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Balance of apoptotic cell death and survival in allergic diseases

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Abstract

Allergic diseases result from over-reaction of the immune system in response to exogenous allergens, where inflammatory cells have constantly extended longevity and contribute to an on-going immune response in allergic tissues. Here, we review disequilibrium in the death and survival of epithelial cells and inflammatory cells in the pathological processes of asthma, atopic dermatitis, and other allergic diseases.

Keywords: Allergic disease; Cell death; Epithelial cells; Inflammatory cells; Apoptosis

1. Introduction

Allergic diseases are considered to be immune disorders dominated by the T-helper 2 cell pathway, accompanied by isotype-switching of B-cells to generate IgE antibodies specific against environmental allergens. Individuals with a genetic predisposition show hypersensitivity to these substances and are more likely to develop allergic diseases in early childhood or adolescence [1,2]. Allergic diseases such as anaphylaxis, asthma, eczema, allergic rhinitis, and food-induced allergies are common and, with increasing incidence, have reached pandemic proportions [3]. Similar to other types of inflammatory reaction, allergic sites recruit inflammatory cells during the initiation and maintenance phases, whereas cell numbers decline in the resolution phase of allergic disease *via* the cell-death clearance pathways [4]. In allergic circumstances, inflammatory cells always have a prolonged survival in allergic tissues, and contribute to the continuous immune response.

The prompt removal of apoptotic cells by phagocytes is important for maintaining tissue homeostasis. Despite the constant turnover of cells through apoptosis, apoptotic cells are rarely seen under physiological conditions, even in tissues with high rates of apoptosis. Apoptotic cells are efficiently removed by professional and non-professional phagocytes, a process thought to be essential for tissue remodeling and the resolution of inflammation. It is reported that, in the steady state, the rate of apoptotic cell removal is high and necessary for their continuous clearance [5].

Here, we review misbalance in the death and survival of epithelial cells, inflammatory granulocytes, and T-cells in the pathological course of asthma, atopic dermatitis, and other allergic diseases (Fig. 1).

2. Classifications of cell death

Cell death is a process classified into several types based on specific morphological and biochemical characteristics,

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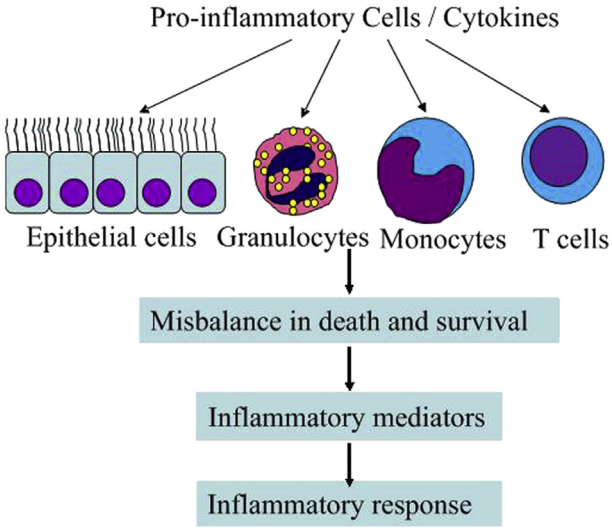

Fig. 1. Overview of the misbalance in death and survival of epithelial and inflammatory cells. Inflammatory mediators secreted by pro-inflammatory cells in the inflamed sites lead to an imbalance between the death and survival of epithelial cells, granulocytes, monocytes, and T-lymphocytes. More cytokines released from these inflammatory cells and structural cells subsequently initiate or maintain the allergic response.

mainly consisting of apoptosis, necrosis or necroptosis, autophagy, and caspase 1-dependent programmed cell death (also known as pyroptosis) [6,7]. Cell death plays many important roles in normal physiological development and tissue homeostasis, as well as defense mechanisms against various diseases [8], leading to favorable or adverse consequences.

The term "apoptosis" was introduced by Kerr et al. in 1972 [9], and is the most clearly described type of programmed cell death so far. Based on electron microscopy, the morphological changes during apoptosis include chromatin condensation, cytoplasmic shrinkage, and plasma membrane blebbing [9]. Besides, on the molecular level, apoptosis involves intranucleosomal DNA cleavage [10] and randomization of the distribution of phosphatidyl serine between the inner and outer leaflets of the plasma membrane [11]. Necrosis or necroptosis is characterized by cytoplasmic swelling (oncosis), rupture of the plasma membrane, swelling of cytoplasmic organelles, and moderate chromatin condensation. For quite some time, necrosis was morphologically defined as merely an accidental and uncontrolled process of cell death. However, accumulating evidence suggests that necrosis also occurs in a regulated manner, involving a precise sequence of signals, and is controlled by specific signaling pathways [12]. The term 'necroptosis' has recently been used as a synonym for regulated necrosis, but it was originally introduced to indicate a specific case of regulated necrosis that is ignited by TNFR1 ligation and can be inhibited by the RIP1-targeting chemical necrostatin-1 [13]. The term "autophagy" (also known as macroautophagy) was introduced by Yang et al. [14] to describe the process of a cell digesting its own contents. This phenomenon can occur as a survival mechanism to maintain cellular homeostasis in response to nutrient depletion or pathogen invasion, oxidative stress, starvation, or other cellular stresses, but may also be involved in programmed cell death [15,16]. Briefly, in the course of autophagy, newly-formed autophagosomes encapsulate damaged, disabled, or dysfunctional organelles and molecules and subsequently fuse with lysosomes to construct autolysosomes, delivering their sequestered cargo to this compartment for enzymatic digestion [17].

3. Death of epithelial cells in allergic diseases

Epithelium is a dynamic tissue which undergoes continuous renewal. As the first tissue that is directly exposed to exogenous allergens, epithelium responds to environmentally-induced damage not only as a physical barrier, but epithelial cell death is also a common phenomenon in allergic inflammation.

The lung also contains professional phagocytes such as macrophages and dendritic cells, and many 'non-professional phagocytes' that can engulf apoptotic cells [18,19]. A recent report has added a further level of complexity to the function of airway epithelial cells and cell death [20]. The authors demonstrated that apoptotic epithelial cells are engulfed by viable bronchial epithelial cells in a process requiring the small GTPase Rac1, which is classically involved in the engulfment of large extracellular material by phagocytes and dendritic cells. Engulfment of apoptotic cells by epithelial cells leads to the production of interleukin 10 (IL-10) and transforming growth factor beta, thus suppressing the activation of immune cells. This report raised the concept that defects in cell clearance in the airways can contribute to the inflammatory responses to common allergens. Therefore, the balance between apoptotic cell clearance and cell death play an important role in the anti-inflammatory process.

Taking asthma for example, allergic asthma is pathologically characterized by overexpression of Th2-related cytokines and infiltration of eosinophils in the airway, leading to a group of clinical symptoms with reversible expiratory airflow limitation or bronchial hyper-responsiveness, and damage to structural cells such as bronchial epithelial cells. Excessive apoptosis is likely to be responsible for damage to airway epithelial tissue. During the pathological process, shedding of bronchial epithelial cells is reported in bronchial biopsy specimens from asthmatic patients [21], and is characterized by the loss of normal bronchial pseudostratified epithelium and the maintenance of a few basal cells on a thickened basement membrane [22]. The shedding of epithelial cells subsequently increases the exposure of underlying tissue elements to the toxins of inhaled allergens or other pathogens and hence to further deterioration [23]. Apoptosis of epithelial cells in asthmatic patients can be regulated by tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ) secreted by activated T-cells and eosinophils, based on *in vitro* data. Besides, recombinant eosinophil cationic protein, one of the potent cytotoxins released by eosinophils, induces necrosis of epithelial cells *ex vivo* (Fig. 2a) [24].

According to previous research, activated epithelial cells in asthmatic patients express higher levels of thymic stromal