Mutation Research 766 (2015) 48–57

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

Super DNAging—New insights into DNA integrity, genome stability and telomeres in the oldest old

Bernhard Franzke[a], Oliver Neubauer[a,b], Karl-Heinz Wagner[a,c,*]

[a] University of Vienna, Research Platform Active Ageing, Althanstraße 14, 1090 Vienna, Austria
[b] Queensland University of Technology, Faculty of Health, School of Biomedical Sciences, Institute of Health and Biomedical Innovation (IHBI), Tissue Repair and Regeneration Group, 60 Musk Avenue, Kelvin Grove Campus, Brisbane, QLD 4059, Australia
[c] University of Vienna, Faculty of Life Sciences, Department of Nutritional Sciences, Althanstraße 14, 1090 Vienna, Austria

ARTICLE INFO

Article history:
Received 3 April 2015
Received in revised form 18 August 2015
Accepted 19 August 2015
Available online 28 August 2015

Keywords:
Genome stability
Centenarians
Nonagenarians
Longevity
Healthy aging
Maximum lifespan

ABSTRACT

Reductions in DNA integrity, genome stability, and telomere length are strongly associated with the aging process, age-related diseases as well as the age-related loss of muscle mass. However, in people reaching an age far beyond their statistical life expectancy the prevalence of diseases, such as cancer, cardiovascular disease, diabetes or dementia, is much lower compared to "averagely" aged humans. These inverse observations in nonagenarians (90–99 years), centenarians (100–109 years) and supercentenarians (110 years and older) require a closer look into dynamics underlying DNA damage within the oldest old of our society. Available data indicate improved DNA repair and antioxidant defense mechanisms in "super old" humans, which are comparable with much younger cohorts. Partly as a result of these enhanced endogenous repair and protective mechanisms, the oldest old humans appear to cope better with risk factors for DNA damage over their lifetime compared to subjects whose lifespan coincides with the statistical life expectancy. This model is supported by study results demonstrating superior chromosomal stability, telomere dynamics and DNA integrity in "successful agers". There is also compelling evidence suggesting that life-style related factors including regular physical activity, a well-balanced diet and minimized psycho-social stress can reduce DNA damage and improve chromosomal stability. The most conclusive picture that emerges from reviewing the literature is that reaching "super old" age appears to be primarily determined by hereditary/genetic factors, while a healthy lifestyle additionally contributes to achieving the individual maximum lifespan in humans. More research is required in this rapidly growing population of super old people. In particular, there is need for more comprehensive investigations including short- and long-term lifestyle interventions as well as investigations focusing on the mechanisms causing DNA damage, mutations, and telomere shortening.

Contents

* Corresponding author at: Department of Nutritional Sciences University of Vienna Althanstraße 14 A-1090 Vienna, Austria. Fax: +43 1 4277 9549.
E-mail address: karl-heinz.wagner@univie.ac.at (K.-H. Wagner).

http://dx.doi.org/10.1016/j.mrrev.2015.08.001
1383-5742/

1. Introduction

Predictions from the World Health Organization [1] estimate that the global number of people aged 85 years and older is going to increase by 351% from 2010 to 2050. Particularly the sub-group of centenarians will increase 10-fold, which makes the oldest old group (aged 85 years or older) the fastest growing segment of the population in developed countries [1].

Especially the group of elderly aged around the statistical life-expectancy of humans (developed countries: men around 72 years, women around 80 years) is most susceptible to disease and disability [2]. With this bio-demographic development the burden of chronic, age-related diseases such as cardio-vascular diseases, type 2 diabetes, cancer, dementia and physical impairments associated with the age-related loss of skeletal muscle and function, is steadily increasing [3].

Aging is considered as a degenerative and multi-factorial process caused by accumulating molecular and cellular damage that leads to cell and tissue dysfunction [4–6]. Proposed mechanisms that contribute to the aging process and the development of chronic, age-associated diseases include increased levels of DNA damage, genotoxicity, oxidative stress, and incidence of shorter telomeres [7–11]. Many theories have been proposed to explain the phenomenon of aging, yet none has been able to fully explain the mechanisms that drive the process of aging [12]. The number of aging theories, focusing on particular mechanisms, increased within the last decades (e.g., the somatic mutation theory, the wear-and-tear theory, the free radical/oxidative stress/mitochondrial theory and the rate-of-living theory) [13]. In parallel to the different aging hypotheses, integrative approaches and "network" theories of aging were developed and gained more and more importance. Based on these integrative theories, aging is a multi-factorial process involving complex interactions between biological and molecular mechanisms, which may be at least as important as single actions [12,14–17]. All theories in common is the idea of with age linearly accumulating processes leading to cellular damage, tissue dysfunction and finally to death of the organism. Importantly, however, people exceeding the statistical life-expectancy, and especially the very oldest age-groups – nonagenarians (90–99 years), centenarians (100–109 years) and super-centenarians (110 years and older) – demonstrate a different picture of age-related diseases compared to study cohorts at or below life-expectancy [18]. This phenomenon of "successful aging" contradicts the theories of aging where age linearly correlates with the accumulation of reactive oxygen species (ROS), DNA damage, mitochondrial dysfunction, and shortening of the telomeres [19].

In this review we therefore investigate the impact of DNA damage for successful and healthy aging in the oldest old of our society and try to explore the crucial difference between elderly individuals at or below life-expectancy and the "super old"—nonagenarians, centenarians and super-centenarians. We focus on reports about DNA damage (double/single strand breaks, DNA repair, antioxidant defense, mitochondrial DNA), mutagenicity (sister chromatid exchange, acentric fragments, nondisjunction, aneuploidy, chromosomal loss, formation of micronuclei) and telomeres (telomere length, telomerase activity) within the oldest age-groups, summarized in Tables 1–3. Furthermore, recognizing the importance of mitochondria and, especially, mitochondrial (mt)DNA stability and integrity for aging [4] as well as the functionality of skeletal muscle in elderly individuals [20] we discuss findings on mtDNA damage in skeletal muscle of aging humans. The primary focus was on data of human studies; however, animal models were additionally included for discussing underlying mechanisms.

Finally we examined potential life-style based strategies for successful "DNAging" and reaching the individually predetermined lifespan.

2. DNA integrity

The process of aging has shown to be linked to increased DNA damage [21]. These findings are supported by the free radical

Table 1
Summary of available studies concerning DNA integrity in elderly at or beyond life-expectancy compared to younger age-groups.

DNA integrity				
Reference	Subjects	Age	Markers/methods	Main results
Hyland et al. [28]	Young controls: $n = 18$ Nonagenarians: $n = 138$	Young controls = 47.4 years Nonagenarians = 90.4 years	Comet assay in PBMCs; FRAP	Higher plasma antioxidant capacity in study group; similar level of DNA damage in PBMCs
Chevanne et al. [29]	Fibroblasts from young ($n = 4$), old ($n = 4$), and centenarian ($n = 3$) donors were cultured	Young = 18–22 years Old = 68–76 years Centenarians = 99–102 years	DNA strand breaks; DNA repair; Glutathione peroxidase activity; Glyceraldehyde-3-phosphate dehydrogenase activity	Less sensitivity of cells from centenarians to H_2O_2 induced DNA damage; comparable levels of DNA strand breaks in all age-groups
Chevanne et al. [30]	PBMCs from young ($n = 5$), old ($n = 3$), and centenarian ($n = 4$) donors were cultured	Young = 19–26 years Old = 69–75 years Centenarians = 100–107 years	Comet assay and DNA repair	Cells from centenarians show similar DNA repair capacity as cells from young donors and improved compared to cells from old subjects
King et al. [31]	PBMCs from young (previous study), mid-aged (previous study), old (previous study), and very old ($n = 31$) subjects	Young = 35–39 years Mid-aged = 50–54 years Old = 65–69 years Very old = 75–80 years	DNA strand breaks and repair (ELISA); antioxidant enzyme activity	Basal DNA damage and DNA repair of the very old were comparable to young cells; increased level of GPx and CAT in the very old
Humphreys et al. [32]	PBMCs from young ($n = 40$), old ($n = 35$), and very old ($n = 22$) subjects	Young = 20–35 years Old = 63–70 years Very old = 75–82 years	Comet assay; DNA repair (OGG1)	Increased oxidative base damage in old age; improved DNA repair in the oldest group
Franzke et al. [84]	6 months lifestyle intervention in institutionalized elderly; resistance training (RT) ($n = 34$), RT & supplement (RTS) ($n = 30$), cognitive training (CT) ($n = 32$)	Age = 65–98 years Mean age = 83.1 years	Comet assay; antioxidant enzyme activity; functional parameters	Significantly increased basal DNA damage in RT and RTS groups; improved resistance against H_2O_2 induced DNA damage in all groups; increased CAT and SOD activity in RT and RTS groups

Five cross sectional studies comparing young vs. old subjects and one lifestyle intervention study investigated "super old" humans.
Main conclusions from comparing very old with old and young humans:

- Increased antioxidant defense capacity in the very old compared to "normal" old
- Subjects above life-expectancy demonstrated improved DNA repair capacity compared to elderly below life-expectancy
- DNA damage and repair of the oldest groups was similar to youngest groups