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Invited review

A systematic review on the role of environmental toxicants in stem cells aging

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ABSTRACT

Stem cells are an important target for environmental toxicants. As they are the main source for replenishing of organs in the body, any changes in their normal function could affect the regenerative potential of organs, leading to the appearance of age-related disease and acceleration of the aging process. Environmental toxicants could exert their adverse effect on stem cell function via multiple cellular and molecular mechanisms, resulting in changes in the stem cell differentiation fate and cell transformation, and reduced self-renewal capacity, as well as induction of stress-induced cellular senescence. The present review focuses on the effect of environmental toxicants on stem cell function associated with the aging process. We categorized environmental toxicants according to their preferred molecular mechanism of action on stem cells, including changes in genomic, epigenomic, and proteomic levels and enhancing oxidative stress. Pesticides, tobacco smoke, radiation and heavy metals are well-studied toxicants that cause stem cell dysfunction via induction of oxidative stress. Transgenerational epigenetic changes are the most important effects of a variety of toxicants on germ cells and embryos that are heritable and could affect health in the next several generations. A better understanding of the underlying mechanisms of toxicant-induced stem cell aging will help us to develop therapeutic intervention strategies against environmental aging. Meanwhile, more efforts are required to find the direct in vivo relationship between adverse effect of environmental toxicants and stem cell aging, leading to organismal aging.

Contents

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1. Introduction

Aging is a complex physiological process accompanied by a progressive decrease in the organismal capacity to maintain homeostasis and regeneration. It involves accumulation of various types of damage in cellular compartments that lead to altered cell function and finally impairment of tissue and organ regeneration as a major manifestation of the aging process (Kirkwood, 2005).

Many attempts have been made so far to find the underlying cause of aging and introducing the therapeutic targets to stop or at least defer this deterioration process, thereby potentially extending healthy life span, which is an old dream of mankind (Manayi et al., 2014; Ghanbari et al., 2012).

Among diverse factors that affect the aging process, environmental exposure to toxicants is defined as one of the most important and strongest risk factors for aging. There are numerous environmental toxicants associated with aging and age-related disease, such as natural toxicants (e.g. aflatoxins, ochratoxin) (Eaton and Groopman, 2013; Sorrenti et al., 2013), metals (Monnet-Tschudi et al., 2006; Bahadar et al., 2014a), radiation (Rittie and Fisher, 2002; Sanches Silveira and Myaki Pedroso, 2014), sunlight (Lastowiecka-Moras et al., 2014) and pesticides (Zhang et al., 2012), etc. However, there is still no common mechanism to explain the effects of these factors on aging, which require fully understanding the detailed mechanism of action of each factor and gaining insight into the process of aging, particularly at the cellular level.

Cellular aging was first described by Hayflick, who showed that somatic cells, after a definite number of cell replications in vitro, stop further divisions and permanently become arrested in cell cycle progression (Hayflick and Moorhead, 1961). Following genotoxic stress, the exhaustion of cell proliferation, namely senescence, is triggered by DNA damage response activation during telomere shortening. Further evidence suggested a role for cellular senescence in organismal aging. Recently, the theory of stem cell aging has gained great attention in the field of gerontology and regenerative medicine. Stem cells are the foundation of embryonic generation and adult tissue regeneration that are divided into embryonic and adult stem cells. They have the capacity of self-renewal and differentiation into different cell types. In the theory of stem cell aging, failure to replace the damaged cells as a result of the decrease in the regenerative potential of stem cells is the main concern associated with organisms aging (Mokarizadeh et al., 2013).

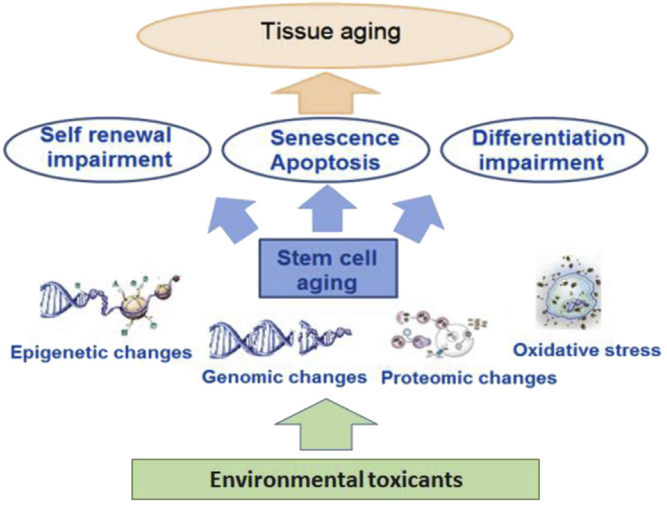

Fig. 1. Environmental toxicants-induced stem cell aging through multiple molecular mechanisms.

Adult stem cells are found in most mammalian tissues where they are involved in tissue homeostasis and repair (Li and Clevers, 2010). As a repair system, stem cells act continually to replenish damaged tissues with healthy ones. Based on the reported evidence, in advancing aging these supportive sources of tissue regeneration undergo age-related changes in their replicative self-renewal capacity and differentiation potential (Sudo et al., 2000; Rossi et al., 2005). The theory of stem cell aging is supported by the evidence that alteration in stem cell function is associated with pathophysiological attributes of aging including cancer, neurodegenerative disease, etc. (Torella et al., 2004). Another piece of evidence for implication of stem cells in organismal aging emerged from the potential usefulness of stem cell transplantation as a therapeutic strategy in the regeneration of aged organs such as brain (Limke and Rao, 2003) and heart (Segers and Lee, 2008). In this regard, bone marrow-bone marrow transplantation was shown as a promising strategy for treatment and prevention of age-related disease in experimental models of diabetes mellitus, osteoporosis, Alzheimer's disease, cancer, etc. (Taira et al., 2005; Takada et al., 2006; Amariglio et al., 2009; Ikehara and Li, 2014).

The functional manifestation of stem cell aging might include changes in the differentiation fate, cell transformation, and exhaustion of the stem cell pool due to impairment in the self-renewal capacity, and/or because of stress-induced cellular senescence (Fig. 1). Several intrinsic and extrinsic parameters have been investigated as possibilities to control stem cell aging. Stem cells, particularly those residing in tissues with higher turnover, experience multiple rounds of replication leading to replicative senescence as an intrinsic aging factor, attributed to chromosomal rearrangement, telomere shortening and genomic mutation. Extrinsic factors include all environmental influences from the stem cell surroundings that could directly affect cell functions and maintenance. Indeed, stem cell functions are dynamically regulated by their environmental area at multiple levels from their local microenvironment, namely niche, where stem cells dynamically interact with other cells, to the higher level of the surrounding tissue, the systemic milieu of the organism and the external environment that influence downstream levels (Scadden, 2006). The systemic microenvironment has an essential role in activation of stem cells in productive tissue regeneration, therefore any changes in the physiochemical properties of the surrounding environment could exert an important effect on stem cells' normal behavior related to aging (Conboy et al., 2005). Identification of extrinsic factors and their effects on stem cell survival and aging will help to identify therapeutic tools for controlling the aging process and age related disease. Furthermore, the knowledge on the factors influencing cellular aging has a significant implication for stem cell-based therapies (Stolzing et al., 2008; Han et al., 2012).

It is noted that not only adult stem cells, but also embryonic stem cells could be affected by environmental factors during em-