Ageing Research Reviews 25 (2016) 55–69

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

Ageing and the telomere connection: An intimate relationship with inflammation

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ARTICLE INFO

Article history:
Received 18 August 2015
Received in revised form
16 November 2015
Accepted 19 November 2015
Available online 23 November 2015

Keywords:
Telomere
Inflammation
Ageing

ABSTRACT

Telomeres are the heterochromatic repeat regions at the ends of eukaryotic chromosomes, whose length is considered to be a determinant of biological ageing. Normal ageing itself is associated with telomere shortening. Here, critically short telomeres trigger senescence and eventually cell death. This shortening rate may be further increased by inflammation and oxidative stress and thus affect the ageing process. Apart from shortened or dysfunctional telomeres, cells undergoing senescence are also associated with hyperactivity of the transcription factor NF-κB and overexpression of inflammatory cytokines such as TNF-α, IL-6, and IFN-γ in circulating macrophages. Interestingly, telomerase, a reverse transcriptase that elongates telomeres, is involved in modulating NF-κB activity. Furthermore, inflammation and oxidative stress are implicated as pre-disease mechanisms for chronic diseases of ageing such as neurodegenerative diseases, cardiovascular disease, and cancer. To date, inflammation and telomere shortening have mostly been studied individually in terms of ageing and the associated disease phenotype. However, the inter-dependent nature of the two demands a more synergistic approach in understanding the ageing process itself and for developing new therapeutic approaches. In this review, we aim to summarize the intricate association between the various inflammatory molecules and telomeres that together contribute to the ageing process and related diseases.

Contents

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http://dx.doi.org/10.1016/j.arr.2015.11.006
1568-1637/

1. Introduction

Ageing is due to an accumulation of detrimental changes over time at both the molecular and cellular levels, which ultimately leads to a functional decline at the tissue and organ level. While ageing itself is not a disease (Hayflick, 2000), the time-dependent decline of function or loss of structural integrity will eventually result in age-related disease such as atherosclerosis, dementia, and cancer, as well as in an increased risk of morbidity and mortality (Singh and Newman, 2011). Although the etiology of ageing has not been fully understood, several cellular and molecular hallmarks may contribute to this process. Among them, telomere attrition and chronic low-grade inflammation are considered as two major underlying mechanisms.

Telomere shortening with increasing age is a part of the normal ageing process. However factors such as inflammation, oxidative stress, and other genotoxic stressors also increase the rate of telomere attrition, leading to telomere dysfunction-mediated cellular senescence and accelerating the ageing process (Aubert and Lansdorp, 2008). "Cellular senescence" denotes a stable and long-term loss of proliferative capacity, but the senescent cells are still metabolically active with altered secretory phenotypes (senescence-associated secretory phenotype, SASP). SASP is associated with the increased production of inflammatory cytokines during the ageing process, which likely contributes to the chronic inflammation connected with ageing (Freund et al., 2010; Rodier and Campisi, 2011). Chronic inflammatory process is a major risk factor underlying ageing and age-related diseases (Chung et al., 2006). During the normal ageing process, pro-inflammatory mediators such as TNF-α, IL-1β, COX-2 and iNOS are continuously up-regulated (Chung et al., 2006; Kim et al., 2002a). Chronic inflammation has been also shown to be the underlying process of many age-related diseases such as dementia (Minghetti, 2005), cardiovascular diseases (Tracy, 2003), arthritis (Banning, 2005) and cancer (Caruso et al., 2004).

In this review, we aim to describe the interplay between inflammation and telomeres/telomerase in the ageing process and ageing-related diseases with an emphasis on how inflammation may lead to telomere dysfunction, thus promoting the ageing process. We will further discuss how pharmacological anti-ageing agents targeting telomerase may prove useful to improve health during the human ageing process.

2. Relationship between ageing and inflammation

Inflammation is a prominent ageing-associated alteration in intercellular communication (Salminen et al., 2012). Multiple causes may contribute to ageing-associated inflammation, such as pro-inflammatory tissue damages, a dysfunctional immune system (Deeks, 2011), proinflammatory cytokines secreted by senescent cells, enhanced NF-κB activation and a defective autophagy response (Salminen et al., 2012). These factors enhance the activation of inflammatory pathways such as the nod-like receptor 3 (NLRP3) inflammasome, and then induce the production of cytokines such as IL-1 β, tumor necrosis factor (TNF), and interferons (IFNs) (Green et al., 2011; Salminen et al., 2012). Long term inflammation could be a major cause of ageing-associated diseases (Perry et al., 2007).

2.1. NF-κB

Over-activation of the NF-κB pathway is one of the transcriptional signatures of ageing (Lepez-Otin et al., 2013). NF-κB can be considered as the master regulator of the inflammatory process; it regulates the transcription of various molecules involved in the inflammatory response, such as TNF-α, interleukins, AMs, and COX (Baeuerle and Baltimore, 1996; Schreck et al., 1992). The ageing process enhances NF-κB activity through an increase of NF-κB DNA binding activity and in consequence transcriptional activity in old rodents (Helenius et al., 1996; Kim et al., 2002b). Inhibition of NF-κB, by either genetic and pharmacological inhibitors or conditional expression of an NF-κB inhibitor in the tissues, prevents ageing associated features in a mouse model of ageing (Adler et al., 2007; Ortega-Molina et al., 2012; Tilstra et al., 2012). According to recent studies, the mechanism of NF-κB over-activation may be attributed to the strongly enhanced activity of IKK and three MAPKs (ERK, P38, and JNK) during the ageing process; these kinases are upstream kinases of NF-κB, therefore their enhancement results in the upregulation of NF-κB activity (Kim et al., 2002a,b). Parallel to the over-activation of the upstream kinases, increased reactive oxygen species (ROS) production in ageing might be another cause for NF-κB activation, which is both sensitive and directly responsive to oxidative stress (Haddad, 2002; Weisberg et al., 2003). In addition, a regulation *via* the hypothalamus might be important for mediating NF-κB-driven ageing-related changes. The activation of NF-κB in the hypothalamus suppresses the production of gonadotropin-releasing hormone (GnRH), which in turn leads to ageing-related changes such as bone fragility, muscle weakness, skin dystrophy, and reduced neurogenesis (Zhang et al., 2013). In contract, the addition of GnRH prevents ageing-related impairment and decelerates ageing development, which suggests that NF-κB-driven GnRH plays a critical role in the ageing process (Zhang et al., 2013).

2.2. Mitochondrial dysfunction

Mitochondria play a key role in initiating inflammatory pathways. Mitochondrial dysfunction drives the ageing process by reducing cellular fitness, inflicting damage to other organelles, or causing mutations of the nuclear genome (Wallace et al., 2010). One critical mechanism underlying the dysfunction of mitochondria is the accumulation of mutations and deletion of aged mitochondrial