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A synopsis on aging—Theories, mechanisms and future prospects

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ABSTRACT

Answering the question as to why we age is tantamount to answering the question of what is life itself. There are countless theories as to why and how we age, but, until recently, the very definition of aging – senescence – was still uncertain. Here, we summarize the main views of the different models of senescence, with a special emphasis on the biochemical processes that accompany aging.

Though inherently complex, aging is characterized by numerous changes that take place at different levels of the biological hierarchy. We therefore explore some of the most relevant changes that take place during aging and, finally, we overview the current status of emergent aging therapies and what the future holds for this field of research.

From this multi-dimensional approach, it becomes clear that an integrative approach that couples aging research with systems biology, capable of providing novel insights into how and why we age, is necessary.

Contents

1. Introduction

Aging is a topic that has captivated both scientists and philosophers throughout history. For Plato (428–347 BC), those who lived longer reached a philosophical understanding of mortal life, which lead to the desire in understanding everlasting ideas and truths, beyond the mortal world (Baars, 2012): "for wisdom and assured true conviction, a man is fortunate if he acquires them even on the verge of old age" (Cary et al., 1852). But perhaps the most accurate depiction of the human perception of aging comes from Giacomo Leopardi (1798–1837): "Old age is the supreme evil, because it deprives us of all pleasures, leaving us only the appetite for them, and it brings with it all sufferings. Nevertheless, we fear death, and we desire old age" (Leopardi et al., 1905).

In its broadest sense, aging merely refers to the changes that occur during an organisms' life-span, though the rate at which these take place varies widely (Kirkwood, 2005). Consequently, such definition comprises changes that are not necessarily deleterious, such as wrinkles and graying hair in humans, which do not affect the individual's viability. As Anton and co-workers put it (Anton et al.,

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2005), the phenotype is the end result of the interaction between genotype and external factors:

[phenotype] = [genotype] + [(diet, lifestyleandenvironment)].

To differentiate these innocuous changes from those leading to increased risk of disease, disability or death, biogerontologists tend to use a more precise term – senescence – when describing aging (Dollemore, 2002). Senescence is, therefore, the progressive deterioration of bodily functions over time and normal human aging has been associated with a loss of complexity in a wide range of physiological processes and anatomic structures (Goldberger et al., 2002), including blood pressure (Kaplan et al., 1991), stride intervals (Hausdorff et al., 1997; Terrier and Dériaz, 2011), respiratory cycles (Peng et al., 2002; Schumann et al., 2010) and vision (Azemin et al., 2012), among others, such as postural dynamics (Manor et al., 2010), ultimately leading to decreased fertility and increased risk or mortality (Chesser, 2015; Lopez-Otin et al., 2013). Herein, however, we will refer to the more inclusive term "aging", due to its extensive use in the literature. Though aging may be defined as the breakdown of self-organizing systems and reduced ability to adapt to the environment (Vasto et al., 2010), this is still a rather complex biological process with poorly understood mechanism(s) of regulation. Explanations of the aging mechanisms have become unexpectedly complicated. Where gerontologists once looked for a single, all-encompassing theory that could explain aging, such as a single gene or the decline of the immune system, they are now finding that multiple processes, combining and interacting on many levels, are on the basis of the aging process (Dollemore, 2002; Guarente, 2014) These processes take place not only at a cellular and molecular level, but also on tissues and organ systems. The relatively young science of aging is now becoming increasingly aware of the biochemical mechanisms that cause or react to aging (Yin and Chen, 2005). Hence, gerontology research currently stands on chemistry and biochemistry, as these are at the core of the aging processes. Advanced analytical studies are underway to observe and identify age-related changes in living organisms. Simultaneously, new synthetic and medicinal chemistry methodologies are yielding small molecule tools for the complete elucidation of complex biological pathways, as well as potential lifespan extending therapeutics (Ostler, 2012). However, to better understand how these could contribute to extend the knowledge of the mechanisms of aging, it is necessary to explore what are the prevailing theories as to why and how we age. Thus, we will extensively review and evaluate the prevalent theories of aging focusing on the major chemical, biological, psychological and pathological aspects of the process. The discussion of the different models of senescence will highlight the urgent need for system-wide approaches that provide a new, integrative view on aging research.

2. Theories of aging and how they shape the definitions of senescence

Many widespread theories as to why aging takes place abound. Generally, these consider it a programmed development (Tower, 2015a), though many disagree and the debate is still ongoing (Blagosklonny, 2013; Goldsmith, 2014, 2012, 2013). By 1990, Medvedev attempted to rationally classify the numerous theories of aging, which exceeded 300 (Medvedev, 1990). Aging has been attributed to molecular cross-linking (Bjorksten, 1968), free radical-induced damages (Harman, 1993), changes in immunological functions (Effros, 2005), telomere shortening (Kruk et al., 1995) and the presence of senescence genes in the DNA (Warner et al., 1987). More recently, however, a unified theory encompassing genes, the performance of genetic maintenance and repair systems, milieu and chance is becoming increasingly accepted (Rattan, 2006), highlighting the need for a systematic and integrative analysis of the aging process. The vast amount of research carried out concerning aging and aging-related processes makes it almost impossible to give a complete overview of the aging theories that have been put forth. Most of these, if not all, can, however, be classified into two categories: error theories and program hypotheses, which will be explored in the following sections. A third category – combined theories –, which contains certain elements of both groups, can be considered (Fig. 1). Such categorization is subjective and others have been suggested (Baltes et al., 2012; de Magalhães, 2005; Jin, 2010; Vina et al., 2007; Weinert and Timiras, 2003). As such, only a brief description of these prevailing theories will be discussed. However, despite whatever the theory, all aim at answering one question: what is the cause of aging? No matter the working hypothesis, one must consider that the underlying assumption that there is *one single* cause for aging may not be correct. Moreover, gerontologists may have to face the possibility that there may not be a universal cause of aging valid for all living organisms.

(1) Program theories

Programmed aging theories, sometimes referred to as active or adaptive aging theories, suggest that there is a deliberate deterioration with age because a limited life span results in evolutionary benefits (Goldsmith, 2012).

For many years, programmed aging has been debated and some studies have substantiated this hypothesis. For example, Ünal et al. (2011) have suggested that there are mechanisms that preserve the integrity of spores of aging diploid yeast cells. Through these mechanisms, aging diploid cells that are induced to sporulate appear to lose all age-associated damage to a point that is no longer detectable, though the assumption that these findings can be extrapolated to higher organisms has been put into question (Biliński et al., 2012).

Yet, though development and morphogenesis can be easily understood as programmed, as they are the end-result of a determined sequence of molecular and cellular events designed to produce a given phenotype (Austad, 2004), aging is mostly thought of as decay. If aging is indeed programmed, the purposes of such program remain unclear. Some have suggested that aging may constitute an altruistic plan (Longo et al., 2005), by eliminating post-reproductive age individuals, who would compete for resources, by avoiding overpopulation and by promoting adaptation through a succession of generations (Kirkwood Thomas and Melov, 2011). The supporters of this view underscore that the similarities between the biochemical pathways that regulate aging in organisms such as yeasts, flies and mice, together with evidence consistent with programmed death in salmon and other organisms, hint at the possibility that programmed aging can occur in higher eukaryotes (Longo et al., 2005). Moreover, this plan could be the result of "aging genes" (de Magalhães, 2013). Nonetheless, if this was the case, than certainly such mechanisms would be susceptible to inactivation, and, despite many gene mutations have been described as life-extending mutations (Barbieri et al., 2003; Fontana et al., 2010; Friedman and Johnson, 1988; Meléndez et al., 2003) none has been reported that abolishes the process of aging (Kirkwood, 2011). It should be noted that, in some model organisms, genes have been demonstrated to play a pivotal role in aging. In fact, the first described mutation to yield a significant extension in the lifespan of *Caenorhabditis elegans* was in the *age-1* gene, which was shown to result in a 65% increase in mean lifespan and a 110% increase in maximum lifespan of this organism (Johnson, 1990). Since then, many mutations that result in lifespan extension in *C. elegans* have been identified, most of which involving genes that are homologs of the of components of the insulin/IGF (insulin-like growth factor) pathway (Mattson, 2003), namely, *daf-2*/*daf-16* (Kenyon, 2010) and *sir2.1* (Guarente and Kenyon, 2000),