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Review

Aging and cardiovascular diseases: The role of gene–diet interactions

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ABSTRACT

In the study of longevity, increasing importance is being placed on the concept of healthy aging rather than considering the total number of years lived. Although the concept of healthy lifespan needs to be defined better, we know that cardiovascular diseases (CVDs) are the main age-related diseases. Thus, controlling risk factors will contribute to reducing their incidence, leading to healthy lifespan. CVDs are complex diseases influenced by numerous genetic and environmental factors. Numerous gene variants that are associated with a greater or lesser risk of the different types of CVD and of intermediate phenotypes (i.e., hypercholesterolemia, hypertension, diabetes) have been successfully identified. However, despite the close link between aging and CVD, studies analyzing the genes related to human longevity have not obtained consistent results and there has been little coincidence in the genes identified in both fields. The *APOE* gene stands out as an exception, given that it has been identified as being relevant in CVD and longevity. This review analyzes the genomic and epigenomic factors that may contribute to this, ranging from identifying longevity genes in model organisms to the importance of gene–diet interactions (outstanding among which is the case of the *TCF7L2* gene).

Contents

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1. Introduction

Over the years, life expectancy has increased throughout the world (Wang et al., 2012). This increase has led to a growing interest in so-called aging-associated diseases, which are diseases that are most often related with senescence. Age is known to be the number one risk factor of cardiovascular diseases (Niccoli and Partridge, 2012); therefore, cardiovascular diseases (CVDs) are not only the first cause of death worldwide, per age group, they are the leading cause of death in people over the age of 65 (Lozano et al., 2012). Cancer is also considered to be an age-related disease, as its risk progressively increases with age (Niccoli and Partridge, 2012; Serrano and Blasco, 2007). Yet, despite its increase as a cause of death worldwide, cardiovascular diseases continue to hold the top spot in the rankings (Lozano et al., 2012). Moreover, it has been estimated that the life expectancy of subjects having main cardiovascular risk factors, such as type 2 diabetes, hypertension, hypercholesterolemia, etc., is lower than that of the general population (Clarke et al., 2009). It is also interesting to note that cardiovascular diseases represent the principal cause of mortality in subjects with Hutchinson-Gilford Progeria Syndrome (HGPS), the best characterized human progeroid disease with clinical features mimicking physiological aging at an early age (Coppedè, 2012). In HGPS individuals, death results from myocardial infarction, stroke, or congestive cardiac failure in 75% of all cases (Capell et al., 2007; Coppedè, 2013).

The relevance of the aging-cardiovascular disease binomial should be taken into account not only because it is the leading cause of mortality, but fundamentally because of the high incidence of these diseases and the effects that they can have in terms of reducing quality of life and increasing health costs (Heidenreich et al., 2011; Pandya et al., 2013). Moreover, before their appearance as clinical phenotypes, cardiovascular diseases are preceded by intermediate phenotypes, among which are high concentrations of plasma lipids, such as LDL-cholesterol and triglycerides, hypertension, high fasting glucose or type 2 diabetes, obesity, etc. (Payne, 2012). For these conditions, increasing age is an important risk factor as are genetic predisposition and non-genetic and environmental risk factors, such as an unhealthy diet, sedentary lifestyle, tobacco smoking, etc. (Huxley and Woodward, 2011; Mozaffarian et al., 2012). Consequently, elderly people often consume various types of drugs over many years in order to minimize the impact of these risk factors on manifestations of the disease (Maraldi et al., 2009; Peron et al., 2011). Moreover, the economic and social environment in which the individual has traditionally lived often deteriorates with old age, social support is often reduced together with a loss of purchasing power, alterations in sleeping patterns often occur, and depression and other mental problems often develop; in turn, these also constitute important cardiovascular risk factors (Almeida, 2012; Crowley, 2011; Everson-Rose and Lewis, 2013; Gellis and Kang-Yi, 2012; Marengoni et al., 2011; Nemeroff and Goldschmidt-Clermont, 2012).

Furthermore, as one grows older, the heart and the different tissues involved in cardiovascular diseases also suffer a series of notable changes, including a decrease in elasticity of the heart walls and a decreased flexibility to respond to changes in the pressure of the arterial system (Stern et al., 2003). In addition, heart valves may thicken or leak and changes in heart rate, as well as a deterioration in the cells of the heart muscle and the ability of the heart to efficiently pump blood, may occur (Shah et al., 2013; Stern et al., 2003). These changes also affect the endothelia, the blood vessels, the blood characteristics, and the volume of blood that can efficiently circulate through those vessels (Shah et al., 2013; Simmonds et al., 2013; Thorin and Thorin-Trescases, 2009). Hence, at the onset of old age, early symptoms of cardiovascular disease, such as atherosclerosis (hardening of the arteries caused by a plaque build-up in the arteries), atrial fibrillation (the heart rate may increase and be irregular), angina (chest pain, pressure or squeezing in the chest caused by a temporary reduction of blood flow to the heart), orthostatic hypotension (a drop in blood pressure when shifting from a sitting to a standing position), etc., often appear (Stern et al., 2003; Shah et al., 2013; Thorin and Thorin-Trescases, 2009). All of this can lead to final phenotypes of cardiovascular disease, outstanding among which are myocardial infarction, stroke, etc. (North and Sinclair, 2012; Stern et al., 2003).

However, despite the fact that all these manifestations are typical of aging, some individuals reach an advanced age without any of those symptoms while, in contrast, others present these manifestations at a very early age (Avogaro et al., 2013; Coppedè, 2012; Niccoli and Partridge, 2012). Therefore, it has been thought that individuals that are free of these symptoms in old age have been exposed to fewer genetic and environmental risk factors, whereas individuals who present symptoms earlier have been exposed to more genetic and environmental factors (Niccoli and Partridge, 2012; Vijg and Campisi, 2008). For many years, the environmental risk factors of cardiovascular diseases and aging have been investigated and healthy lifestyles have been identified as protective factors (Allen and Morelli, 2011; Haveman-Nies et al., 2003; Södergren, 2013). Over the past several decades, dozens of studies have also been conducted on the genetic factors that are implicated in aging and in cardiovascular diseases (Deelen et al., 2013a; Lieb and Vasan, 2013). Nevertheless, in spite of the fact that both processes constitute an important binomial, studies have been mainly undertaken from separate fields of knowledge: cardiovascular diseases and gerontology and aging (North and Sinclair, 2012). Consequently, in most studies carried out to identify the genes related to longevity or aging, interactions with environmental factors have not been taken into account, and the results, as far as the genetic variants identified in humans are concerned, have been less successful and reproducible (Brooks-Wilson, 2013). On the