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Apoptosis in Psoriasis

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SUMMARY Apoptosis is a process of programmed cell death that maintains homeostasis of the skin. Apoptotic cell death regulates keratinocyte proliferation and formation of stratum corneum. The process by which keratinocytes undergo apoptosis is a multistep program mediated by binding of specific death ligands to death receptors or by the release of effector cell granules. Dysfunctional apoptosis has an important role in the development of several skin diseases. Psoriasis is a common chronic inflammatory skin disease characterized by hyperproliferation with incomplete differentiation of epidermal keratinocytes and decreased keratinocyte apoptosis. Psoriatic keratinocytes possess an enhanced ability to resist apoptosis, which might be one of the key pathogenetic mechanisms in psoriasis. In addition, psoriasis is nowadays also recognized as the most prevalent autoimmune disease resulting from aberrant activation of both innate and adaptive immunity. However, the role of cell cytotoxicity mediated by cytotoxic CD8+ T cells and NK cells in psoriasis is as yet unclear. Here, we review the role of different apoptotic pathways in psoriasis.

KEY WORDS: apoptosis, Bcl-2 family proteins, Fas/FasL, perforin, psoriasis

INTRODUCTION

Apoptosis is a unique process of programmed cell death that maintains homeostasis of the skin. Kerr *et al*. were the first to describe apoptosis as an active process morphologically characterized by cell shrinkage, nuclear condensation, cellular fragmentation and phagocytosis by neighboring macrophages and dendritic cells (1). Apoptosis plays a critical role in several physiologic functions such as cell deletion during embryonic development, balancing cell number in continuously renewing tissues, and immune system development (2). In the skin, apoptotic cell death regulates keratinocyte proliferation and formation of stratum corneum. Balance between cell death and cell proliferation maintains homeostasis of epidermal compartment (3). The gradients of antiapoptotic and apoptotic factors control the timing of apoptosis in the epidermis, thus regulating epidermal growth and differentiation. It seems that terminal differentiation of keratinocytes represents simply a special form of apoptosis (4).

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Apoptotic pathways relevant in keratinocyte apoptosis include several mechanisms. The "extrinsic" pathway is triggered by binding of Fas ligand (FasL) or tumor necrosis factor (TNF) to membrane death receptors that recruit adapter molecules leading to the activation of caspase-8 (2,5). The "intrinsic" pathway includes mitochondrial release of cytochrome *c* and along with the cofactor Apaf-1, the formation of an activated caspase-9 apoptosome (2,6). Mitochondria might also trigger apoptosis through the release of Smac/DIABLO blocking inhibitor of apoptosis (IAP) or by apoptosis-inducing factor (AIF) that mediates caspase-independent apoptosis (2). Finally, both pathways end in DNA cleavage followed by the formation of apoptotic bodies and phagocytosis by neighboring cells. Apoptosis is controlled by Bcl-2 family proteins of which some (Bcl-2, Bcl-x_L) may block apoptosis, whereas others (Bax, bak, Bid) stimulate apoptotic process (7).

Dysfunctional apoptosis has an important role in the development of several skin diseases (2,8). Some are characterized by increased keratinocyte apoptosis, e.g., toxic epidermal necrolysis or graft-versus-host disease, whereas others like non-melanoma skin cancers and psoriasis are associated with decreased apoptosis. It seems that diseases with increased apoptosis tend to be acute, whereas those characterized by decreased apoptosis are mostly chronic and associated with epidermal hyperplasia or hyperkeratosis (2).

PSORIASIS AND Bcl-2 FAMILY PROTEINS

Psoriasis is a common chronic inflammatory skin disease characterized by hyperproliferation and incomplete differentiation of epidermal keratinocytes (9). Psoriatic keratinocytes possess an enhanced ability to resist apoptosis, which might be one of the key pathogenetic mechanisms in psoriasis (10). However, up to now limited data exist regarding the underlying mechanisms of this defect in the apoptosis control mechanisms of psoriatic keratinocytes. As mentioned before, the process of apoptosis is controlled by Bcl-2 family proteins including several pro-apoptotic and anti-apoptotic proteins (11). Data regarding expression of Bcl-2 family proteins in psoriatic plaques are controversial. Some groups have reported an overexpression of Bcl-2 protein, whereas others observed no expression of anti-apoptotic Bcl-2 molecule in psoriatic epidermis (12,13). Takahashi *et al*. (14) found higher expression of Bcl-x_L and Bax proteins in psoriatic epidermis, as also reported by other authors (15,16). Tomkova *et al*. observed diffuse staining of pro-apoptotic Bax molecule in psoriatic lesions, however, along with significant overexpression of apoptosis suppressing Bcl-x_L (15). Therefore, additional studies are necessary to determine whether the psoriatic epidermis is in a pro-apoptotic or antiapoptotic status regarding the expression of Bcl-2 and Bax proteins in psoriasis. Data on the expression of anti-apoptotic Bcl-x_L protein showed its overexpression in all layers of psoriatic epidermis (10,14,17). It seems that up-regulation of Bcl-x_L molecule is at least partly responsible for the increased epidermal thickness, a hallmark of psoriasis. Moreover, psoriatic keratinocytes are extremely resistant to apoptosis compared with normal-skin derived keratinocytes (10). So, it has been suggested that overexpression of Bcl-x_L by psoriatic keratinocytes and their resistance to undergo apoptosis finally lead to epidermal acanthosis in psoriasis. It has been recently shown that tumor necrosis factor-α (TNF-α) stimulates the synthesis of anti-apoptotic Bcl-x and bcl-2 as well as pro-apoptotic Bax protein in psoriatic lesions (12,18). Having in mind the important role of TNF-α in psoriatic inflammatory cascade and the efficacy of anti-TNF treatment in psoriasis, it is likely that TNF-α influences the apoptotic process in psoriatic epidermis through changes in the intracellular Bax/Bcl-2 ratio. Delayed apoptosis of psoriatic keratinocytes and subsequent epidermal hyperplasia are partly due to an overexpression of keratinocyte-derived IL-15 cytokine and its receptor IL-15R in psoriatic epidermis (19). Cytokine IL-15 is also a potent chemoattractant like T cell and NK cell growth factor. It has a role in the influx and activation of neutrophils in psoriatic epidermis (19). So, it seems that keratinocyte-derived IL-15 is responsible for prolonged keratinocyte survival and also for T cell and neutrophil accumulation in psoriatic lesions.

The terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling (TUNEL) method is widely used for the detection of apoptotic cells (20). Most keratinocytes in psoriatic lesions are TUNEL-positive cells, however, without morphological evidence of apoptosis (13,21). Moreover, Laporte *et al*. observed a decreased number of apoptotic cells in psoriatic epidermis compared to normal one (21). Kawashima *et al*. report an increase of double-strand DNA breaks in psoriatic lesions as the result of active DNA replication but not apoptosis (17). Therefore, it is likely that abundant TUNEL-positive keratinocytes in psoriatic epidermis are rather proliferating than apoptotic cells.

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PSORIASIS AND PERFORIN/GRANZYME OR Fas/FasL APOPTOTIC MECHANISM

Psoriasis is nowadays also recognized as a T-cell mediated disease resulting from aberrant activation of both innate and adaptive immunity (22). The psoriatic inflammatory cascade is orchestrated by proinflammatory CD4+ T cells producing interferon-γ (Th1 cells) or interleukin-17 (Th17 cells) and cytotoxic CD8+ T cells (CTLs) producing Th1 cytokine pattern. In addition, it is also driven by activated keratinocytes that influence T cell activation and trafficking, as well as by activation of natural killer (NK) cells and natural killer-like T (NK-T) cells representing innate immunity (22). Recently, involvement of IL-17 and IL-22 in psoriasis has been also recognized. It is likely that the secretion of cytokines such as IL-22 and IL-17 could result in keratinocyte hyperproliferation, leading to psoriatic skin lesions (23). Apart from T-cells, certain subsets of dendritic cells (DCs) are found to be important in the orchestration of the disease process (24). Proinflammatory CD11c+ DCs, which produce TNF-α, are increased in psoriasis, whereas Langerhans cells from symptomless psoriatic skin show migratory defects (24-26). Moreover, psoriatic dermal DCs promote increased proliferation of autoreactive T cells and production of Th1 cytokines, IFN-γ and IL-2.

The role of cell cytotoxicity mediated by cytotoxic CD8+ T cells and NK cells in psoriasis is as yet unclear. CTLs and NK cells mediate apoptosis *via* the release of cell granules, perforin and granzymes, or by binding of ligands to their death receptors on target cells (27). Upon activation, CTLs and NK cells release perforin, a pore forming molecule, which enables entry of granzyme into the target cell in order to mediate DNA degradation (28). The importance of perforin-mediated cytotoxicity has been demonstrated in several autoimmune diseases and in some inflammatory skin diseases as well (29,30). We have previously reported on the systemic up-regulation of perforin molecule in the exacerbation phase of psoriasis that were mainly related to perforin-positive CD8+P+ cells, a subpopulation with cytotoxic potential and rapid killing cells (31). A similar situation was found in psoriatic lesions where we observed significant accumulation of perforin-positive cells in suprabasal epidermis in close contact with damaged keratinocytes (32). Yawalkar *et al*. also report on up-regulation of perforin and granzyme-B expression in psoriatic lesions (33). It is likely that perforin-positive T cells induce damage to adjacent keratinocytes subsequently triggering an injury response program and regenerative hyperplasia, a type of hyperplasia programmed in keratinocytes as an injury-repair response pathway (34,35). In addition to the established role for perforin as an effector molecule, it may also act as a regulatory molecule of the immune system (36). In the skin, CTLs might use perforin molecule to regulate antigen presentation by antigen presenting cells, which could result in persistence of the chronic immune system activation (36).

Apoptosis induced by CTLs may also be mediated by the Fas ligand (FasL) binding to Fas (CD95) on target cell (37). In addition, Fas expression on keratinocytes can be up-regulated by Th1 type cytokines that create a microenvironment typical for psoriasis (38). Several groups have reported overexpression of Fas in psoriatic epidermis, so it is likely that Th1 cytokines up-regulate Fas expression in psoriatic lesions (14). Data on FasL expression in psoriatic skin are controversial, as some groups report low FasL expression and the others observed an increase of FasL in all cell layers of psoriatic epidermis (39,40). However, it has been recently suggested that Fas/FasL signaling might induce an alternative pathway promoting the synthesis of inflammatory cytokines, TNF-α and IL-8 instead of apoptosis (41). Assuming the fact that psoriatic keratinocytes are relatively resistant to apoptosis, it is likely that elevated expression of Fas along with anti-apoptotic Bcl-x_L protein in psoriatic epidermis inhibit Fas-mediated apoptosis and induce proinflammatory TNF-α production by keratinocytes. Moreover, it is likely that Fas/FasL pathway is an essential early event in psoriasis induction (41).

In conclusion, all these findings clearly show the importance of apoptotic process in the development and maintenance of psoriatic lesions. Based on these observations, novel apoptosis-based therapies could be directed towards enhancement of apoptotic process in psoriasis.

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