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## Telomeres: New Players In Immune-Mediated Inflammatory Diseases?

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### 18 Abstract

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

31 **Keywords: Telomere, Dynamics, Immune-Mediated Inflammatory Diseases**

32

## 33 **1 Introduction**

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

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

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

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

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

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

## 65 **2 Telomere/telomerase biology**

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

## 74 2.1 Biology

75 Telomeres are composed of hundreds to thousands of tandem DNA repeat sequences associated with  
76 specific proteins. In humans, the hexameric sequence of the repeat is TTAGGG in one strand and  
77 CCCTAA in the other [2,75]. The 3' end of telomere terminates with a single-stranded overhang,  
78 which folds back and invades the double-stranded telomeric helix, forming a specific structure called  
79 T loop [76]. Six protective proteins associated with telomere DNA (TRF1, TRF2, TIN2, POT1,  
80 TPP1, and RAP1), collectively termed shelterin complex, stabilize the T-Loop and prevent telomeres  
81 from inadvertently activating DNA damage signalling and double-strand break repair pathways [75].  
82 Shelterin must prevent hyper-resection under most conditions. Sfeir et de Lange speculate that the  
83 mechanism by which shelterin fulfils this task is related to how it governs the formation of the  
84 correct telomeric overhangs after DNA replication [77] (fig. 1.A).

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

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

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

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

## 111 2.2 Telomeres and lifestyle

112 As mentioned previously, telomere attrition during the highly proliferative early years of life – during  
113 intrauterine life even – is rapid [8,9,33–35,94–100]. Benetos et al. reported an average TL attrition of  
114 40.7 base pairs (bp) per year in leukocytes of children under 14 from the STANISLAS Study, twice  
115 the attrition rate of their parents [35]. Children can thus be greatly impacted by external factors  
116 altering cellular replication pacing, especially in utero. Maternal exposures during pregnancy for

117 instance can reflect on fetal TL [13,99,101–109] and maternal nutrition [110,111], weight  
118 [99,101,112], mental health [102–104,107] and smoking [103,105,106,108] can exert a  
119 ‘programming’ effect on their offspring’s TL.

120 During adulthood on the contrary, telomere attrition is relatively low [33–35] – between 23.6 and  
121 31.2 bp per year in leukocytes – and has little effect on TL ranking in population [33]. Lifestyle is  
122 thus unlikely to exert a major impact on TL. However, the effect of many lifestyle factors which are  
123 involved in IMIDs pathophysiology on telomere dynamics have been reported in the literature, but  
124 the study designs rarely make it possible to decide on causality.

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

### 139 **3 IMIDS and telomere**

#### 140 **3.1 Inflammatory bowel diseases**

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

147 CD is a chronic inflammatory disease potentially affecting the entire gastrointestinal tract while UC  
148 is a chronic, recurrent inflammation localized in the colon. UC patients can be characterized as  
149 progressors when they present a dysplasia elsewhere in the colon, usually with genomic instability  
150 and mitochondrial dysfunction. The term non progressors is used for dysplasia-free patients [182–  
151 184].

152 In 2020, the study of 3 IBD families with 11 affected members over three successive generations  
153 concluded that short telomeres, measured in leukocytes, was unlikely to be involved in mechanisms  
154 of possible genetic anticipation of the disease [57]. Indeed, TL was not associated with earlier age at  
155 onset or severity of IBD in members of successive generations affected by the disease [57]. However,  
156 it was demonstrated that TL was shorter in the colonic mucosa of UC subjects compared to age-  
157 matched controls [185,186] and associated with more severe clinical phenotypes of UC [185]. A  
158 study of TL in colonocytes and leukocytes from UC patients showed shorter telomeres in both cell  
159 types in UC patients than in matched controls [58]. Interestingly, the difference in TL in colonocytes

160 was more pronounced in early-onset UC patients (aged less than 39 years) [58]. The short TL in  
161 colonocytes could explain the increased and early cancer risk in this disease. An increase in  $\gamma$ H2AX  
162 foci, which are early cellular response to DNA double-strand breaks through rapid phosphorylation at  
163 Ser-139 of H2AX – the minor variant of histone H2A –, was also found in colonocytes and may  
164 reflect oxidative damage secondary to inflammation [58]. In a study with 14 UC patients, an  
165 increased load of ultra-short telomeres, as well as a shorter mean TL, were found associated with  
166 dysplasia in longstanding UC. Furthermore, the load of ultra-short telomeres was also increased in  
167 progressors compared to non-progressors [187]. Another study of 9 UC patients with high-grade  
168 dysplasia compared to 4 UC patients without dysplasia supports a model in which inflammation,  
169 short telomeres and senescence are the background to tumour progression in progressive UC [59].  
170 Senescence acts as a tumour suppressor mechanism, preventing colons from progressing beyond low-  
171 grade dysplasia [59]. However, it has been demonstrated that in colonic mucosa, short telomeres are  
172 correlated with chromosomal instability [184]. Eventually some colonocytes bypass senescence and  
173 transform, coinciding with the lengthening of telomeres through activation of telomerase and the loss  
174 of p53 tumor suppression function [59]. This allows colonocytes with genetic damage to proliferate  
175 and progress to high-grade dysplasia and cancer [59]. In contrast to these results, another study with  
176 18 controls, 19 UC and 17 CD concluded that there was no difference in telomere length in  
177 peripheral blood mononuclear cells (PBMCs) between these three groups [60]. (Table 1; Fig. 1.B).

178 Another study, with 18 UC, 13 CD patients and 13 controls, observed the downregulation of TRF2  
179 and RAPI mRNA expression in CD25+ T-lymphocytes in IBD. This could lead to the destabilisation  
180 of the T-loop structure in these cells and may contribute to the telomeric fusions and chromosomal  
181 abnormalities observed in UC [61]. These findings may also indicate a systemic process of telomere  
182 uncapping that could represent a putative biomarker for IBD associated colon cancer risk [61]. (Table  
183 1; Fig. 1.B).

184 Overall, these studies concur on the presence of short telomeres in colon mucosa of IBD patients.  
185 Short TL and telomere dysfunction are also found in leukocytes from these patients. Short telomeres  
186 could be the result of higher telomere attrition due to chronic inflammation and higher cell turn-over  
187 or partially due to the effect of lifestyle factors such as diet and smoking [113,123,135,188] that are  
188 also involved in the aetiology of IBD [189]. However, shorter telomeres could precede IBD and play  
189 a role in the pathogenesis. Indeed, in a study on 33 patients with UC, 14 progressors and 19 non-  
190 progressors, shorter telomeres were found associated with clonal expansions in nondysplastic  
191 biopsies from UC progressors with early-onset of disease (younger than 50 years of age) [62]. Short  
192 TL in leukocyte has already been associated with clonal expansion, known as clonal haematopoiesis  
193 of indeterminate potential (CHIP) [190,191]. Short telomeres and telomere dysfunction may also play  
194 a role in initiating inflammation. Short LTL has been recently linked to the upregulation of NLRP3  
195 inflammasome [192,193], a system that may contribute to IBD susceptibility [194–196]. Moreover, a  
196 recent study showed that telomere dysfunction-induced activation of the ATM-YAP1-pro-IL-18  
197 pathway in intestinal epithelium is a primary initiator and driver of colon inflammation [197]. (Table  
198 1; Fig. 1.B).

### 199 **3.2 Psoriasis**

200 **Psoriasis** is a chronic inflammatory disease of uncertain aetiology characterised by scaly  
201 erythematous plaques that can lead to significant physical and psychological distress, affecting  
202 approximately 125 million people worldwide [198–200].

203 Wu et al demonstrated for the first time that increased telomerase activity can be detected in freshly  
204 obtained non-stimulated PBMCs from patients with atopic dermatitis (AD), indicating the  
205 lymphocytes have already been activated *in vivo* or that a subpopulation of 'immature' lymphocytes  
206 may be present [65]. The relative reduced telomerase activity of PBMCs to multiple stimulators in  
207 patients with AD seemed to be associated with their excessive stimulation *in vivo* and their decreased  
208 functional capacity *in vitro* [65]. The authors have published a second study showcasing similar  
209 results in T lymphocytes from blood of patients with AD and psoriasis: increased telomerase activity  
210 was found together with reduced TL as compared to healthy controls, also indicating an *in vivo*  
211 activation of T lymphocytes [64] (table 1; Fig. 1.B). A third study focusing on patients with psoriasis  
212 confirmed the higher telomerase activity in PBMCs from patients [63]. In addition, telomerase  
213 activity of PBMC in psoriatic patients correlated positively with disease severity [63].

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

### 218 3.3 Spondyloarthritis

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

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

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

244 Regarding axial spondylarthritis (aSpA) – a group that includes ankylosing spondylitis (radiographic  
245 axial spondylarthritis) [204,208] –shorter telomeres were found in CD4+ and CD8+ T cell subsets in

246 young patients (under 35 years), as well as impaired telomerase in aSpA patients with rheumatoid  
247 arthritis [209] (Table 1; Fig. 1.B).

### 248 **3.4 Rheumatoid arthritis**

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

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

### 265 **3.5 Uveitis**

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

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

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

## 282 **4 Perspectives**

283 Unlike studies focused on telomere dynamics and other NCDs, those focused on IMIDs tend to  
284 gather relatively narrow populations with great difficulty to find healthy controls. This is partly due  
285 to the nature of the biological material required for comparison which is difficult to obtain in healthy  
286 subjects and questions the statistical power of the majority of results. In addition, most of these



287 studies used a telomere length measurement methodology based on qPCR that is not the most  
288 suitable method for such narrow populations [217,218].

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

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

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

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

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

321

322

## 323 **5 Conflict of Interest**

324 *Prof. Peyrin-Biroulet reports personal fees from AbbVie, Janssen, Genentech, Ferring, Tillots,*  
325 *Pharmacosmos, Celltrion, Takeda, Boehringer Ingelheim, Pfizer, Index Pharmaceuticals, Sandoz,*  
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330 *The remaining authors declare that the research was conducted in the absence of any commercial or*  
331 *financial relationship that could be construed as a potential conflict of interest.*

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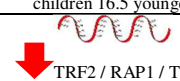
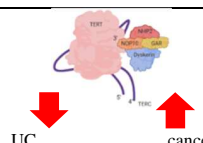


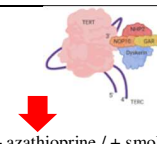
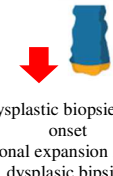
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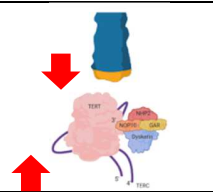
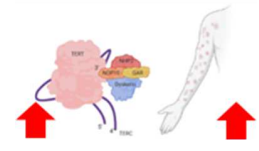
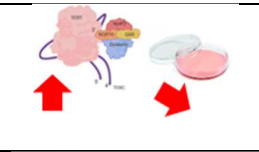
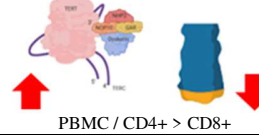

## 1122 **9 Captions figure.**

1123 **Fig.1: (A) Telomere maintenance components, (B) Telomere length reported in IMID's.** (A)  
1124 Telomeres are composed of hundreds or thousands of repeated DNA sequences of TTAGGG in one  
1125 strand and CCCTAA in the other. The shelterin complex consist of six proteins (TRF1, TRF2, RAP1,  
1126 POT1, TPP1 and TIN2) and provides protection of the telomere end, facilitates telomeric DNA  
1127 replication and recruitment of telomerase to the telomere. The telomerase complex consists of the  
1128 enzyme telomerase-transcriptase (TERT), the RNA component (TERC) and the protein complex  
1129 dyskerin (dyskerin, NOP10, NHP2 and GAR1). This complex allows telomere elongation via TERT  
1130 by adding TTAGGG repeats and has extratelomeric functions.

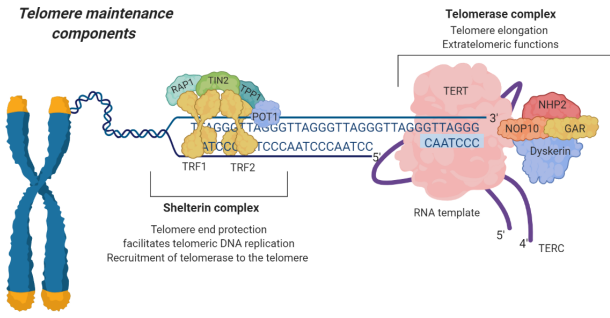
1131 **Table 1: Overview of recent studies investigating the relationship between telomere dynamics and IMIDs.** AD = atopic dermatitis;  
 1132 aSpA : axial spondyloarthritis; CD = Crohn's disease; IBDs = inflammatory bowel diseases; IMIDs = Immune-mediated inflammatory  
 1133 diseases; PBMCs = peripheral blood mononuclear cells; UC = ulcerative colitis. Consistence between methodology and conclusion are  
 1134 highlight in blue.

IMID	Study reference	Populations / design		Results	Authors' conclusion
		Cases	Controls		
<b>Inflammatory bowel diseases</b>					
IBD	Tutra et al. [57]	11 patients (5 UC, 4 CD, 2 IBD-U) 8 parent-child pairs from 3 families <i>Johns Hopkins IBD Family Study</i>		 Median age at diagnosis of children 16.5 younger	Telomere shortening appears unlikely to be involved in mechanisms of possible genetic anticipation in IBD.
IBD	Da-Silva et al. [61]	18 UC / 13 CD patients 49 / 44 years <i>Clinical Sciences Research Institute, Warwick Medical School, University of Warwick, Coventry UK</i>	13 non-IBD controls 56 years	 TRF2 / RAP1 / TRF1	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.
UC	Usselmann et al. [230]	25 UC 11 colorectal cancer 9 adenomatous polyps <i>Department of Gastroenterology, University Hospitals Coventry and Warwickshire NHS Trust UK</i>	21 normal colons	 UC cancer	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.
UC	Tahara et al. [185]	86 UC / 37.3 years ± 11.4 median clinical duration = 6.9 years ± 5.8 <i>Department of Gastroenterology, Fujita Health University School of Medicine Japan</i>	normal appearing proximal colon of same individuals	 + severe clinical phenotypes	Telomere shortening is associated with more severe clinical phenotypes of UC, reflecting severe inflammatory state in the colonic mucosa.
UC	Risques et al. [58]	85 UC (biopsies) / 14-79 years 102 UC (leukocyte DNA) / 31-80 years 43 UC (paraffin-embedded colon) / 31-78 years <i>Department of Pathology, University of Washington, Seattle USA</i>	79 normal colon controls / 2-79 years 45 controls / 3-79 years 53 controls / 31-79 years	 colonocytes / leukocytes	Colonocytes 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.
UC	Getliffe et al. [60]	19 UC / 45 years 17 CD / 48 years <i>Department of Biological Sciences, University of Warwick, Coventry UK</i>	18 controls / 56 years	 + azathioprine / + smoking	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.
UC	Salk et al. [62]	14 Progressors UC patients <i>Cleveland Clinic USA</i>	19 Non-Progressors UC patients	 non-dysplastic biopsies & early onset + clonal expansion in non-dysplastic biopsies	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.

UC-associated colorectal cancer	Risques et al. [59]	9 UC patients with high-grade dysplasia (biopsies located less than 10 cm from HGD) <i>Department of Pathology, University of Washington, Seattle USA</i>	4 UC patients without dysplasia		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.
CD	Meresse et al. [231]	Surgical samples from 27 patients undergoing ileo-colonic resection for CD 19-52 years <i>Service d'Immunologie, EA 2686, Lille France</i>	Non inflammatory mucosa collected in the healthy mucosa of resected ileum from 10 patients with colonic cancers / 53-82 years		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.
<b>Rheumatoid arthritis</b>					
RA	Colmegna et al. [68]	63 patients with diagnosis of seropositive RA according to the American College of Rheumatology 1987 revised criteria 55 years ± 14 <i>Rheumatology Clinic Emory University School of Medicine, Atlanta</i>	48 age-, sex- and ethnically- frequency matched healthy subjects without history of chronic inflammatory diseases or immunosuppressive/chem otherapeutic therapy 52 years ± 14		Decrease 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.
RA	Fujii et al. [70]	69 patients / 50.5 years ± 14 <i>Department of Medicine, Lowance Center for Human Immunology and Rheumatology, Emory University School of Medicine Atlanta, USA</i>	60 healthy control / 47.6 years ± 12		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.
RA	Steer et al. [67]	176 RA patients / 63.8 years <i>Guy's, St Thomas' and Lewisham hospitals in London, UK</i>	1151 controls / 8.2 years		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.
RA	Koetz et al. [211]	51 rheumatoid arthritis / 13-80 years	47 healthy controls / 18-77 years		Increased self-replication of CD4+CD45ROnull 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.
<b>Spondyloarthritis</b>					
	Tamayo et al. [207]	86 rheumatoid arthritis / 31-82 years 56 psoriatic arthritis / 26-79 years 59 ankylosing spondylitis / 21-75 years <i>Hospital Universitario de A Coruña Spain</i>	130 healthy controls / 3-94 years		The presence of chronic inflammatory component in rheumatologic diseases could be associated to higher telomere size in PBL, unlike in healthy controls.
	Tamayo et al. [66]	42 psoriatic arthritis patients / 55.02 years ± 14.33 44 ankylosing spondylitis patients / 49.07 years ± 14.58 <i>Hospital Universitario de A Coruña Spain</i>	53 psoriasis at baseline / 53.75 years ± 16.37		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.

	Fessler et al. [209]	51 axial spondyloarthritis (aSpA) / 40.7 years ± 12.9 51 rheumatoid arthritis / 52.3 years ± 18.2	50 healthy controls / 45.6 years ± 13.3		Increased homeostatic proliferation of T-cells leads to premature shortening of telomeres that is not restored by telomerase enzyme.
<b>Chronic inflammatory skin diseases</b>					
Psoriasis	Liu et al. [63]	30 psoriatic patients / 34.03 years ± 7.38 <i>Department of Dermatology Affiliated Hospital of Dalian Medical University China</i>	13 healthy donors / 29.61 years ± 5.14		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.
Atopic dermatitis	Wu et al. [65]	15 patients with moderate to severe disease activity / 23-47 years <i>Department of Dermatology Marselisborg Hospital, University of Aarhus Denmark</i>	13 healthy donors / 24-40 years		Increased telomerase activity detected in freshly obtained PBMC from patients with AD, indicating the lymphocytes have already been activated <i>in vivo</i> 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 <i>in vivo</i> and their decreased functional capacity <i>in vitro</i> .
Atopic dermatitis	Wu et al. [64]	32 AD patients with moderate to severe disease activity / 17-59 years 16 psoriatic patients / 20-84 years <i>Department of Dermatology Marselisborg Hospital, University of Aarhus Denmark</i>	30 healthy blood donors / 20-84 years	 PBMC / CD4+ > CD8+	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 <i>in vivo</i> .
<b>Birdshot Uveitis</b>					
	Vazirpanah et al. [73]	91 unrelated BU cases of European descent / 60.5 years (9.07) <i>Department of Ophthalmology at the University Medical Center Utrecht The Netherlands</i>	150 unrelated healthy controls / 52.9 years (7.16)		BU is accompanied by significantly longer LTL.

(A) **Telomere maintenance components**



(B) **Telomere length reported in IMID's**

