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CELL DEATH AND DISEASE

Cell death in allergic diseases

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Abstract Apoptosis, the most common form of cell death, is a key mechanism in the build up and maintenance of both innate and adaptive immunity. Central to the apoptotic process is a family of intracellular cysteine proteases with aspartate-specificity, called caspases. Caspases are counter-regulated by multiple anti-apoptotic molecules, and the expression of the latter in leukocytes is largely dependent on survival factors. Therefore, the physiologic rates of apoptosis change under pathologic conditions. For instance, in inflammation, the expression of survival factors is usually elevated, resulting in increased cell survival and consequently in the accumulation of the involved immune cells. In many allergic diseases, eosinophil apoptosis is delayed contributing to both blood and tissue eosinophilia. Besides eosinophils, apoptosis of other leukocytes is also frequently prevented or delayed during allergic inflammatory processes. In contrast to inflammatory cells, accelerated cell death is often observed in epithelial cells, a mechanism, which amplifies or at least maintains allergic inflammation. In conclusion, deregulated cell death is a common phenomenon of allergic diseases that likely plays an important role in their pathogenesis. Whether the apoptosis is too little or too much depends on the cell type. In this review, we discuss the regulation of the lifespan of the participating leukocytes in allergic inflammatory responses.

Keywords Allergy · Apoptosis · Basophils · Caspase · Cytokines · Dendritic cells · Eosinophils · Epithelial cells · Immune system · Inflammation · Mast cells · Neutrophils · Survival factors · T cells

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Introduction

Allergic diseases are the consequence of hyperreactivity reactions of the immune systems towards exogeneous antigens (allergens). Most allergic reactions are associated with an increased T helper (Th) 2 activation, resulting in elevated IgE levels and eosinophilia. Allergic diseases, including asthma, rhinitis, conjunctivitiy, atopic eczema, as well as food and drug allergies are major contributors to morbidity in the civilized world, and sometimes even cause mortality. With the expanding knowledge, the field of allergy, along with the broader framework of immunology, has dramatically changed concepts in recent years. However, in spite of the progress, the regulation of cell death in allergic diseases is relatively little investigated and its contribution to the pathogenesis of the different disorders not well understood and reflected, respectively.

Similar to other types of inflammatory responses, accumulation of subgroups of leukocytes occur during the initiation and maintenance phases, whereas inflammatory cell numbers decline in the resolution phase of allergic inflammation. The changes in cell numbers during inflammation are largely due to changes of rates of both cell generation and cell death. Important leukocyte subgroups believed to play critical roles in the pathophysiology of allergic inflammation involve dendritic cells, T cells, mast cells, and eosinophils. The most common form of cell death of leukocytes is apoptosis.

That apoptosis is deregulated in allergic diseases is often not reflected in reviews dealing with the pathophysiologic relevance of apoptosis in diseases. However, since

approximately one-third of the population within the countries of the industrial world suffers from one or several allergic diseases [1], it is important that apoptosis research in these disorders is not neglected. Here, we review the current knowledge on the regulation of cell death during allergic inflammatory responses. Due to space limitations, we will concentrate on summarizing important molecular events that change apoptosis rates in allergic diseases and will not cover basic knowledge on apoptosis pathways.

Cell death of mast cells

Mast cells are resident in all normal tissues, where they are believed to play an important role in tissue homeostasis, wound healing, and host defense. Mast cell activation is a characteristic feature of allergic responses, leading to the release of a large number of important mediators that can cause chronic inflammation. Mast cells are also involved in the mechanisms leading to bronchial hyperreactivity [2]. Therefore, how mast cell homeostasis is regulated may have significant effects on normal physiology and contributes to the genesis of allergic inflammatory diseases.

Mast cell numbers are increased in allergic inflammatory responses [3], and preventing apoptosis might contribute to this phenomenon. Stem cell factor (SCF), interleukin (IL)-3, IL-4, IL-5, IL-6, and nerve growth factor (NGF) have been described to promote mast cell survival [4–6]. On the other hand, it has been reported that exposure of murine bone-marrow-derived mast cells to IL-3, IL-4, and IL-10 downregulate the SCF receptor kit as well as the high-affinity IgE receptor, resulting in mast cell apoptosis [7].

SCF is considered as being the most crucial survival factor for mast cells. The crucial role of SCF for regulating mast cell numbers is best reflected by experimental in vivo models. Mice with deficient expression of SCF or kit have almost complete lack of mast cells in their tissues [8, 9]. SCF is secreted from several cell types, such as stromal cells, fibroblasts, endothelial cells, and mast cells themselves [10, 11]. Injection of SCF to the skin increases mast cell numbers. Moreover, a gain of functional mutations of kit causes systemic mastocytosis [12].

Following binding of SCF to kit, kit is dimerized and autophosphorylated on tyrosine residues. This initiates multiple intracellular signaling pathways, which involve phosphatidylinositol-3-kinase (PI3K), mitogen activated protein kinase (MAPK), phospholipase C γ (PLCγ), Src kinase, and Janus kinase/Signal transducers and activators of transcription (Jak/STAT), resulting in gene activation [13]. It was found that Bim is both inactivated and reduced due to SCF stimulation of mast cells [14]. Interestingly, cross-linking of the high-affinity IgE receptor also leads to apoptosis inhibition, which is mediated by increased Bcl-xL and A1 expression [15, 16]. Increased survival following mast cell activation may also be the consequence of the release of survival factors, which then act in an autocrine manner [17, 18].

Besides the anti-apoptotic mechanisms, mast cells additionally carry functional death receptors. For instance, mast cell apoptosis can be induced following ligation of Fas and TNF-related apoptosis inducing ligand (TRAIL) receptors [19, 20]. Interestingly, immunoglobulin E (IgE)-mediated activation of mast cells increased their sensitivity to undergo TRAIL-induced apoptosis, although the mechanism(s) responsible for these functional effects remain to be investigated [20, 21]. In the resolution phase of allergic inflammation, in which survival cytokine expression is likely decreased, the induction of mast cell apoptosis critically involves the BH3-only protein Puma [22].

Cell death of eosinophils, neutrophils, and basophils

Eosinophils are prominent effector cells in many allergic and parasitic inflammatory responses [23]. They are constantly generated in the bone-marrow and short-lived [24]. Moreover, eosinophils are relatively rare and their contribution to blood leukocyte numbers does not exceed 4% under physiologic conditions. IL-5 represents a crucial cytokine for eosinophil differentiation, activation, and survival [25]. Therefore, in diseases with elevated levels of IL-5, increased numbers of eosinophils are observed [26]. The importance of IL-5 for delayed eosinophil apoptosis in tissues has been directly demonstrated in nasal polyp explants [27]. Delayed eosinophil apoptosis has also been demontrated in experimental in vivo models of allergic disease [28]. Moreover, there was an inverse correlation between numbers of apoptotic eosinophils in sputum from asthmatic patients and levels of IL-5 and eotaxin, again indicating that IL-5 (and perhaps eotaxin) acts as an eosinophil survival factor in vivo [29]. Besides IL-5, other eosinophil survival cytokines are IL-3 and granulocyte/macrophage colony-stimulating factor (GM-CSF). Interestingly, eotaxin-1 [30], leptin [31], and CD40 ligand [32] are also able to prolong eosinophil survival in vitro.

The molecular mechanisms involved in cytokine-mediated enhanced eosinophil survival include increased expression of Bcl-xL [33], delayed Bid cleavage [34], inhibition of Bax translocation to mitochondria [35], and delayed Bax cleavage [31], resulting in delayed mitochondrial cytochrome c and second mitochondria-derived activator of caspase (Smac) release and caspase activation [31, 35]. IL-5 has also been shown to induce cIAP2 and survivin, suggesting that delay of apoptosis can also be achieved by blocking caspases [36]. The signal

transduction mechanisms leading to gene expression of anti-apoptotic proteins involve tyrosine kinases [37, 38], MAPK [37], PI3K [39], Jak/STAT [40, 41], and NF-κB pathways [42]. In contrast, the c-Jun N-terminal kinase (JNK) pathway seems to mediate constitutive eosinophil apoptosis [43].

Eosinophils also carry functional death receptors. For instance, eosinophils express Fas receptors that initiate apoptosis upon activation, even in the presence of survival cytokines [44]. In contrast, nitric oxide, that is increasingly generated during allergic inflammatory responses, counterregulates Fas receptor-induced apoptosis [45]. TRAIL and TNF receptors are also expressed on eosinophils, and were reported to mediate eosinophil survival [46, 47]. In contrast, recombinant surfactant protein-D (SP-D) has been shown to induce apoptosis in eosinophils from allergic patients, but not from healthy donors, although the mechanism remains unclear [48]. Eosinophil apoptosis can also be induced as a consequence of sialic acid binding immunoglobulin-like lectin (Siglec)-8 ligation [49]. Moreover, IL-5 increases Siglec-8 mediated death in a partially caspase-independent manner (Fig. 1) [50]. Therefore, the eosinophil cell death under these condition is unlikely apoptosis, but may represent an autophagic-like cell death [51]. Recently, a natural ligand for Siglec-8 has been identified [52]. Interestingly, Siglec-8 can also be ligated by physiologic anti-Siglec-8 autoantibodies [53]. Moreover, ligation of mouse Siglec-F, the closest functional paralog of human Siglec-8, selectively reduces blood and tissue eosinophils in experimental mouse models [54].

Glucocorticoids that are often used as anti-inflammatory drugs in allergic inflammatory responses directly induce eosinophil apoptosis, although the molecular mechanism of this drug's action on cell survival remains unclear [55]. Nevertheless, this effect might be important since asthmatic patients exhibit an increased proportion of apoptotic eosinophils in their airway secretions following clinical improvement with successful glucocorticoid therapy [56]. Theophylline has also been reported to induce eosinophil apoptosis [57], but the clinical significance of this finding is unclear. Agents that increase intracellular cAMP may also modify eosinophil apoptosis, depending on the inflammatory cytokine environment [58].

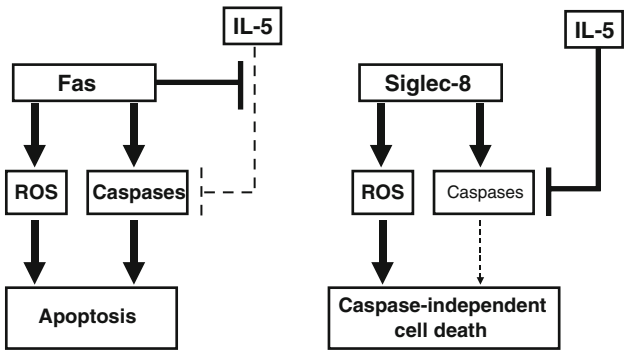

Fig. 1 Different forms of cell death in eosinophils following Fas and Siglec-8 ligation in the presence of IL-5. Both Fas and Siglec-8 ligation induce caspase activation and ROS generation in the absence of concurrent survival cytokine stimulation, leading to apoptosis. In the presence of IL-5, however, death programs are different. In contrast to Fas ligation, which blocks anti-apoptotic signaling, Siglec-8 ligation does not prevent IL-5-mediated caspase inactivation. Caspase inhibition is associated with a largely caspase-independent cell death, which depends on ROS

Although neutrophils can be present in bronchial asthma [59], they are usually not dominant in chronic allergic inflammatory responses. However, it is interesting to compare the regulation of apoptosis between eosinophils and neutrophils, since both cell types are granulocytes. Neutrophils and eosinophils express surface molecules, which initiate either survival or death signals. Both cell types respond with enhanced survival when stimulated with GM-CSF, and with enhanced apoptosis following ligation of Fas receptors. Like in eosinophils, Fas stimulation results in neutrophil apoptosis even in the presence of survival factors [60]. On the other hand, there are also surface receptors, which are expressed on either eosinophils or neutrophils. For instance, IL-5 is a specific survival factor for eosinophils, whereas G-CSF specifically prolongs the lifespan of neutrophils. In addition, the complement factor C5a enhances neutrophil [61], but not eosinophil survival (unpublished observation). Siglec-8 transduces death signals in eosinophils, but not neutrophils. In contrast, Siglec-9 is a death receptor on neutrophils that is not expressed on eosinophils [62]. Moreover, the nicotinic acid receptor GPR109A was recently identified on the surface of neutrophils, but not eosinophils [63]. There seem to be also differences regarding the mechanism of cell death regulation in association with DNA release between neutrophils and eosinophils [64, 65]. Interestingly, hypoxia, which induces apoptosis in most cell types, delays apoptosis in neutrophils [66]. The effect of hypoxia on eosinophil apoptosis is unknown.

Apoptosis in eosinophils and neutrophils is also regulated by drugs and/or compounds. Glucocorticoids, which induce eosinophil apoptosis (see above), delay the neutrophil apoptotic program [55]. On the other hand, nitric oxide donors promote neutrophil apoptosis, but somehow block eosinophil apoptosis [45]. Furthermore, the effect of phenylarsine oxide on apoptosis is different in neutrophils and eosinophils at a given concentration [67]. These data suggest that differences exist in the expression of intracellular components of cell death pathways between eosinophils and neutrophils. Indeed, caspases, although present, are somehow more difficult to activate in eosinophils compared with neutrophils [68]. In contrast, the expression of Bcl-2 family members seems to be similar in

eosinophils and neutrophils. Interestingly, Bcl-2, although present in immature precursors, is no longer present in both granulocyte types upon full maturation [69]. This observation may, at least partially, explain the short lifespan of these cells. Bim, a BH3-only protein, seems to play a major role in the regulation of neutrophil apoptosis [70]. The expression and function of Bim in eosinophils remains to be investigated. Taken together, the regulation of apoptosis in eosinophils and neutrophils is at least partially different, providing the opportunity to selectively target one granulocyte type without affecting the other by pharmacological means.

In contrast to eosinophils and neutrophils, little is known about the regulation of apoptosis in basophils, which represent the least abundant granulocyte population. Basophils are considered, besides mast cells and eosinophils, as key effector cells in allergic inflammation. Proinflammatory and immunomodulatory activities of basophils include secretion of histamine and the lipid mediator leukotriene C4 as well as rapid production of IL-4 and IL-13, Th2-type cytokines crucial for the development of allergy. The regulation of basophil apoptosis is likely to be important for the length and strength of allergic inflammation, since negative regulators on basophil activity have not been identified. IL-3 appears to be the only ligand that protects basophil apoptosis with high efficacy [71]. In contrast, ligation of Fas results in basophil apoptosis [72]. A recent study demonstrated that IL-3 mediates its anti-apoptotic effect on basophils through a Pim1-dependent signaling pathway [73].

Cell death of T cells

T cells, in particular T cells producing Th2 cytokines, play an important role in allergic inflammatory responses. For instance, IL-4 and IL-13 enhance IgE production, IL-4, IL-9, and IL-10 enhance mast cell growth; and IL-5 promotes eosinophil accumulation [74]. This Th2 response is the result of clonal expansion of allergen-specific T cells and involves both increased proliferation and inhibition of apoptosis. Although some observations in allergic inflammatory responses suggest prolonged survival of Th2 cells [75], most of our information on the role of T cell apoptosis in immune responses comes from experimental models. Bcl-2 expression is required for the survival of mature, resting T cells [76]. IL-4, IL-6, or IL-7 are required to maintain Bcl-2 and Bcl-xL levels in these cells [77, 78]. Interaction of the T cell receptor (TCR) with major histocompatibility complex (MHC) class II molecules is required to keep memory T cells alive [79].

The antigen-mediated stimulation of T cells results in a change in requirements for survival. Activated T cells produce IL-2 and are dependent on IL-2, and related cytokines, for their survival [77, 78, 80]. IL-2 and related cytokines maintain Bcl-2 and Bcl-xL levels [77, 78], and IL-2 withdrawal requires activation of Bim to induce death [81]. Repeated TCR activation sensitizes T cells to apoptosis, a process known as activation-induced cell death. Upon activation, Th1 cells are initially resistant to Fas ligand-induced death, but they gain sensitivity after several days [82]. This increased susceptibility towards Fas receptor-mediated apoptosis has been attributed to lower levels of FLICE-like inhibitory protein (FLIP) and is IL-2-dependent [83]. In Th2 cells, however, FLIP levels may not decrease, resulting in Fas resistance [84]. Therefore, Th2 predominance in allergic diseases may largely be due to increased Th1 cell apoptosis [85, 86].

In the resolution phase of inflammatory responses, most activated T cells are killed. T cell apoptosis may occur by two mechanisms: (1) by repeated stimulation of the TCR with antigen in conjunction with MHC class II molecules, and (2) by reduction in cytokine levels due to decreased inflammation. The first mechanism requires Fas in Th1 cells, and Fas-deficient patients develop a lymphoproliferative disease [87, 88]. In Th2 cells, which are Fas resistant [84], granzyme B is critical for activation-induced cell death (Fig. 2) [89]. This second mechanism requires Bim [81] and can be blocked by high levels of Bcl-2 [90]. Th2 cell apoptosis in allergic diseases may also be achieved by drug treatment. For instance, calcineurin

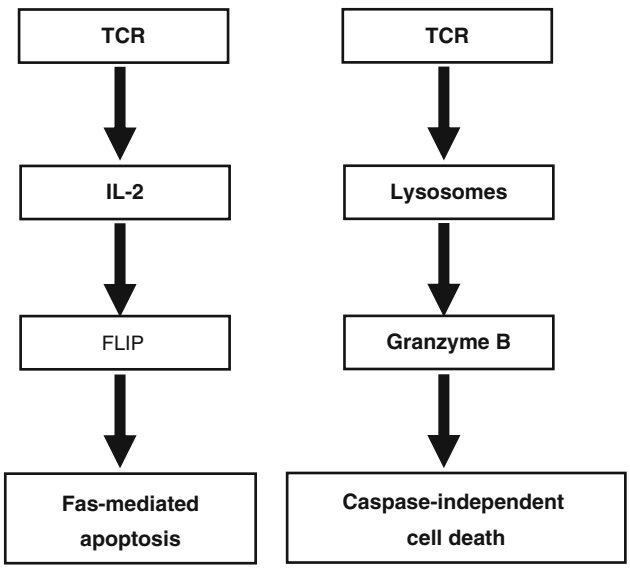

Fig. 2 Distinct T cell receptor (*TCR*)-mediated death pathways in Th1 and Th2 cells. Whereas Th1 cells gain Fas sensitivity due to IL-2-dependent downregulation of FLIP during an immune response, Th2 cells stay Fas resistant following TCR activation. In Th2 cells, granzyme B is released from lysosomes mediating a caspase-independent cell death

inhibitors have been described to induce T cell apoptosis in atopic eczema [91].

Almost nothing is known about the regulation of apoptosis of regulatory T cells. It is tempting to speculate, however, that dysregulated apoptosis in these cells contributes to the pathogenesis of allergic inflammatory responses. Interestingly, it has been suggested that T regulatory cells induce effector CD4+ T cell apoptosis in an experimental model of inflammatory bowel disease [92]. Therefore, it is possible that regulatory T cells also fulfill their function, at least partially, by mediating effector T cell apoptosis in allergic diseases. Clearly, such a potential mechanism deserves further investigation.

Cell death of dendritic cells

The role of dendritic cells in driving Th2 allergic responses has received considerable attention in recent years. Dendritic cells have direct contact to incoming antigens. In the presence of a danger signal, dendritic cells mature to professional antigen-presenting cells, and interact with naive T cells in draining lymph nodes. Dendritic cells can influence polarization of T cells by the release of cytokines [93] and their expression of costimulatory molecules [94] that are both influenced by the local environment [95]. Dendritic cells have been shown to be essential in the pathogenesis of allergic diseases [96, 97].

The lifespan of mature dendritic cells is thought to be approximately three days [98]. This short time may limit the availability of antigen for T cells, and apoptosis induction in dendritic cells may serve to regulate immune responses. The lifespan of dendritic cells is determined by both antigen-mediated and T cell signals. For instance, ligands for Toll-like receptors (TLRs), CD40 ligand, or tumor necrosis factor-related activation-induced cytokine (TRANCE) promote dendritic cell survival via NF-κB pathways [99–101]. One of the NF-κB target genes is Bcl-xL, which is induced by both TLR ligands and T cell signals. In addition, TLR ligands, but not T cell signals, reduce Bcl-2 and induce Bim, thus limiting the lifespan of dendritic cells [102]. One might, therefore, speculate that immature dendritic cells receive first TLR ligands, which are likely to set the lifespan of dendritic cells, before they even enter the lymph node. A function of T cells might then be to prolong the survival of dendritic cells, possibly leading to a temporary and local enrichment of dendritic cells.

It is has been demonstrated that increasing the lifespan of mature dendritic cells is an important factor to strengthen the inflammatory response under in vivo conditions [102]. Therefore, it is likely that increased dendritic cell survival also plays a role in allergic inflammatory responses. Indeed, it has recently been reported that apoptosis-resistant dendritic cells promote Th2 responses, including IgE production in an experimental mouse model [103]. Therapeutic approaches promoting dendritic cell apoptosis appear to be promising [104], further pointing to the possibility that the lifespan of dendritic cells is a critical element in the generation and/or maintenance of allergic diseases.

Cell death of epithelial cells

Epithelial cell apoptosis is a common phenomenon of allergic inflammation. For instance, bronchial epithelial apoptosis leads to epithelial shedding in asthma. Apoptosis is mediated by activated T cell and eosinophils [105]. Another example of epithelial cell apoptosis in association with allergy is seen in atopic eczema. Apoptosis of keratinocytes has been reported to be a major cause of spongiosis, which represents one of the hallmarks of atopic eczema [106]. IFN-γ, even at very low concentrations, increases Fas expression on keratinocytes and renders these cells susceptible to apoptosis [106]. Taken together, allergic diseases are often associated with epithelial cell damage, which likely amplifies or at least maintains the inflammatory process.

Conclusion

A look at the molecular basis of many allergic diseases reveals a cell death component that either accounts for the disease or contributes to disease progression. Therefore, current and future anti-allergic therapies should also be analyzed in respect to their effects on cell death pathways.

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