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Review

Mechanisms of fetal epigenetics that determine telomere dynamics and health span in adulthood

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ABSTRACT

Advances in epigenetics now enable us to better understand environmental influences on the genetic background of human diseases. This refers especially to fetal development where an adverse intrauterine environment impacts oxygen and nutrient supply to the fetus. Recently, differences in telomere length and telomere loss dynamics among individuals born with intrauterine growth restriction compared to normal controls have been described. In this paper we propose possible molecular mechanisms that (pre)program telomere epigenetics during pregnancy. This programming sets differences in telomere lengths and dynamics of telomere shortening in adulthood and therefore dictates the dynamics of aging and morbidity in later life.

1. Introduction

In recent decades, and especially in the last few years, there is a growing interest in the process of fetal programming. It has become obvious that many common diseases that progressively develop in later life such as cardiovascular disease, obesity, type 2 diabetes and various allergies, have their origins in conditions of altered embryonic or fetal development. It is therefore of particular interest for science and medicine to investigate all factors and mechanisms that lead to this phenomenon. In particular, mechanisms of DNA methylation and histone acetylation, which are the main factors in chromatin modification, lead to epigenetic changes that last a lifetime and some are also inherited to future generations.

In the numerous literature pertaining to this topic, the majority of papers describe the modification of the genome, in particular regulatory regions of some genes that lead to their altered function (Heijmans et al., 2008; Park et al., 2008; Raychaudhuri et al., 2008). On the other hand, mounting evidence describes the great impact of telomeres on health, dynamics of aging, longevity and the development of many genetic diseases (Blasco, 2005) but they are poorly described as a factor in fetal programming. Therefore, in this paper we consider the mutual impact of changes in fetal environment and altered telomere/subtelomere methylation and acetylation on premature birth and changes in telomere biology and health in later life.

2. Telomere structure and function

Human telomeres are repetitive noncoding DNA sequences (TTAGGG) that protect the ends of linear chromosomes from DNA repair and degradation (Chan and Blackburn, 2002; de Lange, 2005). In human cells telomeres are 4–15 kb long depending on tissue type and the age of the donor (de Lange et al., 1990). They are organized in the form of dsDNA with a G rich 3′ overhang (Makarov et al., 1997) which folds back and invades the telomere/subtelomere border region forming a lariat like structure called t-loop (Griffith et al., 1999; Rubelj and Vondracek, 1999). The t-loop is additionally stabilized by a specialized multiprotein complex called shelterin (de Lange, 2005).

Telomeres are dynamic structures and in normal somatic cells they shorten with every cell division due to special enzymatic processing (Harley et al., 1990; Wu et al., 2012). Critically short telomeres cannot form a t-loop which then triggers a DNA damage response (DDR), leading to replicative senescence or apoptosis (Karlseder et al., 2002, 1999; Kim et al., 1998). Only one critically short telomere is sufficient to induce replicative senescence (Hemann et al., 2001; Rubelj et al., 2000). It is believed that this mechanism controls cellular aging *in vitro* as well as *in vivo* (Bodnar et al., 1998; Herbig et al., 2006; Jaskelioff

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et al., 2011). All cycling cells, including tumors, have to maintain their telomeres in order to retain their dividing potential. This is usually achieved by the enzyme telomerase, a ribonucleoprotein which *de novo* adds telomere repeats to chromosome ends during each round of cell division (Chan and Blackburn, 2002). For telomere maintenance some tumor cells use a telomerase independent mechanism called ALT (alternative lengthening of telomeres) which is based on homologous recombination (Bryan et al., 1997; Henson et al., 2002). After birth, telomerase is active at all times in stem and germ cells as well as in some progenitor cell types, enabling their limitless proliferation (Forsyth et al., 2002; Harley, 2002; Kim et al., 1994; Kyo et al., 1997; Mason, 2003). Importantly, overexpression of telomerase in normal human cells is sufficient for their immortalization and they maintain their normal phenotype (Bodnar et al., 1998).

2.1. Telomere chromatin and epigenetic regulation of telomere length

Telomere chromatin and adjacent subtelomeric regions in mammals are organized in nucleosomes like the rest of chromosomal DNA, but with a shorter nucleosomal spacing (Makarov et al., 1993; Pisano et al., 2008; Tommerup et al., 1994). Telomeric chromatin shares some characteristics with pericentromeric heterochromatin in terms of sequence organization and epigenetic marks. Human telomeres are exclusively repetitive sequences whereas subtelomeres contain less organized degenerative repeats and various other sequences and include a low density of genes (Riethman et al., 2005, 2004, 2003). Depending on their length, telomeres have the ability to silence the transcription of nearby genes, through a variegation based phenomenon known as 'telomere position effect' (TPE) (Baur et al., 2001; Koering et al., 2002). Mammalian telomeres and subtelomeres are enriched in epigenetic marks such as trimethylation of histone H3K9 and H4K20 and HP1 isoforms that are involved in telomere capping and function (Fanti et al., 1998; García-Cao et al., 2004; Gonzalo et al., 2006, 2005; Perrini et al., 2004). Another characteristic of telomeric chromatin is lower acetylation of histones H3 and H4 at both telomeric and subtelomeric regions (Benetti et al., 2007). In addition, unlike the telomere TTAGGG sequence, subtelomeric DNA contains CpG dinucleotides heavily methylated by DNA methyltransferases DNMT1, DNMT3a and DNMT3b (Fig. 1a) (Brock et al., 1999; Steinert et al., 2004). Disruption of either telomere histone modifications or subtelomere DNA methylation causes telomere length deregulation (García-Cao et al., 2004; Gonzalo et al., 2006, 2005), resulting in extremely elongated telomeres. It is proposed that these marks serve as negative regulators of telomere length in a manner that represses homologous recombination on telomeres (Benetti et al., 2007; Gonzalo et al., 2006).

Telomere shortening affects epigenetic status in telomeric and subtelomeric chromatin which is accompanied by the loss of trimethylated H3K9 and H4K20 on telomeres and subtelomeres, reduced subtelomeric DNA methylation and increased H3 and H4 acetylation (Benetti et al., 2007). It is believed that these changes in the epigenetic status of short telomeres lead to their more open chromatin configuration so that they can interact with telomerase or engage in telomere recombination (Benetti et al., 2007; Hemann et al., 2001; Vidaček et al., 2010) (Fig. 1). All of this point to the existence of a higher order telomere structure that is epigenetically regulated and therefore important for telomere length control (Blasco, 2005).

2.2. Diseases associated with altered telomere length and function

The impact of altered telomere function on human health is demonstrated through several syndromes caused by genetic defects in telomere replication and maintenance, referred to as "telomeropathies" or "telomere disorders" (Stella et al., 2016). Telomeres were, for the first time, related to human disease when mutations in the telomerase binding protein gene *DKC1* were detected in a rare progressive congenital disorder *Dyskeratosis congenita*. Soon, more telomere related diseases were connected to mutations in other genes involved in telomere maintenance, stability and function, causing several bone marrow failures, aplastic anemia, pulmonary fibrosis and liver diseases (Aubert and Lansdorp, 2008). Moreover, mutations in genes linked to telomeres also cause syndromes of accelerated aging, like Werner syndrome or Huttchinson-Gilford progeria (Chang et al., 2004; Huang et al., 2008).

In addition to pathological conditions, a large body of literature affirms telomere shortening as a primary molecular cause of general aging in mammals. Indeed, telomere shortening with increasing age is used as a reliable biomarker of biological aging in different species, with prognostic value for life expectancy and many different age-associated diseases (Barrett et al., 2013; Epel et al., 2004; Ledford, 2012; Monaghan, 2010). In the human population, short telomeres are connected with earlier appearance of Alzheimer, cardiovascular diseases, osteoarthritis, diabetes and cancer, commonly associated with progression of aging (Blasco, 2005; Ogami et al., 2004; Panossian et al., 2003; Price et al., 2002; Salpea and Humphries, 2010).

In the vast majority of studies, telomere length is measured in peripheral leukocytes (LTL). It has been shown that LTL correlates well with telomere length in other body tissues (Starkweather et al., 2014), affirming the LTL as a reliable parameter for specifying average telomere length in various population studies.

2.3. Environmental contributors to telomere length

In addition to genetic factors, there are numerous environmental factors that have an influence on telomere dynamics (Vidacek et al., 2017). It has been reported that hormones, diet, physical activity, smoking, obesity, alcohol consumption, psychological disorders, stress, socioeconomic status and other external factors can greatly influence the dynamics of telomere shortening and might have an impact on telomere chromatin modifications (Blackburn et al., 2015; Gilley et al., 2008).

Twin studies have been of great value in determining to what extent telomere length is genetically or environmentally conditioned. Studies have shown that telomere length has a high heritability of 62–82% depending on the cohort investigated (Broer et al., 2013; Jeanclos et al., 2000; Slagboom et al., 1994). Different lifestyles among identical twins over time result in differences in their telomere lengths (Cherkas et al., 2008). Bishoff et al. (Bischoff et al., 2005) reported heritability of telomere length of only 34% at older age (73–95 years), indicating that different lifelong environmental exposure could variously influence proliferative pressure on the leukocyte stem cell population. Andrew et al. (Andrew et al., 2006) suggest that heritability of telomere length contributes ~36% while common environmental factors contribute ~49% to average telomere length during lifetime. Therefore, high heritability determined in some identical twin studies is probably a consequence of environmental factors generally shared by these individuals (Andrew et al., 2006).

3. Developmental programming

Epidemiological studies have shown that diseases evident in adult life have their origins in fetal/postnatal development, particularly in infants of lower birth weight and intrauterine growth restriction. Early observations linking lower birth weight and coronary heart disease (Langley-Evans, 2013; Langley-Evans and McMullen, 2010; Sedaghat et al., 2015) led to the positing of the "Fetal Programming Hypothesis" or the theory of the "Developmental Origins of Health and Diseases (DOHaD)" which became the foundation for numerous research studies in reproductive epidemiology and morbidity in later life (Olsen, 2014). More detailed is the "Thrifty phenotype" theory, based on a similar inverse correlation between birth weight and later life glucose tolerance or insulin resistance (Hales et al., 1991; Hales and Barker, 2001). This hypothesis attempts to outline a putative mechanism of fetal programming suggesting that poor nutrition during gestation induces a