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REVIEW

# Endothelial Cell Senescence and Age-Related Vascular Diseases

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## ABSTRACT

Advanced age is an independent risk factor for ageing-related complex diseases, such as coronary artery disease, stroke, and hypertension, which are common but life threatening and related to the ageing-associated vascular dysfunction. On the other hand, patients with progeria syndromes suffer from serious atherosclerosis, suggesting that the impaired vascular functions may be critical to organismal ageing, or *vice versa*. However, it remains largely unknown how vascular cells, particularly endothelial cell, become senescent and how the senescence impairs the vascular functions and contributes to the age-related vascular diseases over time. Here, we review the recent progress on the characteristics of vascular ageing and endothelial cell senescence *in vitro* and *in vivo*, evaluate how genetic and environmental factors as well as autophagy and stem cell influence endothelial cell senescence and how the senescence contributes to the age-related vascular phenotypes, such as atherosclerosis and increased vascular stiffness, and explore the possibility whether we can delay the age-related vascular diseases through the control of vascular ageing.

**KEYWORDS:** Endothelial cell senescence; Genetic; Vascular ageing; Age-related diseases; Stem cell

## INTRODUCTION

Ageing may be described as a gradual loss of control in the physiological functions over time, and is an independent risk factor for the increased morbidity and mortality associated with ageing-related diseases, such as dementia, cardiovascular diseases, and the loss of acuity in hearing and vision. These diseases are mostly related to the vascular dysfunction and becoming huge burdens for the families and societies, as the proportion of elderly population is rapidly enlarged. It would be very provocative to consider the control of vascular ageing as a common target for preventing those age-related diseases (Minamino et al., 2004a).

A vessel consists of tunica intima, tunica media, and tunica adventitia. The intima is a barrier between blood stream and vessel, consisting of one layer of endothelial cells and basement membrane (an internal elastic lamina). The media is made up of smooth muscle cells, and adventitia is connective tissue hosting fibroblast cells. The endothelial cell is essential for vasculogenesis during embryonic development and for angiogenesis in adult tissues where more vessels are needed in the setting of wound healing, ischemic condition, and tumorigenesis. In addition, the endothelial cell senses and responds to the stimuli from blood stream and regulates the vascular smooth muscle cell by producing vasoactive substances, such as NO (vasodilator) or Ang II (vasoconstrictor). The vessels serve as transportation tools, bringing in the nutrient, oxygen,

*Abbreviations:* Ang II, angiotensin II; APOE, apolipoprotein E; AQP1, aquaporin 1; ASS1, argininosuccinate synthase 1; CDK2, cyclin-dependent kinase 2; CDKN2A, cyclin-dependent kinase inhibitor 2A; CDKN2B or p15, cyclin-dependent kinase inhibitor 2B; EDRF-1, endothelial differentiation related factor-1; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; ICAM, intercellular adhesion molecule 1; IFN, interferon; ILGF-1, insulin-like growth factor-1; ILGFBP-3, insulin-like growth factor-binding protein-3; iNOS, inducible nitric oxide synthase; IL, interleukin; NO, nitric oxide; NOX4, NADPH oxidase 4; OX-LDL, oxidized low density lipoprotein; PITGIS, prostaglandin $I_2$ synthase; PWV, pulse wave velocity; ROS, reactive oxygen species; SA-β-gal, senescence-associated β-gal.

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and active substances, and taking away the wastes or by-products and carbon dioxide produced in tissues. Thus, vessels are critical to maintain physiological homeostasis *in vivo*.

Vascular ageing was initially described as "become hard" and "lost of contracting" (Quinn et al., 2012). On the other hand, human ageing has been noticed to be associated with vascular phenotypes, as it was mentioned, "man is only as old as his arteries" (Stein, 2004; Yeh, 2004; Kovacic et al., 2011). In addition to the fact that vascular dysfunction is a common substrate for various complex age-related diseases as mentioned above, patients with progeria syndrome mostly suffer from atherosclerotic diseases (Villa-Bellosta et al., 2013). Notably, numerous genes that are linked to senescence or longevity trait have profound impacts on vascular functions, for example, forkhead box O1A (*FOXO1A*), forkhead box O3A (*FOXO3A*), adrenoceptor beta 2 (*ADRB2*), sirtuin 1 (*SIRT1*), and apolipoprotein E (*APOE*) (Willcox et al., 2008; Li et al., 2009; Deelen et al., 2011; Zhou et al., 2011; Zhao et al., 2012). These suggest that there should be an intrinsic link connecting vascular ageing, organismal ageing, and ageing-related diseases.

However, it remains largely unknown how genetic and environmental factors influence endothelial cell senescence and organismal ageing and how the senescent endothelial cell contributes to the phenotypes related to vascular ageing, such as atherosclerotic diseases and increased vascular stiffness. Here, we review the recent progress on endothelial cell senescence, debate how the senescence is affected by genetic and epigenetic factors as well as autophagy and stem cell, discuss how the senescence influences vascular ageing and ageing-related diseases, and explore the possibility if we can prevent the age-related vascular diseases *via* the control of vascular ageing.

## CHARACTERISTICS OF VASCULAR AGEING

Vascular ageing presents several morphological and ageing-related functional changes. Morphologically, the small vessels are degenerated, and thus the vascular densities, particularly capillary density in tissues, are decreased (Sadoun and Reed, 2003; Chang et al., 2007; Brown and Thore, 2011; Kuznetsova and Schliebs, 2013; Pavlidis et al., 2013). Other morphological changes, such as thickened intima-media layer, increased collagen but decreased elastin deposition, and enlarged vascular lumen have been observed (Bonithon-Kopp et al., 1996; Behnke et al., 2006; Kim et al., 2013).

Functionally, an increased vascular stiffness and susceptibility to atherosclerosis (pro-atherosclerosis) as well as an elevated blood pressure with age are shown in the elderly population (Gu et al., 2002; Lloyd-Jones et al., 2005; Zhang et al., 2010; Wang and Bennett, 2012; Choi et al., 2013; Reece and Hulse, 2013). These functional changes can be assessed by some noninvasive techniques in clinical practices. Pulse wave velocity (PWV) analysis, for example, can be used to evaluate endothelial function and vascular stiffness in combination with the usage of vasodilator, such as salbutamol, a β2 adrenoreceptor agonist, providing epidemiological information on how vessels functionally and structurally change with ages (Weber et al., 2009; Stoner et al., 2012). The increased intima stiffness disrupts endothelial integrity, an early event for atherosclerosis (Huynh et al., 2011). In addition, the angiogenesis is decreased under stimuli, such as hypoxia in the aged animals (Rivard et al., 1999; Bojovic and Crowe, 2010; Groleau et al., 2011; Di et al., 2013). In model organisms, the vascular responses to neurohormones have been investigated. For instance, vascular contractile responses induced by angiotensin II (Ang II) are decreased in adult rats with the increased age beyond nine months (senescent rats) (Vamos et al., 2013). The vasoconstrictor effects of serotonin are augmented, while the tachyphylaxis to the monoamine is reduced with age (Vanhoutte, 1988). Endothelium-dependent relaxation of aortic smooth muscle induced by acetylcholine and the calcium ionophore A23187 is decreased significantly with the increased ages (Soltis, 1987). Thus, the decreased ability for angiogenesis and aberrant responses to stimuli are the additional age-related vascular phenotypes.

It should be noted that the responses of different types of vessels (artery *vs* vein, or vessels from different tissues) or vascular cells (endothelial *vs* smooth muscle cell) may be different to the same stimulus (Vanhoutte, 1988; Barton et al., 1997; Vamos et al., 2013). For example, the norepinephrine content is maintained through senescence in the veins and the superior mesenteric artery, but declined in other arteries studied in aged rats. The β-adrenergic responsiveness is markedly declined in arteries from 1 to 6 months of age, but remains unchanged in the jugular vein from 3 to 27 months (Duckles, 1987). The genetic background influences vascular structural changes with age in human and model organisms as well (Virmani et al., 1991; Rudner et al., 1999).

## CHARACTERISTICS OF ENDOTHELIAL CELL SENESCENCE

As mentioned above, the endothelial cell plays critical roles in the regulation of vascular functions, and therefore the endothelial cell senescence has severe impact on vascular ageing and related diseases (Minamino et al., 2004b).

The endothelial cells are supposed to be quiescent *in vivo*, and only about 0.1% of them are maintained at replicative status under physiological conditions. However, an endothelial cell can be activated and becomes proliferative when exposed to pathological stimuli. Early studies showed that the daily rate of endothelial cell replication in the aortic endothelium declined from a maximum of 13% at birth to 0.1%−0.3% at ages of 5−6 months in normal rats (Schwartz and Benditt, 1977).

Stresses, such as hypoxia, shearing, endotoxin, and injury, increase the replication rate dramatically without observing much denudation of endothelial cells, suggesting that, under the short-term or mild stress, the replication or regeneration of the adjacent endothelial cells may be sufficient to replace the impaired or dysfunctional endothelial cells, or to cover the segments where endothelial cells are denudated (Schwartz and Benditt, 1973; Reidy and Schwartz, 1983; Hansson et al.,