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Editorial

Apoptosis of inflammatory cells in Asthma

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Apoptosis is programmed cell death in which the cell's contents are packaged into small packets of the membrane to eliminate damaged and infected cells (1, 2). Apoptosis is mediated by two signaling cascades, the intrinsic and extrinsic. Intrinsic pathway commonly occurs due to a disruption of cellular homeostasis, and extrinsic apoptosis occurs via extracellular signaling and death receptors (Figure 1). While both apoptosis pathways have unique initiating steps in the activation of cysteine proteases called caspases (3). Initiator caspases like caspase 8/9 begin a series of proteolytic steps that lead to activation of executioner caspases 3/7 (4). Executioner caspases cleave thousands of substrates and are responsible for the enzymatic degradation of organelles, DNA fragmentation, and characteristic phosphatidylserine exposure. Mitochondrial outer membrane permeabilization (MOMP) commits cells to undergo intrinsic apoptosis. MOMP occurs when B-cell lymphoma 2 (BCL2)-associated X apoptosis regulator (BAX) and BCL2 antagonist/killer 1 (BAK) form outer mitochondrial membrane pores. MOMP causes the release of cytochrome c and second mitochondria-derived activator of caspase (SMAC). Cytochrome c binds apoptotic protease activating factor 1 (APAF1) and initiator caspase 9 to form the apoptosome, where caspase 9 is activated. SMAC neutralizes the cytoplasmic proteins maintained by cells to restrain caspase activation (inhibitor of apoptosis proteins, IAPs) (5). Extrinsic apoptosis is triggered by binding of Fas plasma membrane death receptor to Fas ligand (Fas-L), and form the death-

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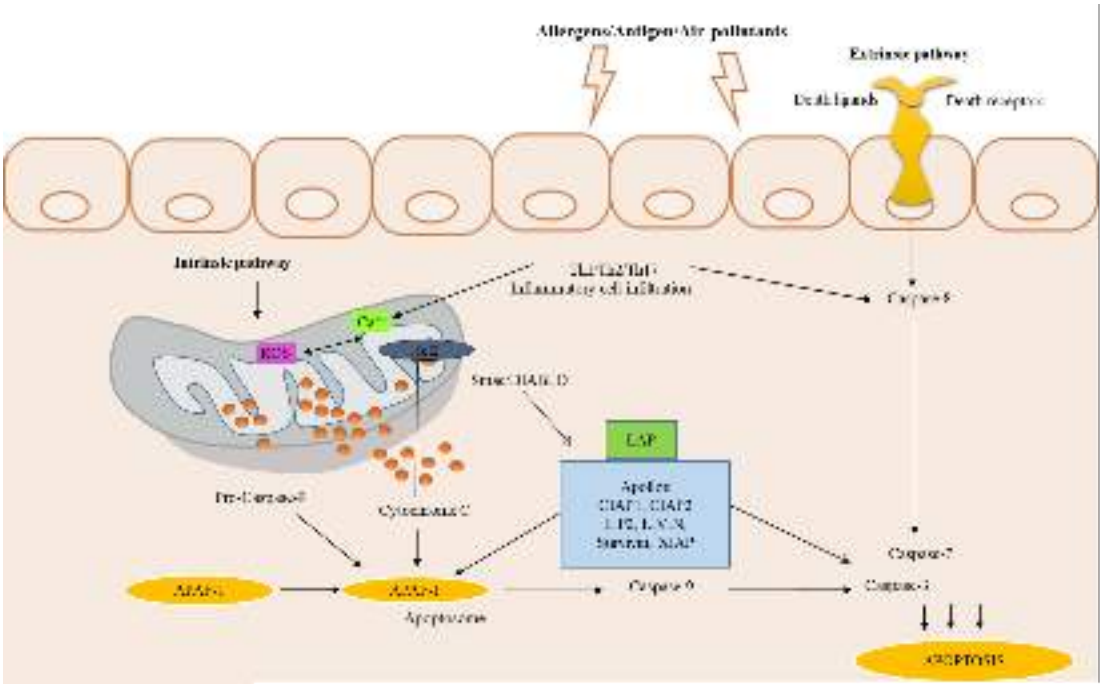

Figure 1. Extrinsic and intrinsic pathways of apoptosis in Asthma. The extrinsic pathway Is initiated by ligand binding to death receptors on the plasma membrane. The intrinsic Pathway is mediated by mitochondrial factors such as Ca^{++} into the mitochondria, Reactive Oxygen Species (ROS) release. Both pathways lead to the activation of caspases.

complex (DISC) composed of caspase 8. Upon activation, cleavage of caspase 8 leads to cleavage of executioner caspases and apoptosis. Inhalation of different allergens can promote reactive oxygen species (ROS) potentially lead to cell death by directly oxidizing or triggering various downstream pathways in the mitochondria. ROS enhance the infiltration of the lung airspaces with leukocytes. Mediators secreted by airway epithelial cells (AECs) and infiltrating leukocytes, in turn, affect the differentiation of the AE and the cell death processes of epithelial cells (6-8). Asthma is a chronic inflammatory disease, which can lead to the progressive decline of lung function and affects 25 million people in the United States (9). It involves an integrated response in the conducting airways of the lung to known or unknown triggers, involving abnormal responses of many different cell types
in the lung mainly epithelial cells that initiate airway inflammation in asthma and are the source of excess airway mucus. The cell-cell communications that drive asthma is that known and unknown inhaled stimuli (i.e., proteases and other constituents of inhaled alle-

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allergens, respiratory viruses, and air pollutants) stimulate airway epithelial cells to secrete the cytokines which act on subepithelial dendritic cells, mast cells, and innate lymphoid cells to recruit both innate and adaptive hematopoietic cells and initiate the release of T helper 2 (Th2) cytokines such as IL-4, IL-5 and IL-13 (10).

The macrophage activation in asthma helps to eliminate apoptotic cells that is an important factor that stimulates the release of IL-10, as well as other anti-inflammatory mediators, such as TGF-β and prostaglandin E2 by these cells (11). The recent studies have revealed a more diverse role of eosinophils. In addition to their potential to release an array of products that damage epithelium, they also induce bronchoconstriction, mucus production, and vascular permeability, and have been shown to have an important role in Th2 polarization and airway remodeling. Resolution of eosinophilic inflammation is an important goal in the treatment of allergic asthma. Eosinophils can stimulate Th-cell activation, proliferation, and production of IL-4, IL-5, and IL-13. Evidence exists on the role of eosinophil-derived TGF-β in mediating airway remodeling. Apoptosis may also provide a mechanism for the removal of activated T-cells in healthy individuals (12,13). Macauley et al. (14) findings suggest that STALs (SIGLEC, sialic acid–binding Ig-like lectin -engaging tolerance-inducing antigenic liposomes (STALs) could be used to minimize harmful B cell-mediated immune responses. The CD103+ dendritic cells (DCs) are so effective in causing antiviral CD8 lymphocyte immunity and are the exclusive DC subtype able to capture and cross-present apoptotic epithelial cells that succumb to viral infection (15). The Bcl-2 inhibitors were more effective than steroids at inducing granulocyte apoptosis in the blood granulocytes from patients with severe asthma (16).

The use of a pan-caspase inhibitor has been demonstrated to decrease airway inflammation (17). Oxidative stress in asthmatic bronchial epithelial cells is a consequence of infiltrating immune cells or aerosolized toxins such as cigarette smoke, and airway epithelial cells from asthmatic patients diminish antioxidant capacity (18). Cytokines from T cells, macrophages, and epithelial cells, including IL-3, IL-5, IL-9, IL-13, IL-18, IL-25 generate an

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inflammatory condition in the asthmatic airway that antagonizes eosinophil apoptosis. JAK/STAT, AKT, ERK, ROS, and FADD signaling have all been implicated in regulating eosinophil apoptosis. Abreu et al. (19) studies showed the sevoflurane therapy was also associated with inhibition of inflammatory cell invasion into BALF and reduced serum levels of IgE and OVA-induced Th2 cytokines in BALF and reduced NLRP3 expression.

The studies suggest that understanding the role of apoptosis pathways may be a valuable avenue of study for asthma (20, 21). Apoptosis help to eliminate these harmful cells and development of drugs targeting eosinophil apoptosis is one possible strategy for the therapy of allergic asthma. The understanding of the cellular mechanisms that mediate regulated cell death continues to grow, there is increasing evidence that these pathways are implicated in the pathogenesis of Asthma. It is important to summarize recent advances on regulated cell death in the pathogenesis of asthma and ideal therapeutic approach for allergic airway disease is to achieve inflammatory control. The role of apoptosis in the pathogenesis of severe lung diseases is highly complex. Chronic inflammation may cause persistence of immune cells and susceptibility to apoptosis in asthma. Developing therapies that modulate apoptosis-mediated cell fate in the lungs will be a beneficial approach to treat asthma mediated cell death.

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