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Birth weight predicts aging trajectory: A hypothesis

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ABSTRACT

Increasing evidence suggests that risk for age-related disease and longevity can be programmed early in life. In human populations, convincing evidence has been accumulated indicating that intrauterine growth restriction (IUGR) resulting in low birth weight (< 2.5 kg) followed by postnatal catch-up growth is associated with various aspects of metabolic syndrome, type 2 diabetes and cardiovascular disease in adulthood. Fetal macrosomia (birth weight > 4.5 kg), by contrast, is associated with high risk of non-diabetic obesity and cancers in later life. Developmental modification of epigenetic patterns is considered to be a central mechanism in determining such developmentally programmed phenotypes. Growth hormone/insulin-like growth factor (GH/IGF) axis is likely a key driver of these processes. In this review, evidence is discussed that suggests that different aging trajectories can be realized depending on developmentally programmed life-course dynamics of IGF-1. In this hypothetical scenario, IUGR-induced deficit of IGF-1 causes "diabetic" aging trajectory associated with various metabolic disorders in adulthood, while fetal macrosomia-induced excessive levels of IGF-1 lead to "cancerous" aging trajectory. If the above reasoning is correct, then both low and high birth weights are predictors of short life expectancy, while the normal birth weight is a predictor of "normal" aging and maximum longevity.

1. Introduction

Life expectancy has increased dramatically during the last decades across the globe. This increase, however, was not accompanied by the same increase in health span. Since aging is a major risk factor for most chronic pathological conditions, prevalence of age-associated disorders including cardiovascular disease (CVD), type 2 diabetes (T2D), neurodegenerative disease, osteoporosis and cancer rises steadily with increasing life expectancy. This rise represents a great socio-economic challenge in most modern societies and an increasingly urgent frontier for biomedical research (Olshansky, 2016).

Research in the field of gerontology has traditionally tended to focus on adult lifestyle factors as the main determinants of aging and longevity. However, there is consistent evidence that age-related chronic disorders can originate early in life. Indeed, all organisms are highly plastic and environmentally sensitive in early development. As a consequence, the same genotypes can give rise to different phenotypes depending on environmental conditions in early life (Nettle and Bateson, 2015). Such non-genomic phenotypic tuning ('developmental programming') is usually advantageous because it allows match the organism's responses to the environmental conditions that are likely to prevail in later life; inappropriate prediction, however, increases the subsequent risk for chronic disease (Bateson et al., 2014). These ideas were first expressed by Barker et al. (1993) based on the observation that small birth size is related to an increased risk of abnormal lipid metabolism, hypertension, insulin resistance and CVD in adulthood. Subsequently, the Barker's 'fetal origins of adult disease' hypothesis was supported by a large body of evidence and is generally accepted by scientific community, even though it was challenged by several authors (Huxley et al., 2002; Huxley and Neil, 2004). Over the next decades, the Barker's concept has evolved into the Developmental Origins of Adult Health and Disease (DOHaD) hypothesis. This hypothesis states that exposure to environmental stressors during the prenatal and early postnatal periods can permanently determine physiological responses and ultimately produce dysfunctions and diseases in adult life (Bateson et al., 2014). Inadequate nutrition during critical periods of development is likely a key factor contributing to developmental programming processes, although other factors such as hypoxia and stress may also be important (Fernandez-Capetillo, 2010; Tarry-Adkins and Ozanne, 2011). Together, these factors can largely affect not only adult health and disease, but also the rate of aging *per se* (Fernandez-Capetillo, 2010; Heo et al., 2016; Langie et al., 2012).

In this Viewpoint article, evidence is provided that the aging trajectory can be programmed in early development. A special emphasis is made on the possible role of the growth hormone/insulin-like growth factor (GH-IGF) axis, particularly insulin-like growth factor (IGF)-1 as one of the most important longevity-determining factors. It is hypothesized here, largely on the basis of available epidemiological associations, that different aging trajectories can be realized depending on developmentally programmed life-course dynamics of IGF-1.

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2. Basic mechanisms of developmental programming

Molecular and cellular mechanisms underlying developmental programming are elucidated in many animal models [for review, see (Tarry-Adkins and Ozanne, 2011)]. One potential mechanism of developmental programming is through permanent structural alterations of different organs. One good example for this is permanent changes in endocrine pancreas induced by inadequate nutrition during intrauterine development. Such modifications, particularly a reduction in beta-cell mass and islet vascularization, were revealed in many rodent models, such as the maternal caloric or protein restriction and also intrauterine placental ligation models (Tarry-Adkins and Ozanne, 2011). Other potential mechanism underlying these processes is accelerated cellular aging, in particular, accelerated telomere attrition. Telomeres are repeated sequences that cap the ends of chromosomes and shorten with every cellular division in the absence of telomerase activity. Age-dependent telomere attrition, however, depends not only on their replicative shortening, but also on the oxidative stress level (known to be, in turn, associated with most age-related chronic diseases), because of the deficiency of a telomere-specific damage repair (Koliada et al., 2015). Accumulating evidence suggest that life-course dynamics of telomere length can be programmed in early development. For example, both initial telomere length and age-related telomere length dynamics were different in persons born with intrauterine growth restriction (IUGR) and in normal controls (Ravlić et al., 2017). On the basis of these findings, a hypothesis has been proposed by Entringer et al. (2012) on the central role of telomere biology in mediating fetal programming and later health outcomes. According to this hypothesis, it is assumed that both initial telomere length and life-course telomere attrition rate are plastic and highly susceptible to early-life conditions. Consequently, different stress exposures (oxidative, immune and inflammatory stresses, as well as maternal-placental-fetal endocrine disturbances) during the prenatal development could reprogram the telomere biology system in a way that accelerates cellular senescence, and also the organism's aging rate.

All changes on the cellular and tissue level are accompanied by changes in epigenetic regulation of gene expression (Bianco-Miotto et al., 2017). Epigenetic modifications refer to heritable changes in gene expression occurring without changes in DNA sequence. The epigenetic code is changed dramatically in the course of embryonic development to initiate varying patterns of gene expression in different developing tissues. This code consists of modifications of chromatin histones and DNA playing a central role in packing DNA by forming nucleosomes. Most important mechanisms of epigenetic regulation are DNA methylation at cytosine residues in promoter or enhancer gene regions, as well as intragenic DNA methylation usually leading to transcriptional silencing (Kulis et al., 2013), and also post-translational modifications of core histone proteins, such as acetylation usually resulting in transcriptional activation (Chrun et al., 2017). Non-coding microRNAs which can govern gene activity at both transcriptional and post-transcriptional levels are one more recently discovered key component of epigenetic control (Wei et al., 2017). Importantly, the microRNA expression may be modulated by histone modifications or DNA methylation and vice versa, thereby causing feedback loops in epigenetic regulation.

It has been indicated that the epigenome (the totality of epigenetic marks across the genome) is most vulnerable to environmental factors during early developmental stages, particularly in the course of establishment of cell lineage-specific and differentiation-dependent patterns of gene expression (Cortessis et al., 2012), *i.e.*, when the epigenetic landscape [in terms of Conrad Hal Waddington (Waddington, 1957)] is formed. In mammal development, there are two periods of epigenetic reprogramming when genome-wide DNA demethylation occurs followed by remethylation, namely, gametogenesis and pre-implantation embryo development (Iurlaro et al., 2017; Monk, 2015). After the establishment in early ontogenesis, most epigenetic marks are stably propagated during mitotic cell divisions and contribute to determination and differentiation of cell lines. In human beings, the window of developmental epigenetic plasticity extends from preconception through weaning (Hochberg et al., 2011; Vaiserman, 2015). In recent decades, accumulating evidence has been provided on the role of epigenetic regulation in the process of developmental programming of adult-onset pathologies (Yamada and Chong, 2017). Dysregulation of epigenetic pathways in early life might also affect the aging process *per se* and contribute to longevity (Vaiserman, 2014). For example, *in utero* malnutrition (both under- and overnutrition) resulted in altered methylation profiles and transcriptional dysregulation of genes responsible for metabolic diseases and aging in young (9-week-old) adult rat offspring; this deregulated epigenetic pattern was similar to those seen in aged (20-month-old) animals (Heo et al., 2016). The epigenetic deregulation processes can be associated with offspring intrauterine growth in a gender-dependent manner. For instance, in studying developmental programming events associated with the extremes of human fetal growth, substantially greater epigenetic dysregulation was observed in long-lived CD34 + hematopoietic stem/progenitor cells in IUGR male infants and in large-for-gestational-age (LGA) female infants (Delahaye et al., 2014).

Among *in-utero* conditions that are most evidently associated with developmental programming, there are IUGR and fetal macrosomia. Long-lasting adverse health outcomes caused by these conditions are discussed in detail in subsequent sections.

3. Developmental programming in response to IUGR

IUGR is most commonly associated with prenatal malnutrition, although other factors such as stress and hypoxia may also contribute (Devaskar and Chu, 2016). Changes in the fetal glucose and insulin homeostasis emerge in such circumstances in order to conserve energy for the survival in conditions of insufficient nutrition. Severe starvation throughout *in utero* development leads to long-term adaptive alterations in the glucose-insulin metabolism, including reduced ability to secrete insulin and insulin resistance. These changes may enhance survival under conditions of nutritional deprivation in postnatal life because of an increased capacity to store fat (Wells, 2011). However, since the window of epigenetic susceptibility and plasticity closes shortly after birth, the selected adaptive trajectories can become inappropriate under certain environmental conditions, thereby causing adverse health outcomes in adulthood (Mueller et al., 2015). If mismatch exists between the prenatally “predicted” environments and environments experienced in postnatal life (e.g., sufficient food supply), then rapid weight gain during early infancy (“catch-up growth”) follows IUGR. It can result in development of insulin resistance, central adiposity, T2D and other aspects of metabolic syndrome in adult life (Dulloo, 2008; Ziegler, 2015). IUGR conditions are generally associated with higher apoptosis rate (Sharp et al., 2010), as well as reprogramming of the fetal hypothalamic-pituitary-adrenal (HPA) and GH/IGF axes (Fowden et al., 2005, 2006). Most common endocrine consequences of such conditions include increase in catabolic hormone levels and decrease in anabolic hormone levels (Fowden et al., 2006). In humans, IUGR usually results in low birth weight (< 2.5 kg) followed by catch-up growth by adequate postnatal nutrition (Meas, 2010). IUGR-triggered modification of epigenetic patterns is likely a central mechanism in determining such programmed phenotypes (Kitsiou-Tzeli and Tzetis, 2017). The IUGR-induced changes include long-term epigenetic modification of key genes involved in beta-cell development (*PDX1*) and glucose transport in muscle (*GLUT4*) (Pinney and Simmons, 2010), energy metabolism, including *PPARα* and *PPARγ*, regulation of HPA axis (*NRC31,* GFI1 and *HSD11β1/2*), and also some imprinted genes, e.g., *H19* and *IGF2* (Kitsiou-Tzeli and Tzetis, 2017). These epigenetic rearrangements lead to life-long metabolic and endocrine abnormalities, such as altered concentrations of GH, insulin, IGFs, cortisol and catecholamines (Fowden et al., 2005), and also cause, decades later,