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**Telomere shortening as a mechanism of long-term cost of infectious
diseases in natural animal populations**

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Abstract

Pathogens are potent selective forces that can reduce the fitness of their hosts. While studies of the short-term energetic costs of infections are accumulating, the long-term costs have only just started to be investigated. Such delayed costs may, at least in part, be mediated by telomere erosion. This hypothesis is supported by experimental investigations conducted on laboratory animals which show that infection accelerates telomere erosion in immune cells. However, the generalizability of such findings to natural animal populations and to humans remains debatable. First, laboratory animals typically display long telomeres relative to their wild counterparts. Second, unlike humans and most wild animals, laboratory small-bodied mammals are capable of telomerase-based telomere maintenance throughout life. Third, the effect of infections on telomere shortening and ageing has only been studied using single pathogen infections, yet hosts are often simultaneously confronted with a range of pathogens in the wild. Thus, the cost of an infection in terms of telomere-shortening-related ageing in natural animal populations is likely to be strongly underestimated. Here, we discuss how investigations into the links between infection, immune response and tissue ageing are now required to improve our understanding of the long-term impact of disease.

Introduction

Parasites are a potent selective force, as they reduce the fitness of their hosts through the direct cost of parasitism itself, and the indirect cost of an immune activation^{1,2}. Costs of immune responses could be both short- and long-term. Short-term costs are reduced resource availability for other demanding activities such as growth, reproduction, and other forms of self-maintenance³. These costs have been well documented⁴. In addition to reduced investment in tissue maintenance due to trade-offs, infections can lead to accelerated ageing through direct effects of inflammatory processes on telomere erosion (Figure 1). These long-term costs in terms of ageing rate have until recently been largely overlooked. Telomeres are regions of non-coding DNA at the end of linear eukaryotic chromosomes that shorten during each cell division and in response to oxidative stress^{5,6}. While the link between ageing and telomere erosion has to be interpreted with caution, since questions about mechanisms and direction of causality complicate this association⁷, telomere erosion has been proposed as an essential component of the ageing phenotype⁵ and a major driving force behind immunosenescence¹². In fact, telomere shortening due to other natural processes (i.e. stress, cellular ageing) leading to the senescence of the immune system can be viewed as an opposite, non-mutually exclusive causal pathway linking ageing rate and immune responses (Figure 1).

The long-term costs of an infection on telomere dynamics in wild animals remain mostly unclear. Most studies investigating these costs have been conducted on small laboratory mammals, but the generalizability of the results obtained in these studies to natural animal populations remains debatable for several reasons. First, laboratory studies usually disregard the importance of individual variation in disease resistance and tolerance, yet unlike traditional laboratory model species, wild animals exhibit extensive variation in responses to infection⁸.

Second, while laboratory studies usually focus on one type of immune challenge at a time, multiple infections are the rule rather than the exception in wild animals⁹. Multiple infections may, on the one hand, accumulate immune-mediated pathology. On the other hand, activation of one arm of the immune system can suppress the other arm, preventing immune pathology in case of coinfections⁹. We thus suggest that telomere dynamics in wild individuals might be shaped by the interaction between the whole pathogen community, the inherent immune capacity, and the prioritized life-history and/or immune strategy (resistance *vs* tolerance). Accordingly, we can distinguish between hypotheses that should be studied in order to support either the “aging cost of infections pathway” or “immunosenescence pathway” (Figure 1). In this article, we will review the available evidence on the link between infections and telomere dynamics in wild animals, and describe possible associated physiological mechanisms that are relevant in the context of optimal fitness outcome in the wild, but would be difficult to study in laboratory conditions.

What do we know?

Studies in humans have repeatedly shown that patients with chronic infections have shorter telomeres in immune cells than healthy individuals, and that individuals with shorter telomeres have increased mortality rates¹⁰. This literature in humans has established a relationship between health status and the rate of ageing, but the causal role of immune activation on telomere shortening and human longevity remains elusive owing to obvious experimental limitations with human subjects¹¹. A handful of experimental studies in animal model species have demonstrated that exposure to pathogens results in accelerated telomere erosion in immune cells. The generalizability of these results to humans and wild animals has

been questioned, since laboratory strains are often heavily inbred and display unusually long telomeres relative to their wild counterparts^{12,13}. In addition, humans (characterized by short telomeres and repressed telomerase in somatic tissues) and some smaller-bodied mammals including laboratory rats and mice (characterized by long telomeres and telomerase-based telomere maintenance in somatic tissues) do not present the same telomere dynamics throughout life¹⁴. Accordingly, similar experimental setups that have been used on classical laboratory models should be applied in wild animal species.

According to the hypothesis suggested in the current study (the aging cost of infections pathway), infections should lead to faster aging. According to the alternative hypothesis (the immunosenescence pathway), aging should lead to weaker immunity (Figure 1). How much support can we find for either of these hypotheses from studies in wild populations? Non-experimental studies showing age-related declines in telomere length and immunity (i.e.¹⁵) do not allow to determine the direction of causality that is important for distinguishing between the two pathways. It is noteworthy that while the immunosenescence hypotheses seems to be the “null hypothesis” here, there is a lack of studies experimentally manipulating aging rate and/or telomere shortening rate and recording the resulting changes in immune responses or infection rates. This shortage can be explained with the scarcity of experimental approaches allowing to manipulate telomere length (but see¹⁶ for a possible method). Current knowledge of the consequences of infections on telomere dynamics in wild populations remains also limited. In a cross-sectional study that, by definition, cannot measure telomere erosion and the pre-infection variation in telomere length, Watson *et al* (2017)¹ did not find a significant relationship between gastrointestinal nematode parasites load and leucocyte telomere length in Soay sheep (*Ovis aries*). In contrast, using the same approach, Karell *et al.* (2017)¹⁸ found that tawny owls (*Strix*

107 *aluco*) carrying *Leucocytozoon* disease had shorter telomeres than uninfected individuals.
108 Longitudinal studies have shown associations between telomere erosion and bovine tuberculosis
109 infection status in wild European badgers (*Meles meles*)¹⁸ and with malaria in great reed warblers
110 (*Acrocephalus arundinaceus*)¹⁹. The study on badgers is also noteworthy in the context of the
111 current hypothesis, because it showed that age-related declines in immune response are unrelated
112 to immune cell telomere length in a wild mammal¹⁸. On the one hand, it does not provide direct
113 support for the hypothesis that immune responses can lead to accelerated ageing, on the other
114 hand, it indicates that at least in this model system, the alternative pathway (the
115 immunosenescence pathway, Figure 1) is not supported.

116 The discrepancies between these studies could be attributed to different types of
117 pathogens studied, time scales, and levels of infection. Only three studies have, so far, used an
118 experimental approach to investigate this topic in wild animals. In a study performed in captivity
119 with the F2 offspring of wild-caught house mice, where animals were exposed to an infectious
120 agent (*Salmonella enterica*), infected animals showed faster telomere erosion compared to non-
121 infected individuals¹². Inversely, in a field experiment, an antimalarial treatment administered to
122 adult blue tits had no effect on telomere shortening rates²⁰. Finally, in a study combining field
123 and captive experimental approaches, Asghar *et al.* showed the long-term costs of a malaria
124 infection on life span and survival in great reed warblers, potentially mediated through a
125 significantly greater rate of telomere shortening in six tissues^{19,29}. Given the higher inter-
126 individual than intra-individual variability in telomere length, any cross-sectional study will
127 have a very low power to detect any cost of infection. Thus, in addition to experimental studies
128 manipulating infection status in non-model animals, we recommend longitudinal and long-term

studies to understand these costs in the context of ageing (with telomere measurement in blood samples).

What to measure?

A significant part of the studies on the long-term costs of an infection on ageing in the wild have used avian species with telomere length measured in red blood cells^{19,20}, where it is supposed to reflect telomere length in haematopoietic tissues (but see²²). The next step, in birds but also in other organisms, is thus to measure telomere shortening in immune cells in order to study how the type and extent of immune response mounted impact the rate of ageing of the immune system. Immune cells are expected to be particularly vulnerable to telomere shortening under an infection because of their rapid proliferation. In addition, the enzymes and enzyme complexes of immune cells such as phagocytes and lymphocytes can rapidly produce large amounts of ROS (reactive oxygen species)²³. Due to their cytotoxic character, ROS can directly contribute to the degradation of the pathogen but this increased production of ROS may also be costly by impacting immune cells through DNA damage and telomere shortening⁶.

Recent studies in humans have shown that the rate of telomere attrition and telomerase activity are significantly different between cell types, suggesting cell-specific susceptibility and telomere length regulation mechanisms^{24,25}. Even more, it has been recently shown in a wild mammal (mandrill, *Mandrillus sphinx*) that leukocyte composition varies temporally and that these variations are mirrored by change in blood telomere length²⁶. Thus, any conclusion based on whole blood or total white blood cells are likely to be biased, especially in the case of infections that affect white blood cell count and composition²⁷. A next step will therefore involve measuring telomere shortening in specific populations of immune cells¹⁸. This approach would

also make it possible to discern whether any effects of infection on telomeres were due to changes in circulating immune cell sub-types, which may differ in mean telomere length (e.g. an increasing representation of memory T-cells with shorter telomeres relative to naive T-cells with longer telomeres) versus within-cell telomere erosion in response to infection²⁵. However, since sample amounts are generally small in studies of wild animals, methodological advancements would be needed before this approach can be used, since cell sorting would have to be followed by DNA extraction and the analysis of telomere length.

Living in the real world: tolerance, resistance and coinfections

Defense against parasites can be divided into two conceptually different components: resistance, the ability to limit parasite burden, and tolerance, the ability to limit the disease severity induced by a given parasite burden²⁸. Tolerance does not reduce the parasite burden, but decreases the host susceptibility to tissue damage²⁹. Currently, very little is known about the full spectrum of tolerance mechanisms. However, studies on mice with malaria infection have demonstrated that protecting tissues from the toxic byproducts of immune responses is one of the mechanisms²⁹. Telomere shortening accompanies strong responses to chronic parasite exposure from both innate and acquired arms of the immune system¹². Preventing telomere shortening caused by inflammation could be one of the molecular mechanisms behind parasite tolerance. Accordingly, individuals exhibiting tolerance to parasites should also demonstrate lower telomere shortening rate and have longer telomeres in comparison with individuals that apply immune responses for fighting off parasites. In line with this hypothesis, in a natural population of juvenile brown trout (*Salmo trutta*), individuals that were less sensitive to parasite-induced impaired growth (and therefore demonstrated higher tolerance), showed longer telomeres³⁰. We therefore predict that

host phenotypes that demonstrate higher levels of tolerance also show reduced telomere attrition rate during the infection when compared to host phenotypes that are more prone to fight off the parasites (higher resistance phenotypes), and suggest that host telomere attrition rate should be an important trait to analyse in future studies of disease tolerance in the wild.

Wild animals are usually affected by several pathogens at the same time. While this could lead to amplified long-term costs of infection, multiple infections can sometimes lead to lowered inflammatory responses to specific type of parasites⁹. For example, chronic helminth infections typically induce an anti-inflammatory type 2 immune response that limits damage to host tissues by down-regulated inflammatory type 1 immune response usually triggered by bacterial infections⁹. The possible amplifying or subduing effects of co-infections on telomere shortening have so far not been studied, partly because the already complex dynamics of an immune response through time will be compounded by immunological variation among hosts in their pathogen exposure, age, nutrition and other varying aspects found in natural populations¹⁰. At the same time, natural variation among individuals should be viewed as an unused potential for new discoveries, rather than a nuisance. We therefore encourage studies on telomere dynamics looking at the simultaneous effect of co-infections, as these could give more reliable answers to the question about long-term costs of infection for wild animals.

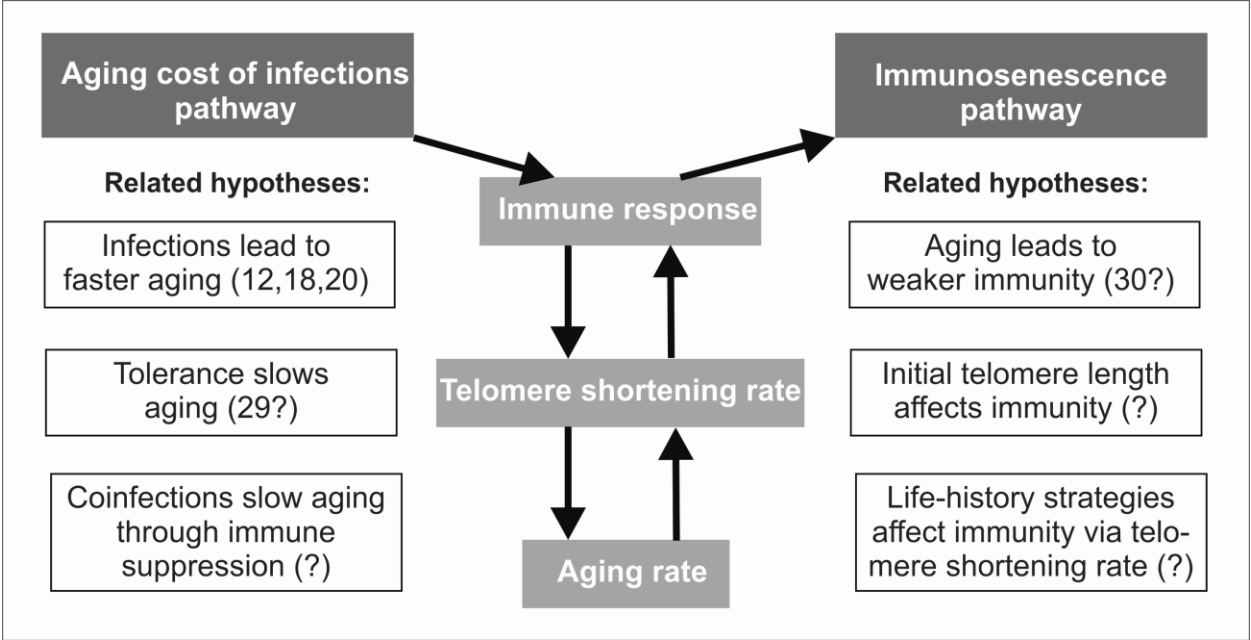
Conclusion

While our understanding of the short-term energetic costs of infection are accumulating, the longer-term consequences of infection on ageing remain to be explored. Tissue damage and intense cell proliferation associated with infection is likely to accelerate ageing, a process possibly mediated by increased rates of telomere shortening. Studying the impact of infection on

telomere dynamics in natural animal hosts is thus essential, since natural selection has optimized these processes in the context of lifetime fitness, and the costs and benefits associated with telomere shortening cannot be understood outside the ecological context. Experimental studies manipulating infection levels and immune responses, and measuring telomere dynamics in the wild could shed light on the causality. However, longitudinal and long-term studies are crucial for understanding the telomere-mediated effect of infectious diseases on ageing in wild populations, with important implications for our understanding of the long-term cost of infection in humans.

Figure legend:

Two non-mutually exclusive pathways with reversed causality directions that link responses to infections with aging rate. Numbers indicate references supporting related hypotheses in wild populations, question marks indicate either indirect support or missing support in wild populations.



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