TANG [HUMANITAS MEDICINE]

Review

Apoptotic cell clearance and human diseases

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ABSTRACT

The efficient removal of dead cells is an evolutionarily conserved process essential for homeostasis in multicellular organisms. The phagocytosis involves a series of steps that ultimately leads the detection of apoptotic cell by the phagocytes and the subsequent engulfment and degradation of corpse. The uptake of apoptotic cells by phagocytes not only removes debris from tissues but also generates an anti-inflammatory signal that blocks tissue inflammation. Conversely, impaired clearance of dead cells can cause loss of immune tolerance and the development of various inflammation-associated diseases such as autoimmunity, but can also affect cancer development. This review will discuss current understanding of the molecular mechanism of apoptotic cell phagocytosis and how they may be related to human diseases.

Keywords apoptotic cell clearance, phagocytosis, inflammation, autoimmunity

INTRODUCTION

Our body turns over billions of cells every day (Ravichandran, 2010). Cells undergo apoptosis, a programmed cell death process. The rapid scavenging of apoptotic cells by phagocytes is crucial for preserving normal tissue development and tissue homeostasis (Arandjelovic and Ravichandran, 2015). Cellular and molecular events such as the detection and uptake of apoptotic cells, and the subsequent biological processes, are increasingly becoming better understood. The efficient, immediate, and immunologically tolerant removal of apoptotic cells is accomplished by multiple steps, through which phagocytic cells selectively find, detect, and uptake apoptotic cells and process the corpses (Poon et al, 2014; Toda et al, 2015). Recently, many studies have revealed an important role of soluble releasing factors secreted by apoptotic cells in the recruiting of phagocytes, known as "find-me signals," such as nucleotides, CX_3CL1, and annexin A1 (Blume et al, 2012; Chekeni et al, 2010; Elliott et al, 2009; Truman et al, 2008). In a recent study, it was found that apoptotic cellular events are fairly intensely involved in the immediate clearance of these cells via find-me signals from apoptotic cells (Gregory, 2009). When cells are dying, apoptotic cells expose phosphatidylserine on their surfaces. New studies have also identified various receptors that can recognize phosphatidylserine on the surfaces of apoptotic cells (Penberthy and Ravichandran, 2016). Phosphatidylserine functions as a key "eat-me signal" which is detected by phosphatidylserine receptors on phagocytes. Other multiple eat-me signal proteins, eat-me signal receptors, and eat-me signal-bridging molecules have also been identified. Phosphatidylserine receptors are a highly various set of receptors categorized by their ability to recognize the typical eat-me signal of phosphatidylserine on apoptotic cells (Penberthy and Ravichandran, 2016; Ravichandran, 2010). Most phosphatidylserine receptors attenuate inflammation by inducing the production of anti-inflammatory molecules during the engulfment of dead cell corpses (Poon et al, 2014). On the other hand, many phosphatidylserine receptors are also able to recognize other ligands, categorized as scavenger receptors (Bonecchi et al, 2016; Penberthy and Ravichandran, 2016). These diverse sets of receptors can lead to different phagocytic intracellular signaling events for particular ligands (Gumienny et al, 2001). The recognition and removal of apoptotic cells generally accompany an anti-inflammatory process at the tissue level, as well as immune tolerating responses (Green et al, 2009). Distinct types of cell death lead different types of immune response. Specifically, physiological cell death (apoptosis) is intrinsically tolerogenic, whereas pathological cell death (necrosis) is inherently immunogenic and induces inflammatory reactions (Thompson, 1995). In addition, the impaired scavenging of apoptotic cells is associated with numerous uncontrolled immunological diseases. Apoptotic cells are rarely found in tissue under normal physiological conditions, but the presence of uncleared dead corpses has been directly linked to several different diseases that involve infection, inflammation, autoimmunity and cancer (Poon et al, 2014). After the phagocytosis of infected bacteria, neutrophils usually undergo phagocytosis-induced cell death following uptake by neighboring phagocytes, leading to the next round of pathogen removal (Zemans et al, 2011). Phagocytic cells also facilitate a pro-resolving lipid mediator release, such as resolvin E1, with enhanced host-directed bacterial killing (El Kebir et al, 2012). During inflammation, the clearing defect of dying neutrophils can lead to a prolonged inflammatory status (Green et al, 2016). The uncleared dead corpses provide a greater opportunity to generate auto-antibodies against self-antigens. The production of auto-antibodies is the key feature of autoimmune diseases (Tanaka and Miyake, 2007). Conversely, under certain conditions, such as the destroying of tumor cells by specific cell-death-inducing compounds, the detection of dead tumor cells can potentiate an immunogenic response and anti-tumor immunity (Gregory and Pound, 2011). Thus far, many lines of studies have provided new information about therapeutic interventions for both mitigating

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inflammation in specific inflammatory or autoimmune diseases and enhancing effective immune responses against tumor-associated antigens. The next challenge in this field is to apply the benefits of the apoptotic cell clearance process to human disease therapies.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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