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Mini-review

Bcl-2 family members: Essential players in skin cancer

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ABSTRACT

Skin cancer has reached epidemic proportions and is considered to be a direct consequence of ultraviolet (UV) radiation exposure. Excessive exposure of epidermal cells to UV results in apoptosis of irreparably damaged cells to avoid malignant transformation. The Bcl-2 family of proteins is emerging as a crucial regulator of epidermal homeostasis and cell's fate in the stressed skin. Not surprisingly, deregulation of Bcl-2 family members is also chiefly involved in skin carcinogenesis and response to cancer therapy.

Here we discuss the physiopathological role of epidermal Bcl-2 family members, their implications in skin carcinogenesis and as potential targets in cancer therapy.

1. Introduction: the skin and skin cancer

The skin consists of an outer squamous epithelium, the epidermis, and an inner connective tissue, the dermis (also containing pilosebaceous units, nails and sweat glands). The epidermis fulfils the crucial barrier function of the skin and undergoes continuous self-renewal due to mitotic activity of the stem cells in the basal layer that provide the new keratinocytes. The keratinocytes (the major cellular skin component constituting about 90–95% of the epidermis) complete a differentiation-induced cell death program (called cornification) while moving upward through the different epidermal layers to become the corneocytes in the outer layers of the epidermis, before they are shed from the skin [1,2] (Fig. 1).

In the epidermal layer, the keratinocytes reside in close contact and interact with the melanocytes, specialized pigment-producing cells, mainly derived from the neural crest. Melanocytes are able to survive considerable genotoxic stress, forming the so called 'epidermal melanin unit', whereby a constant, skin type-independent, ratio of keratinocytes to melanocytes is maintained (approx. 35:1) [3] (Fig. 1).

Malignant transformation of keratinocytes and melanocytes can respectively give rise to non-melanoma and melanoma skin cancer (Fig. 1). Squamous cell carcinoma (SCC; non-melanoma) and cutaneous malignant melanoma (CMM) are the most important malignant tumors of the skin. SCC is, together with basal cell carcinoma (BCC; non-melanoma), the most frequent cancer within the Caucasian population, while CMM is one of the deadliest human diseases showing the highest increase in incidence. The steep rising incidence of non-melanoma (SCC, BCC) and melanoma (CMM) skin cancer during the last decade is considered to be a direct consequence of the increased exposure to genotoxic and mutagenic UV radiation [4,5]. Although there is no doubt that long wave UVA (320–400 nm) can also contribute to skin cancer, most of the mutagenic and carcinogenic properties of sunlight have been attributed to UVB (290–320 nm) [6].

When a normal UVB exposed epidermal cell is too severely damaged and all repair systems have failed, this cell will undergo apoptosis. The importance of epidermal cell death after severe UVB exposure is to limit the survival of irreparably damaged cells, which often carry mutations in tumor-suppressor genes or proto-oncogenes that could be transmitted to their offspring. Therefore this UVB-induced epidermal stress response is considered to be an essential and final defense mechanism against skin carcinogenesis [7].

Interestingly, the Bcl-2 family of proteins has been shown to play an important role in both maintaining the epidermal homeostasis and regulating the epidermal UVB-induced apoptotic response.

Knowledge of these Bcl-2 family-mediated pathways is essential to understand how, from one hand, an epidermal cell is maintained and is protected against potential malignancy and how, on the other hand, skin cancer misuses/misleads these Bcl-2 family-mediated pathways for its own advantage. Such knowledge could provide us with much needed new targets for treatment.

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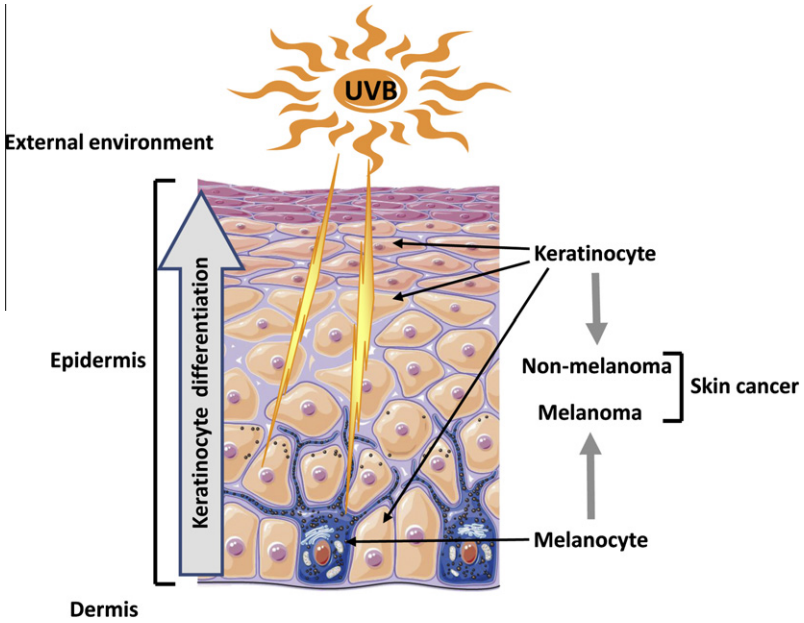

Fig. 1. Schematic representation of the human epidermis. The epidermis of the human skin mainly exists out of epithelial keratinocytes completing terminal differentiation, which reside in close contact with the pigment-producing melanocytes in the basal compartment. Following excessive UVB exposure, (non-)melanoma skin cancer may develop.

2. The Bcl-2 family: an overview of their role in cell death

The key role of apoptosis as a tumor suppressor mechanism is well illustrated by the relevance of a regulated apoptotic response in preventing carcinogenesis [8].

Two distinct pathways can lead to the activation of apoptosis. The extrinsic or death receptor pathway is mediated by ligand-dependent activation of death receptors (DRs) belonging to the tumor necrosis factor (TNF) receptor family. DR engagement leads to the formation of a death inducing signaling complex (DISC) that recruits initiator procaspase 8(/10) and triggers their dimerization-induced activation. Caspase 8 then activates the effector caspases (e.g. caspase 3/7), thereby committing the cells to apoptosis [9] (Fig. 2).

The intrinsic or mitochondrial pathway for caspase activation is engaged by the permeabilization of the outer mitochondrial membrane (MOMP) and the release of intermembrane proteins, such as cytochrome c, into the cytosol following a variety of cellular insults like reactive oxygen species (ROS) and DNA damage. In the cytosol the apoptotic protease activating factor-1 (Apaf-1), together with cytochrome c and (d)ATP, forms the apoptosome, a molecular platform for the recruitment and activation of procaspase 9. Subsequently, initiator caspase 9 directly cleaves and activates the effector caspases, resulting in the orchestration of the biochemical execution of the cell [10,11]. In addition, caspase 8 has been shown to cleave Bid, a member of the Bcl-2 family of proteins, generating tBid, a C-terminal fragment that engages the mitochondrial pathway (illustrating that mitochondria can function both as initiators or amplifiers of caspase activation) (Fig. 2).

At the level of integrity/permeability of the outer mitochondrial membrane, intrinsic apoptosis is crucially regulated by the interplay/balance of pro- and anti-apoptotic Bcl-2 family members. Consequently, the Bcl-2 family proteins play a pivotal role in determining whether a cell will live or die. They are found in the cytosol or localized in membranes of the mitochondria, the endoplasmic reticulum (ER) and nucleus. Although their overall amino acid homology is relatively low, all Bcl-2 family members possess at least one of the four highly conserved motifs known as Bcl-2 homology (BH) domains (BH1–BH4), which correspond to the α-helical segments that confer their specific structure and function (Fig. 2A).

Based on their structure and functional role the Bcl-2 family can be grouped into three classes (Fig. 2A). Whereas the multidomain members containing BH1 to 4 inhibit apoptosis (e.g. Bcl-2, Bcl-xL, Mcl-1), a second class promotes apoptosis (containing BH1 to 3; e.g. Bax, Bak). A final class, the pro-apoptotic BH3-only proteins (e.g. Bid, Bim, Noxa, Puma, BNIP3), are characterized by a conserved BH3 domain that can negatively regulate the anti-apoptotic Bcl-2 members. The pro-apoptotic family members Bax and Bak, either directly or indirectly, appear to be crucial for inducing MOMP and the resulting release of apoptotic molecules (e.g. cytochrome c), eventually leading to caspase activation. It is typically thought that Bax and Bak induce pores in membranes and are therefore strictly necessary for the induction of apoptosis. However, the molecular nature of such pores and how anti-apoptotic Bcl-2 family proteins might regulate them remains an unresolved question. Whereas it is clear that the anti-apoptotic proteins can directly inhibit Bax and Bak, the precise mechanism of action for BH3-only proteins is still controversial. On the one hand these BH3-onlies could de-repress Bax and Bak by binding to and inhibiting the anti-apoptotic family members. On the other hand direct activation of Bax and Bak by some BH3-only proteins (specifically Bim, tBid and Puma) has also been suggested [12] (Fig. 2B).

3. Bcl-2 family members in the skin

3.1. Mcl-1 and Bcl-2 as essential determinants of epidermal homeostasis

Thanks to or next to their key role in apoptosis, several members of the Bcl-2 family perform distinct functions in the epidermis. They have been shown to correlate with and also regulate general survival and/or differentiation of epidermal cells.

Especially the anti-apoptotic Mcl-1 has recently been illustrated to function as a major survival protein required for proper