Ageing Research Reviews 29 (2016) 50–65

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review

The emerging role of Notch pathway in ageing: Focus on the related mechanisms in age-related diseases

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ARTICLE INFO

Article history:
Received 21 March 2016
Received in revised form 10 June 2016
Accepted 16 June 2016
Available online 17 June 2016

Keywords:
Notch pathway
Ageing
Age-related diseases
a signaling complex network
Involved mechanisms
Biomarkers and targets for personalized treatments

ABSTRACT

Notch signaling is an evolutionarily conserved pathway, which is fundamental for the development of all tissues, organs and systems of human body. Recently, a considerable and still growing number of studies have highlighted the contribution of Notch signaling in various pathological processes of the adult life, such as age-related diseases. In particular, the Notch pathway has emerged as major player in the maintenance of tissue specific homeostasis, through the control of proliferation, migration, phenotypes and functions of tissue cells, as well as in the cross-talk between inflammatory cells and the innate immune system, and in onset of inflammatory age-related diseases. However, until now there is a confounding evidence about the related mechanisms. Here, we discuss mechanisms through which Notch signaling acts in a very complex network of pathways, where it seems to have the crucial role of hub. Thus, we stress the possibility to use Notch pathway, the related molecules and pathways constituting this network, both as innovative (predictive, diagnostic and prognostic) biomarkers and targets for personalised treatments for age-related diseases.

Contents

1. Introduction

Cardiovascular system, extensively distributed among cells, tissues, organs, apparatuses and systems of the human body, has the fundamental role to supply oxygen and nutrients and brings

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http://dx.doi.org/10.1016/j.arr.2016.06.004
1568-1637/

away metabolic wastes. In addition, it also has capacity to sustain tissue growth and repair, and to provide cells and molecules for inducing immune surveillance. Alterations in genesis, homeostasis, structure and function of cardiovascular system determine, with advancing age, the onset and the progression of several age-related diseases. For examples, abnormalities in cardiovascular self repair/regeneration and growth maintenance may exacerbate ischemic conditions, such as stroke and myocardial infarction (MI). Excessive angiogenesis, on the one hand, and abnormal vascular endothelium damage, on the other, may, while, induce cancer, inflammation, atherosclerosis, thrombosis, hypertension, diabetes and neurodegenerative disorders, such as Alzheimer disease (AD). This evidence has drawn attention of entire scientific community for searching urgent interventions, both in preventive measures and biomedicine research, in order to decrease the growing incidence of these diseases associated with "old population phenomenon". On the other hand, the most important determinant of cardiovascular health is person's age, and precisely *the person biological age*, as recently suggested in our studies (Balistreri et al., 2012, 2014). By 2030, approximately 20% of the population will be aged 65 or older (Edwards, 2012). In this age group, age-related diseases, and particularly cardiovascular diseases (CVDs), will result in 40% of all deaths and rank as the leading cause (Heidenreich et al., 2011). Accordingly, in the last years the study of "*endothelium dysfunction*" and the related cellular and molecular mechanisms has obtained the major interest in a large number of research groups. This is in accordance to well recognized evidence that endothelium dysfunction is the first pathological condition associated not only with all CVDs, but also with other age-related diseases, being the endothelial cells (ECs) components of the stroma of all tissues and organs. Accumulation of EC damages followed by death and impaired cardiovascular self repair, due principally to altered age-related function of tissue-specific resident and circulating stem or progenitor cells, characterize the onset of endothelial dysfunction (Regina et al., 2016). Precisely, when an imbalance between damage/death and regeneration of the endothelium occurs, integrity and function of endothelium is threatened, and the origin and progression of CVDs, or other age-related diseases, is favored (Madonna et al., 2016a, 2016b).

Experimental studies on endothelium have led to relevant and promising discoveries and advances. Among these findings, strong opinion has been emerging that the solution, to counteract the onset of age-related diseases, has the roots in the cellular mechanisms and evolutionally conserved signaling pathways of the cells, as the *stem and progenitor cells* (i.e. hematopoietic and no-hematopoietic stem cells and their progenitors), involved in the genesis of vessels, "*vasculargenesis*", tissues, organs and systems. This is in accordance to the innovative concepts of *fetal programming-imprinting* based on theory popularized, for the first time in 1989, by Dr David Barker, and defined as "*the fetal origin of adult disease (FOAD)*" (Barker et al., 1989, 2009; Barker, 2004) (see Box 1). Such concepts have been corroborated by valid data obtained from diverse human cohorts and various animal models, leading to other emerging speculations as the concepts of *fetal vascular ageing* proposed in 2011 by Pitale and Sahasrabuddhe (2011). Thus, David Barker's observations continue to be confirmed and tested in the time across multicultural populations and animal models subjected to various constraints (Barker et al., 1989, 2009; Barker, 2004; Calkins and Devaskar, 2011). Indeed, the important implications of FOAD hypothesis has been also underlined by the following statement of World Health Organization, "*The global burden of death, disability and loss of human capital as a result of impaired fetal development is huge and affects both developed and developing countries* (http://www.who.int/int/nutrition/topics/fetal_dev)".

Based on these observations, the field of stem cell biology and evolutionally conserved signaling pathways is becoming the gold

Box 1: From the theory of Dr David Barker defined as "the fetal origin of adult disease (FOAD)" to concepts of fetal programming-imprinting.

The FOAD hypothesis holds that events during early development have a profound impact on one's risk for development of future adult disease Barker et al., 1989, 2009; Barker, 2004; Calkins and Devaskar, 2011). Precisely, it sustains "the fetal programming concept". The notion of fetal programming implies that, during critical period of prenatal growth, a complex interplay in genetic composition, intrauterine conditions and epigenetic transmission between maternal milieu and fetus evocated by hormonal (i.e. hormonal status may be modified and exacerbated by assisted reproductive technologies, as recently demonstrated by Padhee and colleagues study; Padhee et al., 2015) and nutrient maternal changes may alter the full expression of fetal genome leading to permanent effects on large range of physical conditions, characterizing the modified and permanent phenotype of fetus. For example, low birth weight, a surrogate marker of poor fetal growth and nutrition, is linked to coronary artery disease, hypertension, obesity, and insulin resistance. Clues originally arose from large 20th century, European birth registries. Today, large, diverse human cohorts and various animal models have extensively replicated these original observations.

object of research of a large number of studies. Accordingly, it is emerging the fundamental role of an evolutionally conserved signaling pathway, *the Notch pathway*, in stem/progenitor cell fate decision, as well as in the life cycle of adult cells (Fiúza and Arias, 2007). Notch signaling pathway, by itself or cross-talking with other pathways (see below), has been shown to have a large range of critical functions during the development not only of cardiovascular system, but also in that of all tissues and systems. In addition, aberrant Notch signaling (both hyper- and hypoactive) has been implicated in a number of human developmental disorders (i.e. Alagille syndrome or cerebral autosomal dominant arteriopathy _CADASIL disease; see Box 2) and many cancers (see Box 3). Recently, it is also emerging its involvement in age-related diseases, by manifesting itself pleiotropic effects and acting through mechanisms not completely clear.

Here, we will report critical genes and signaling pathways involved in the ageing of stem and progenitor cells, focusing the interest on the role of Notch pathway (which seems to act by hub in an intricate signaling pathway network) and the related main mechanisms. In addition, we will discuss on the possibility to use Notch pathway, the related molecules and pathways constituting a network, both as innovative (predictive, diagnostic and prognostic) biomarkers and targets for personalised therapies of age-related diseases, which are the very challenges for the maintenance of heath in our populations. The concepts stressed, here, are fruit of considerations derived by expert opinion on the findings from author's studies on ageing, age-related diseases (particularly CVDs) and inflammation.

2. Critical genes and signaling pathways in stem cell ageing and rejuvenation

It is well recognized that the decline of tissue regenerative potential accompanies ageing. It may be due to age-related changes in tissue-specific stem cells. Adult stem cells, which divide throughout the life of an individual, experience both chronological and replicative ageing (Charville and Rando, 2011). This determines an enhance of the burden of mutations with age, as well as an increase in probability of cells, and particularly of stem and progenitor cells, to undergo apoptosis, malignant transformation, or senescence (Kuilman et al., 2010). The underlying cause of