reduced telomerase activity of PBMC to multiple stimulators in patients with AD seemed to be associated with their excessive stimulation in vivo and their decreased functional capacity in vitro.</td>
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<tr>
<td>Atopic dermatitis</td>
<td>Wu et al. [64]</td>
<td>32 AD patients with moderate to severe disease activity / 17-59 years 16 psoriatic patients / 20-84 years Department of Dermatology Morselshorg Hospital, University of Aarhus Denmark</td>
<td>30 healthy blood donors / 20-84 years</td>
<td>The increased telomerase activity and shortened telomere length indicates that T lymphocytes in atopic dermatitis and psoriasis are chronically stimulated and have an increased cellular turnover in vivo.</td>
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<tr>
<td>Birdshot Uveitis</td>
<td>Vazirpana et al. [73]</td>
<td>91 unrelated BU cases of European descent 60.5 years (9.07) Department of Ophthalmology at the University Medical Center Utrecht The Netherlands</td>
<td>150 unrelated healthy controls / 52.9 years (7.16)</td>
<td>BU is accompanied by significantly longer LTL.</td>
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