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Review

Senescent endothelial cells: Potential modulators of immunosenescence and ageing

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ABSTRACT

Recent studies have demonstrated that the accumulation of senescent endothelial cells may be the primary cause of cardiovascular diseases. Because of their multifunctional properties, endothelial cells actively take part in stimulating the immune system and inflammation. In addition, ageing is characterized by the progressive deterioration of immune cells and a decline in the activation of the immune response. This results in a loss of the primary function of the immune system, which is eliminating damaged/senescent cells and neutralizing potential sources of harmful inflammatory reactions.

In this review, we discuss cellular senescence and the senescence-associated secretory phenotype (SASP) of endothelial cells and summarize the link between endothelial cells and immunosenescence. We describe the possibility that age-related changes in Toll-like receptors (TLRs) and microRNAs can affect the phenotypes of senescent endothelial cells and immune cells via a negative feedback loop aimed at restraining the excessive pro-inflammatory response. This review also addresses the following questions: how do senescent endothelial cells influence ageing or age-related changes in the inflammatory burden; what is the connection between ECs and immunosenescence, and what are the crucial hypothetical pathways linking endothelial cells and the immune system during ageing.

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Pro-inflammatory substances (cytokines, chemokines, growth factors, extracellular matrix components) produced by immune or non-immune cells are involved in the development of physiological or pathological ageing. The main cause of chronic inflammation is the progressive activation of immune cells. Nevertheless, recent studies indicate that endothelial cells can be an important contributor to chronic inflammation and to the development of age-related diseases.

Senescent cells can acquire a specific phenotype, which is abbreviated SASP, and this phenomenon is well documented in "immune cells", such as macrophages, and in fibroblasts and endothelial cells. Overall, this review summarizes the current research focusing on target molecules and mechanisms relevant to endothelial and immune function in ageing. We try to clarify the relationship between endothelial cells and the immune system, and we identify pro- and anti-inflammatory factors that contribute to the development of EC senescence. Our review provides new insight into the underlying molecular mechanisms of senescence-associated immunosenescence, vascular dysfunction, and age-related diseases.

Further studies are needed to understand the exact nature of the relationship between the immune system and vascular alterations in ageing and developing new strategies to modify these changes. These forthcoming results will give us the opportunity to improve the quality of life of patients and preserve the development of cost-effective treatments for age-related diseases in a growing aging population.

1. Introduction

The vascular endothelium is a versatile structure with multifunctional properties that include the regulation and maintenance of blood fluidity, water and nutrient delivery, metabolic homeostasis, immune cell trafficking, activation of innate and acquired immune responses, and angiogenesis (Aird, 2012; Cugno, 2012; Potente et al., 2011). Changes in the morphology and function of the endothelium can contribute to the development of many pathological disorders (Hwang and Kim, 2014; Mordi and Tzemos, 2014; Niwano, 2014).

The endothelium is composed of a monolayer of endothelial cells (ECs) that separates the circulating blood from the tissues. It wields significant paracrine and endocrine actions by producing fibrinolytic, pro- and anticoagulants, vasoactive, pro- and anti-inflammatory factors, as well as growth factors (Celik et al., 2009; Dib et al., 2012; Mai et al., 2013; Nilsen et al., 1998; Suzuki et al., 2013; Vielma et al., 2014). Similar to other cell types, endothelial cells will undergo cell cycle arrest as part of their self-repair/renewal process and undergo senescence following modulations in paracrine function. The primary characteristic of dysfunctional endothelial cells is the loss of the nitric oxide (NO)-mediated protective effects on the vessel walls and surrounding cells (Niwano, 2014). Endothelium-dependent and NO-mediated vasodilation decreases during ageing, which has been demonstrated in both *in vitro* and *in vivo* studies (El Assar et al., 2012). Senescent endothelial cell dysfunction can lead to the progression of atherosclerosis and its associated clinical outcomes. An increased number of senescent endothelial cells (ECs) is found in the atherosclerotic plaques located in the human aorta, as well as the coronary arteries in diabetic rats (Farhat et al., 2008; Tian and Li, 2014). Senescence of vascular endothelial cells is a common substrate for various complex age-related diseases. Patients with Hutchinson-Gilford progeria syndrome primarily suffer from atherosclerotic diseases (Villa-Bellosta et al., 2013). These findings suggest an intrinsic link between vascular ageing, organism ageing, and ageing-related diseases. It has been observed that human ageing is associated with vascular phenotypes and can be expressed by the axiom—"*man is only as old as his arteries*" (Kovacic et al., 2011; Tian and Li, 2014). However, it is still unclear how endothelial cell senescence phenotypes are associated with age-related vascular diseases such as atherosclerotic disorders, diabetes, and increased vascular stiffness.

Because of their location and multifunctional assets, ECs are also involved in activating the innate and adaptive immune systems (Mai et al., 2013). ECs are one of the first line cells that detect pathogens and endogenous danger signals in the bloodstream. In the presence of inflammatory stimuli and risk factors, endothelial cells are changed from the anti-inflammatory state to the pro-inflammatory state and stimulate the early innate immune response (Mai et al., 2013). Many current studies and reviews focus on the alterations of immune system during ageing (*e.g.*, immunosenescence and chronic inflammation termed as inflammaging) (Barnes, 2015; Macaulay et al., 2013; Ostan et al., 2008; Palma et al., 2014; Schmitt et al., 2013; Stepanova et al., 2015), but questions regarding how age-related changes in the cytokine profile of ECs and the interaction with other immune cells can influence immune status remain unanswered (Olivieri et al., 2013a,b).

In this review, we discuss the various approaches of EC senescence development and associated mechanisms;, describe how the senescent endothelial cells dysfunction can influence on immunosenescence, and hypothesize how alterations of ECs senescence-associate secretory phenotype (SASP) modulate organism ageing and age-related diseases.

2. Cellular senescence, SASP and cytokines

2.1. Cellular senescence

Half a century ago, Hayflick and Moorhead (1961) revealed that primary human cells in culture have a limited capacity for replication, and after a finite number of replication cycles, these cells entered into a permanent cell-cycle arrest marked by telomerase activity reduction and telomere shortening (Allsopp et al., 1992). This type of cell senescence was termed replicative senescence (RS). Numerous findings suggest that both DNA damage and the initiation of the senescence programme are induced not only by ageing but also by ionizing radiation, UV light, chemotherapeutic drugs, oncogenic activation and by a pathological increase in intracellular and extracellular ROS (Borodkina et al., 2014; Jee et al., 2009; Kim et al., 2014; Sasaki et al., 2014; Yentrapalli et al., 2013). This process is often referred to as stress-induced premature senescence (SIPS). The role of SIPS in normal physiological ageing is still unclear. Despite current research (Menck and Munford, 2014; Vargas et al., 2012; Alimbetov et al., 2016; Baker et al., 2016; Lowe et al., 2016; Uryga and Bennett, 2016; Yamazaki et al., 2016) showing a link between senescence and natural ageing, premature senescence is primarily associated with tumour suppression. Moreover, genomic studies suggest that there is a significant difference between replicative senescent cells and premature senescent cells (Aan et al., 2013; Bielak-Zmijewska et al., 2014; Gonzalez et al., 2016; Li et al., 2016).

Cellular senescence is a programmed arrest of cell cycle progression in which gene expression is altered as described above by many stresses. Cell cycle progression is governed by cyclin-dependent kinases (cdk) and inhibited by cdk inhibitors that belong to two families (Morgan, 1995; Sherr and Roberts, 1999). The inhibitor of cdk4 (INK4) family members (p15INK4b, p16INK4a, p18INK4c and p19INK4d) inhibit cdk4 and cdk6, whereas the kinase inhibitor protein (KIP) family (p21WAF1/Cip1, p27Kip1 and p57Kip2) inhibits a broader spectrum of cdks than INK4. There are numerous signals that lead to the stimulation of cdki, but one of the most impor-