

Review article

Eosinophil apoptosis – pathophysiologic and therapeutic implications

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Eosinophils are prominent effector cells in many chronic allergic and parasitic inflammatory responses (1). Like other leukocytes, they are constantly generated in the bone marrow. To maintain cellular homeostasis, aged leukocytes have to die and need to be removed in the absence of inflammation. Apoptosis is the most common form of such physiologic cell death. Dysregulation of apoptosis can lead to pathophysiologic changes that result in either loss of cells (e.g., acquired immunodeficiency syndrome, degenerative diseases) or accumulation of cells (e.g., cancer, autoimmune and inflammatory diseases). The physiologic cell death of eosinophils is also apoptosis (Fig. 1), and delayed eosinophil apoptosis has been considered an important mechanism contributing to eosinophilia (2).

Apoptosis can be induced in response to specific ligands or stress stimuli that either engage so-called “death receptors” of the tumor necrosis factor (TNF)/nerve growth factor (NGF) receptor superfamily (3), or destroy the integrity of the genome (e.g., irradiation) (4). Lack of survival factors can also trigger apoptosis in many cells (5). It is currently believed that the apoptotic stimuli converge on the mitochondria, resulting in the release of cytochrome C (6). The release of cytochrome C is an irreversible step, leading to the activation of proteases known as caspases (7). The death of the cell is thought to result from the proteolytic degradation of important cellular proteins that in turn leads to the characteristic morphologic and biochemical changes of apoptotic

cells, including reduction of the cellular volume, chromosome condensation, and DNA laddering (Fig. 2). I have reviewed earlier the specific morphologic features of apoptotic eosinophils (8). This review focuses on the regulation of eosinophil apoptosis in chronic allergic diseases and describes how known anti-inflammatory drugs interfere in these pathophysiologic mechanisms.

Regulation of eosinophil apoptosis under inflammatory conditions

Interleukin-5 (IL-5) appears to be a specific survival factor for eosinophils, at least within the human system (9). Therefore, and not surprisingly, eosinophilia and high IL-5 expression have often been associated, especially in chronic allergic disorders such as bronchial asthma and atopic dermatitis. The phenomenon of delayed eosinophil apoptosis has been demonstrated in nasal polyp explants (10), as well as in purified blood eosinophils from patients with atopic dermatitis (11) and some patients with the hypereosinophilic syndrome (12). Moreover, it appears that the severity of asthma negatively correlates with the amount of eosinophil apoptosis in the airways (13). These data suggest that delayed apoptosis represents one important mechanism leading to tissue eosinophilia (14).

Some of the intracellular signaling mechanisms initiated by IL-5 have been identified in eosinophils (15). These studies revealed that the story is less

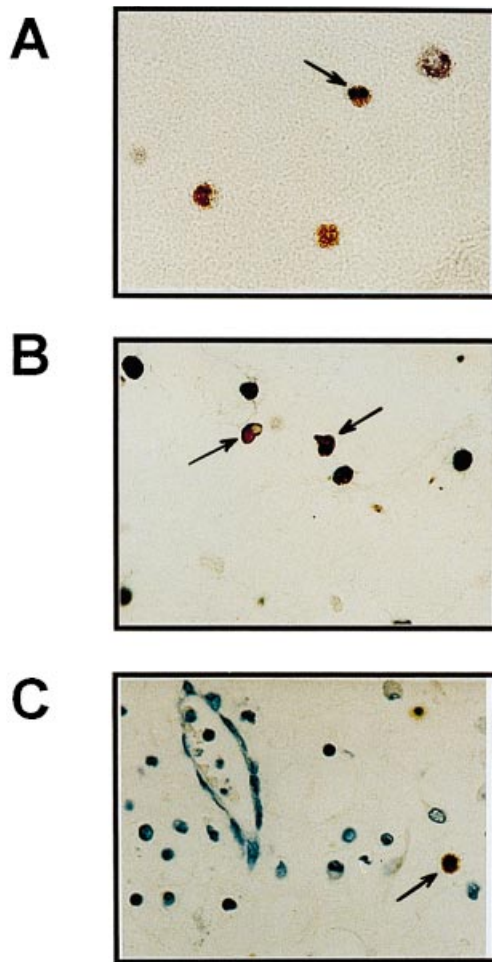


Figure 1. *In situ* detection of apoptotic eosinophils in nasal mucosa tissues. A) Fragmented DNA in apoptotic cells was detected by terminal deoxynucleotidyl transferase uridine triphosphate nick end labeling (TUNEL) technique (blue nuclei). Eosinophils were identified by peroxidase staining (brown). B) Fragmented DNA in apoptotic cells was detected by antibody against single-strand DNA (red). Eosinophils were specifically stained with antieosinophil-specific protein (ECP) antibody (blue). C) Apoptotic cells detected by Annexin V binding (brown). Sections were stained by hematoxylin. In all panels, apoptotic eosinophils are indicated by arrows. $\times 400$.

simple than we thought. Many signaling pathways control more than one cellular function. For instance, the eosinophil priming and degranulation pathways appear to share many events of the antiapoptotic pathway (16). However, there are differences. Whereas degranulation of eosinophils does not require protein synthesis, it is clear that prolonged survival is dependent on the expression of antiapoptotic genes. In eosinophils, it appears that Bcl- χ_L appears to be an important antiapoptotic gene induced by IL-5 stimulation in eosinophils (17). The antiapoptotic Bcl-2 appears to be less important, although some authors have observed increased Bcl-2 expression in IL-5-treated eosinophils (18).

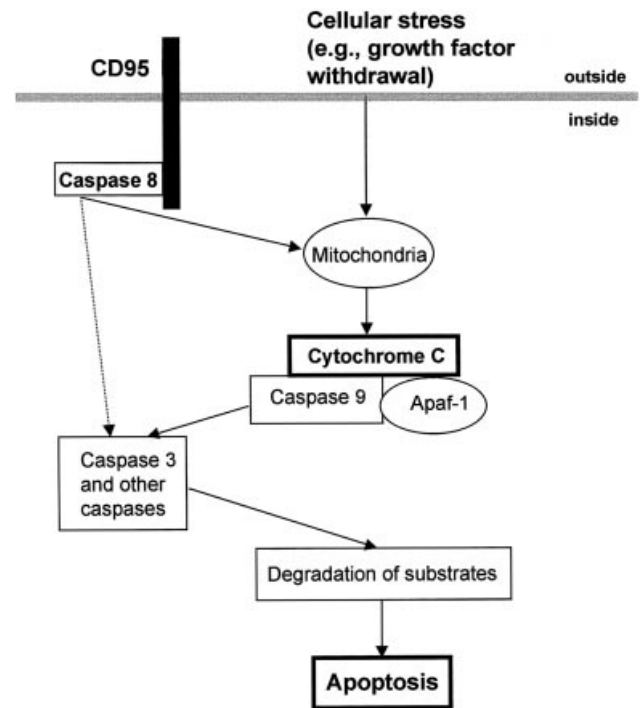


Figure 2. Various apoptotic stimuli lead to release of cytochrome C into cytoplasm. Cytochrome C is required for activation of caspase 9 via adapter molecule Apaf-1. Caspase 9 activates caspase 3 and perhaps other effector caspases, which degrade key cellular substrates and lead to apoptosis. Direct activation of caspase 3 via caspase 8 after CD95 activation is unlikely in eosinophils (24). Note that cytochrome C release after cytokine withdrawal has been demonstrated in cytokine-dependent cell lines. No work has been published on role of cytochrome C in induction of eosinophil apoptosis.

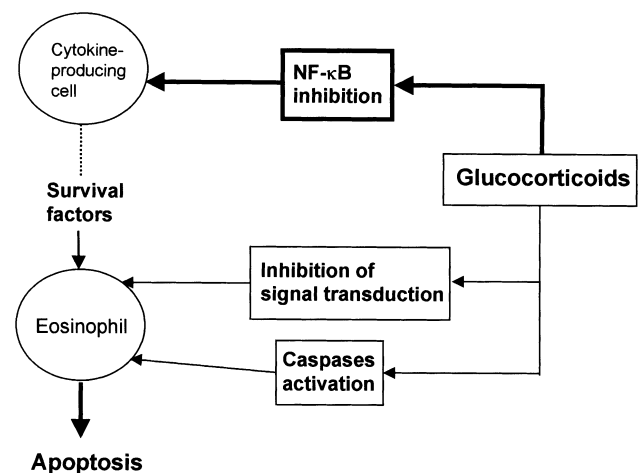


Figure 3. Effects of glucocorticoids in eosinophilic inflammation. Glucocorticoid therapy is often associated with reduction of eosinophil numbers due to induction of apoptosis. Most important mechanism responsible for this observation is probably decreased expression of eosinophil survival factors due to NF- κ B inhibition in cytokine-producing cells. Other possible mechanisms might be inhibition of signal transduction pathways initiated by survival factors and direct induction of apoptosis in eosinophils.

Like many other cells, eosinophils do not only undergo apoptosis in the absence of survival factors, but can also be triggered to die via specific surface death receptors. One of these death receptors expressed by eosinophils is CD95 (Fas/APO-1) (19–22). The ligand of CD95 (CD95L, FasL, APO-1L) is highly expressed by activated T cells (23). Thus, the same cells that produce eosinophil survival factors also express at least one death factor for eosinophils. Interestingly, activation of the CD95-mediated apoptotic pathway in eosinophils occurs even in the presence of eosinophil survival factors (19, 20). Therefore, the newly discovered additional ability actively to induce eosinophil apoptosis makes sense: CD95L/CD95 molecular interactions may serve to limit eosinophil expansion independently of eosinophil hematopoietin expression within inflammatory sites.

However, tissue eosinophils within inflammatory sites may not always undergo apoptosis after CD95 stimulation (22). This phenomenon, also called CD95 resistance, could result in an unlimited expansion of eosinophils. Indeed, in nasal polyp tissues, where CD95 resistance has been observed, an extraordinary infiltration of eosinophils is usually observed. What is the mechanism of CD95 resistance in eosinophils? The observation that eosinophil apoptosis following CD95 activation can be induced even in the presence of IL-5 or GM-CSF makes it unlikely that eosinophil survival factors account for this phenomenon. We have observed that nitric oxide (NO) prevents CD95-mediated apoptosis in eosinophils (24). This striking protective effect of NO appears to be of pathophysiologic relevance since increased concentrations of NO are present within allergic inflammatory sites (25).

Do glucocorticoids induce eosinophil apoptosis?

Glucocorticoids have been used for decades as clinical tools to suppress both the immune response and the process of inflammation. However, only recently have we begun to understand the molecular mechanisms of the effects of glucocorticoids. For instance, administration of glucocorticoids to patients with eosinophilia results in a marked decline in the number of circulating eosinophils (1). The reduction of eosinophil numbers appears to be, at least in part, due to the induction of eosinophil apoptosis (26). In addition, we have also obtained evidence for the induction of eosinophil apoptosis by glucocorticoids in nasal polyp explants (unpublished).

What is the mechanism of the induction of eosinophil apoptosis by glucocorticoids *in vivo*? Asthma and other allergic disorders are characterized by T-cell activation (27). T cells produce cytokines,

among them eosinophil survival factors such as IL-5 (28, 29). It is now clear that glucocorticoids suppress the transcription of the IL-5 and other cytokine genes. This inhibition of transcription is the consequence of inhibition of the potent inflammatory transcription factor NF- κ B (30). Therefore, one possible way that eosinophil apoptosis can be mediated by glucocorticoids is the reduced expression of eosinophil survival factors.

There is, however, the possibility that glucocorticoids directly act on eosinophils. Indeed, there is experimental evidence from *in vitro* studies that glucocorticoids inhibit the activity of eosinophil survival factors (31). Such inhibition of survival signals may be the consequence of disruption of signaling pathways (32), although this has not formally been demonstrated in eosinophils. Recently, it has been observed that glucocorticoids may also directly induce eosinophil apoptosis (33) (Fig. 3).

Effects of phosphodiesterase blockers, antihistamines, and antileukotrienes on the regulation of eosinophil apoptosis

Theophylline has been used for the treatment of bronchial asthma because it elicits bronchial dilation (34). More recent studies suggested that theophylline also has anti-inflammatory effects (35–37), whereby phosphodiesterase (PDE) inhibition appears to play a crucial role (38). This pharmacologic effect results in increases of cAMP and/or cGMP levels. The effects of drugs that elevate cAMP levels on apoptosis have been investigated. Increases in cAMP resulted in reduced apoptosis in both eosinophils (39) and neutrophils (40) *in vitro*. Similarly, increased cAMP and cGMP concentrations prevent Fas receptor-mediated apoptosis in eosinophils (24). How increased cAMP levels lead to inhibition of apoptosis is unclear. It is possible that cAMP activates antiapoptotic genes via protein kinase A (41), although other studies argue against this pathway (39). Surprisingly, but in agreement with its anti-inflammatory effects *in vivo*, theophylline does not appear to prolong eosinophil survival *in vitro*. Theophylline has been shown to accelerate spontaneous apoptosis in both eosinophils and neutrophils (42), as well as partially to block IL-5-mediated delayed eosinophil apoptosis (43). Since increased cAMP levels block apoptosis, it is unlikely that the apoptosis-inducing effects of theophylline are due to PDE inhibition. However, the possibility exists that PDE inhibition by theophylline prevents the release of antiapoptotic cytokines from eosinophils, thereby promoting apoptosis (41). Clearly, more work is required to elucidate the exact proapoptotic mechanism(s) of theophylline.

Nevertheless, these studies add to the notion that theophylline has anti-inflammatory properties besides its bronchodilatory effects.

Antihistamines have also been claimed to have anti-inflammatory effects. For instance, antihistamines may reduce the activation of both epithelial (44) and endothelial (45) cells. This in turn may decrease the recruitment of eosinophils into the allergic inflammatory site. However, it should be noted that antihistamines do not appear to influence IL-3, IL-4, IL-5, or GM-CSF expression by inflammatory cells in late-phase reactions (46). Blocking of leukotrienes may partially block the inflammatory cascade, thereby reducing eosinophilic inflammation. There is no published work reporting on the effects of antihistamines or antileukotrienes on eosinophil apoptosis.

Anticytokine and cytokine therapies that reduce eosinophil numbers

Since IL-5 is crucial for differentiation, activation, and survival of eosinophils, there have been attempts to block this cytokine as a therapeutic approach in allergic diseases. Glucocorticoids (see above), cyclosporin A (47), or anti-CD4 monoclonal antibody (48) therapy mostly reduce eosinophil numbers by reducing the numbers of IL-5-producing T cells. Similarly, treatment with IL-10 may shut off IL-5 gene expression in activated T cells (49). Interferon (IFN)- α is a new treatment for severe asthma (50) and the Churg-Strauss syndrome (51). One potential antieosinophilic effect of IFN- α appears to be increased sensitivity to glucocorticoids (50). Taken together, all these approaches result in survival factor withdrawal from eosinophils. This means that eosinophil apoptosis is induced by loss of suppressor activity.

Investigators have also used neutralizing antibodies (52) or antisense technology (53) to block IL-5 more specifically. In all these studies, IL-5 was efficiently blocked, resulting in a dramatic reduction of eosinophil numbers. Therefore, these studies confirmed the importance of IL-5 for eosinophil differentiation and survival. However, and perhaps more importantly, these studies help us to understand both the physiologic and the pathophysiologic function of eosinophils. Whereas some of the studies suggested that eosinophils are essential for the development of airway hyperreactivity (54), a hallmark of asthma, other studies did not confirm such a relationship (55). Therefore, further work is required to clarify the role of eosinophils in allergic inflammation and innate immunity.

Inhibition of apoptosis – a general biologic mechanism accumulating effector cells during inflammatory responses?

Delayed apoptosis of inflammatory effector cells does not appear to occur only in eosinophilic inflammations. Prolonged neutrophil survival *ex vivo* has also been associated with many neutrophilic inflammatory responses (56). The suppression of neutrophil apoptosis is at least partially due to the overexpression of survival factors, such as GM-CSF and G-CSF, that reduce the expression of the proapoptotic Bax molecule in these cells (56). Therefore, it appears that quantitative and qualitative properties of the cytokine microenvironment determine how many and which effector cells accumulate in inflammatory tissues.

Conclusion

Apoptosis is the physiologic cell death of eosinophils. There is increasing evidence from several laboratories that eosinophil numbers are regulated *in vivo*, not only by eosinophil production in the bone marrow, but also by the amount of eosinophil apoptosis. Eosinophil apoptosis at the inflammatory site appears to be delayed when IL-5 is generated by neighboring cells, or, perhaps, this delay is due to autocrine production of this cytokine. Another means to suppress apoptosis is the disruption of death pathways. Many known anti-inflammatory drugs have the potential, either directly or indirectly, to influence the regulation of eosinophil apoptosis. The induction of apoptosis by drugs represents an efficient, non-inflammatory way to remove eosinophils from inflammatory sites. There are many urgent questions to be answered in the near future. For instance, what are the mechanisms that limit eosinophil accumulation by delayed apoptosis? How long do eosinophils act as effector cells in allergic inflammation when they do not undergo apoptosis? Which other death receptors (in addition to CD95) are expressed in eosinophils? What is their function? Which caspases play a role? What are the differences in the apoptosis regulation between eosinophils and neutrophils? How does a cell decide its outcome when it receives survival and death signals at the same time, a situation that probably occurs *in vivo*? Clearly, there is much more to learn about eosinophil apoptosis.

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