Ageing Research Reviews xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Ageing Research Reviews

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

Review

Phagocyte dysfunction, tissue aging and degeneration

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ARTICLE INFO

Article history:
Received 21 May 2013
Accepted 28 May 2013
Available online xxx

Keywords:
Phagocytosis
Aging
Phagocyte dysfunction
Macrophage
Microglia
Retinal pigment epithelium

ABSTRACT

Immunologically-silent phagocytosis of apoptotic cells is critical to maintaining tissue homeostasis and innate immune balance. Aged phagocytes reduce their functional activity, leading to accumulation of unphagocytosed debris, chronic sterile inflammation and exacerbation of tissue aging and damage. Macrophage dysfunction plays an important role in immunosenescence. Microglial dysfunction has been linked to age-dependent neurodegenerations. Retinal pigment epithelial (RPE) cell dysfunction has been implicated in the pathogenesis of age-related macular degeneration (AMD). Despite several reports on the characterization of aged phagocytes, the role of phagocyte dysfunction in tissue aging and degeneration is yet to be fully appreciated. Lack of knowledge of molecular mechanisms by which aging reduces phagocyte function has hindered our capability to exploit the therapeutic potentials of phagocytosis for prevention or delay of tissue degeneration. This review summarizes our current knowledge of phagocyte dysfunction in aged tissues and discusses possible links to age-related diseases. We highlight the challenges to decipher the molecular mechanisms, present new research approaches and envisage future strategies to prevent phagocyte dysfunction, tissue aging and degeneration.

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Contents

1. Introduction

The steady increase in life expectancy and aged population has presented us with a new challenge: age-related diseases. Tissue aging is a complex process with intertwined molecular

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1568-1637/$ – see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.arr.2013.05.006

Please cite this article in press as: Li, W., Phagocyte dysfunction, tissue aging and degeneration. Ageing Res. Rev. (2013), http://dx.doi.org/10.1016/j.arr.2013.05.006

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mechanisms. Accumulation of genetic mutations, epigenetic regulation and shortening of telomeres play important roles in tissue aging (Luo et al., 2010; von Bernhardi et al., 2010). Slow buildup of deleterious products, such as reactive oxygen species (ROS), oxidized proteins, advanced glycation end products (AGEs) and advanced lipoxidation end products (ALEs), generated by organism itself is the consequence of metabolism (Baquer et al., 2009; Grillo and Colombatto, 2008). Exposure to UV light and chemicals can cause tissue damage. Pathogen infection and immune response can induce bystander damage on tissues (Fricker et al., 2012). Normal aging is characterized by slow accumulation of metabolic products and mild chronic inflammation. In most cases, the chronic inflammation in aged tissues has no detectable microorganism and therefore is termed "sterile inflammation" (Chen and Nunez, 2010). Recently, the term "inflammaging" (inflammation + aging) was coined by Franceshci et al., to describe a common phenomenon that tissue aging is accompanied by low-grade chronic sterile inflammation (Franceschi et al., 2007). Abnormal tissue aging with excessive buildup of metabolic products and increased chronic inflammation may cause age-related diseases, thereby exacerbating tissue damage and degeneration. For example, Alzheimer's disease is an age-related neurodegeneration characterized by amyloid plaques with activated microglia for pro-inflammatory response (Meda et al., 1995). Formation of drusen deposits in the retina is the hallmark of age-related macular degeneration (AMD), which is now widely regarded as an intraocular inflammatory disease (Ding et al., 2009).

Phagocytosis is crucial to maintaining tissue homeostasis and innate immune balance, and can ingest both foreign pathogens and autologous apoptotic cells (Erwig and Henson, 2007; Napoli and Neumann, 2009). Despite the similarities in the physical process for cargo internalization, these two phagocytic events have distinct outcomes for innate and adaptive immune response (Fig. 1). Phagocytosis of infectious pathogens elicits the release of pro-inflammatory cytokines. Presentation of foreign antigens by professional phagocytes further induces adaptive immune response, including activation of antigen-specific lymphocytes. In contrast, phagocytosis of apoptotic cells or cellular debris triggers immunosuppressive signaling with the release of anti-inflammatory cytokines, leading to peripheral immune tolerance. Although aging affects both phagocytic events, this review mainly focuses on phagocytosis of autologous apoptotic cells or debris for in-depth understanding of how phagocyte dysfunction may exacerbate tissue aging, chronic sterile inflammation and degeneration. We also discuss newly-developed tools for elucidation of age-related molecular mechanisms and predict future research directions of the field.

2. Different phagocytic receptors for pro- and anti-inflammatory response

Phagocytosis of foreign pathogens or autologous apoptotic cells is mediated by different sets of phagocytic receptors to induce pro- or anti-inflammatory response (Erwig and Henson, 2007). Infectious pathogens are phagocytosed through Toll-like receptors (TLRs), Fc receptors (FcRs), complement receptors (CRs) and scavenger receptors (SRs) to elicit the release of pro-inflammatory cytokines (Napoli and Neumann, 2009). By contrast, apoptotic cells or cellular debris is internalized through a set of different receptors, such as phosphatidylserine receptors (e.g., BAI1, stabilin-2 and Tim-4), MerTK, αvβ3 and αvβ5 integrins, TREM2, FcRs, CRs and SRs, to trigger immunosuppressive signaling with the release of anti-inflammatory cytokines (Li, 2012a).

Different receptors in the families of FcRs, CRs and SRs are capable of promoting pro- or anti-inflammatory phagocytosis with distinct intracellular signaling cascades. For example, human FcR family consists of FcγRIA, FcγRIIB (CD32B), FcγRIIA (CD32A), FcγRIIC, FcγRIIIA (CD16), and FcγRIIIB. Except FcγRIIB as an inhibitory receptor, all other FcRs induce pro-inflammatory signaling and immune activation (Ivan and Colovai, 2006). Antibody-opsonized cargos, including pathogens with neutralizing antibodies and apoptotic cells or tissue debris with autoantibodies in autoimmune diseases, can be phagocytosed via different FcRs with distinct innate immune responses. A dichotomy is that microglial phagocytosis of neuronal antigens in the initiation and recovery phase of multiple sclerosis (MS) triggers both pro- and anti-inflammatory response, respectively (Huizinga et al., 2012; Takahashi et al., 2007). Whether microglia phagocytose myelin debris through different FcRs at different stages of MS or whether aging may affect the expression profile of FcRs on microglia remain to be determined.

Ligand diversity further increases the complexity of the molecular regulations of phagocytosis. For example, MerTK has at least five known ligands, including Gas6, protein S, tubby, Tulp1 and galectin-3 (Gal-3) (Caberoy et al., 2012a, 2010b; Stitt et al., 1995). All these five ligands are bridging molecules with two binding domains: phagocytic receptor-binding domain (PRBD; i.e., MerTK-binding domain) and phagocytosis prey-binding domain (PPBD). Different preys or cargos will be selected for phagocytosis by their interaction with the PPBD of different MerTK ligands. One of the examples is that Gal-3 is a well-known binding protein for AGEs (Vlassara et al., 1995) and therefore may facilitate AGE clearance through the MerTK pathway.

Ligand-receptor cross-reactivity may also regulate the outcomes of the innate immune response. Phosphatidylserine is a well-characterized ligand or "eat-me" signal that facilitates phagocytosis of apoptotic cells through several immunosuppressive receptors, including BAI1, stabilin-2 and Tim-4 (Miyanishi et al., 2007; Park et al., 2007, 2008). A recent study showed that RAGE is also a phosphatidylserine receptor for clearance of apoptotic cells (He et al., 2011). Activation of RAGE induces NF-κB activation and inflammation (Schmidt et al., 1995, 2001). It is still unclear whether phosphatidylserine-RAGE interaction may stimulate pro-inflammatory phagocytosis and promote chronic inflammation in tissue aging.

Under some circumstances, the protective role of phagocytosis via anti-inflammatory phagocytic receptors may unintentionally result in tissue damage. For instance, neuroinflammation may transiently increase the exposure of phosphatidylserine on neurons, leading to microglial phagocytic clearance of viable but stressed neurons (Fricker et al., 2012). Deletion or blockade of MFG-E8, which is a bridging molecule linking phosphatidylserine on apoptotic cells to $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrin on phagocytes, preserves live neurons.

3. Phagocyte dysfunction and tissue damage

Defects in phagocytosis are known to cause tissue damage. For instance, mutations of MerTK cause defects of retinal pigment epithelium (RPE) phagocytosis, leading to accumulation of unphagocytosed debris in the subretinal space, photoreceptor degeneration and blindness (D'Cruz et al., 2000; Dowling and Sidman, 1962). MerTK deletion in mice also results in a defect of macrophage phagocytosis with unphagocytosed debris and increased production of autoantibodies (Scott et al., 2001). There are several mechanisms by which phagocyte dysfunction may exacerbate tissue aging and degeneration (Fig. 2). First, accumulation of unphagocytosed debris can disrupt tissue homeostasis by directly exerting cytotoxicity on cells. One of the well-known examples is the direct neurotoxicity of amyloid plaques in Alzheimer's disease.

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Please cite this article in press as: Li, W., Phagocyte dysfunction, tissue aging and degeneration. Ageing Res. Rev. (2013), http://dx.doi.org/10.1016/j.arr.2013.05.006

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