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A B S T R A C T

Non-melanoma skin cancers (NMSC) are the most common malignant tumors in white population and their incidence has been increasing worldwide. Molecular events regulating cell survival, apoptosis, growth arrest as well as cell differentiation, are important contributors to the overall kinetics of benign and malignant cell growth and play a role in their development, progression and regression. Failure of these pathways can result in the loss of control over proliferation and lead to tumor development through the inactivation of tumor suppressor genes or the activation of oncogenes. Also, immunological mechanisms have been implicated in a phenomenon of tumor progression as well as spontaneous tumor regression. We have tried to summarize the main events in etiopatogenesis, development, progression and in some cases skin cancer regression. Further studies are needed to elucidate completely the details of apoptotic control in normal skin and determine factors resulting in apoptotic disbalance and disease.

Key words: *apoptosis, basal cell carcinoma, keratoacanthoma, squamous cell carcinoma*

Introduction

Skin tumors include malignant melanomas and non-melanoma cancers (NMSCs) that are neoplasms of epithelial origin such as basal cell carcinoma (BCC), keratoacanthoma (KA) and squamous cell carcinoma (SCC). NMSC are the most common malignant tumors in white population and incidence has been increasing at an astonishing rate over the past several decades worldwide[1]. Hundred years after its initial description, there is much controversy in the literature regarding whether KA is to be considered a variant of well-differentiated SCC or a separate entity[2]. In contrast to KA initial intensive growth and tendency to regress, SCC is characterized by locally destructive growth and tendency to metastases[2]. Occasionally, otherwise typical KA characterized by initial intensive growth and usually spontaneous regression, can behave aggressively showing the signs of perineural and perivascular invasion and form metastases in regional lymph nodes[2]. The most important feature that separates KA from SCC is a tendency of KA to regress but causes and detailed mechanism of this regression are still not completely elucidated.

It has become clear that molecular events regulating cell survival, apoptosis, growth arrest as well as cell differentiation, are important contributors to the overall kinetics of benign and malignant cell growth and play a role in development, progression and regression of benign and malignant cell growth[3,4]. Failure of these pathways can result in the loss of control over proliferation and lead to tumor development through the inactivation of tumor suppressor genes or the activation of oncogenes. Also, immunological mechanisms have been implicated in a phenomenon of tumor progression as well as spontaneous tumor regression[5,6].

UV Irradiation in Epidemiology of Non-Melanoma Skin Cancer

Ultraviolet (UV) irradiation can be both beneficial and harmful to normal human skin. The most important harmful effects of UV irradiation are immune suppression, photoaging and, the most importantly, skin carcino-

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genesis. It is well known that skin tumors result from co-carcinogenic effect of different factors such as UV light, irradiation, chemical carcinogens, genetic factors and oncogenic viruses[2,7–9]. Interaction of these factors with genetic predisposition in a certain individual can lead to skin cancer development.

Recent developments in molecular biology and research on laboratory animals have determined a central role of UV irradiation in the pathogenesis of NMSC. Majority of NMSC, 90% of SCCs[2,8,10], 85–90% of KAs[11] and 80% of BCCs[12], occur on sun-exposed skin. It is clear that wavelengths in UVB region of the solar spectrum are absorbed in the skin producing erythema, burns and eventually skin cancer. By contrast, UVA region cause not only ageing and wrinkling of the skin, but also skin cancer when given in high doses over a long period of time[13]. UVA, which is less potent than UVB, can trigger apoptosis through oxidative damage[14]. On the other hand, UVC as a more potent apoptotic stimulator than UVB and can damage cellular DNA, it is largely absorbed in the atmosphere and does not reach the Earth's surface.

UV irradiation in UVB region from 245 to 290 nm is maximally absorbed by DNA inducing mutagenic photoproducts or lesions in DNA between adjacent pyrimidine residues in the form of dimmers[10]. If not repaired, UV-induced DNA lesions can lead to mutations in the DNA sequences[10]. These mutations are in the form of C to T and CC to TT transitions, known as UV »signature« mutations.

DNA Repair Mechanisms

Cells are equipped with several DNA repair systems that are able to protect the cell from the effects of DNA-damage factors. These pathways include photoreactivation, base excision repair, mismatch repair, double-stranded break repair and nucleotide excision repair (NER) that removes bulky DNA damage. UV-induced DNA damage is primarily repaired by NER. Defects in NER can lead to three distinct human diseases: xeroderma pigmentosum, Cockayne syndrom and trichothiodystrophy; among these xeroderma pignentosum patients exhibit predisposition to skin cancer and photosensitivity[15]. These patients have a more than 1000-fold increased risk of skin cancer. Basal and squamous cell carcinomas and less frequently melanomas appear almost exclusively in sun-exposed areas.

Major Pathways of Apoptosis

Apoptosis is active, genetically controlled process of programmed cell death leading to cell destruction with no involvement of surrounding cells or inflammatory response[16,17]. The balance between apoptosis, proliferation and differentiation is responsible for maintaining of tissue homeostasis, also keratinocyte differentiation is considered a type of apoptosis[16,17]. Alterations in apoptotic process have been implicated in many skin diseases[16,17].

Bcl-2 family proteins play a central role in controlling the intrinsic pathway, triggered by most cytotoxic drugs and DNA damage, which involves mitochondrial release of cytochrome c, which combines with the cofactor Apaf-1 (ced-4 homoloque) in the formation of activated caspase-9 »apoptosome«. Mitochondria may also promote apoptosis through release of Smac/DIABLO, which blocks inhibitor of apoptosis (IAP), and apoptosis inducing factor (AIF) responsible for caspase-independent apoptosis. Release of different pro-apotptotic factors is regulated by Bcl-2 family proteins able to form homodimers and heterodimers controlling mitochondrial membrane permeability[17]. Some Bcl-2 family proteins (bcl-2, bcl-x) block apoptosis while others (Bak, Bax, Bid) promote apoptosis. The intrinsic and extrinsic pathways are linked in an amplification loop by Bid protein, cleaved by caspase-8 to fragment (tBid), which translocates to the mitochondria and triggers cytochrome-c release and activation of caspase-9. Activation of either of these upstream caspases leads to activation of terminal caspase-3 and caspase-7 leading to cell death[17].

The balance between pro-apoptotic and anti-apoptotic proteins has been shown to be disturbed in skin tumors with pro-apoptotic proteins being reduced and anti-apoptotic proteins being increased. Studies have detected decreased expression of pro-apoptotic bak and bax in BCC and SCCand increased in KA[4,18–20]. On the other hand anti-apoptotic bcl-2 and bcl-x_L proteins expression were found to be decreased or unaltered in SCC and actinic keratosis and increased in BCC[3,4,20].

The extrinsic pathway is stimulated by binding of death ligands such as Fas ligand (Fas-L) and tumor necrosis factor (TNF) to extracellular membrane »death receptor« that recruit adapter molecules and leads to activation of caspase-8, an subsequently a proteolytic cascade. Fas expression is weak in SCC and BCC that strongly express FasL[21–23]. On the other hand KA has been shown to consistently express high levels of Fas[21].

Apoptosis Induced by UV Irradiation

Skin cells have the ability to repair UV-induced DNA damage preventing skin carcinogenesis. Apoptosis of cells damaged by UV irradiation is partly mediated by tumor suppressor protein p53. Protein p53 is a well-described tumor suppressor that has a central role in the initiation of apoptosis and in cell cycle control[24,25]. Following acute UV light irradiation activation of p53 protein can arrest cell cycle at the G1 phase allowing extra time for DNA repair or induces apoptosis of significantly damaged cells. P53 protein protective function against UV-light induced skin tumors is clearly determined in mice models. On the other hand insufficient pre-carcinogenic effect of clonal patches of p53-mutated keratinocytes[10] suggests importance of p53-dependent and p53-independent mechanisms in process of UV-light induced carcinogenesis[19].

Acute sun exposure mainly results in formation of apoptotic cells, called sun-burn cells, in the epidermis

while chronic sun exposure leads to accumulation of p53 gene mutations[8,10,24,25]. In contrast to acute chronic sun exposure results in p53 gene mutation, p53 protein stabilization and its increased expression as detected in actinic keratosis, Mb. Bowen, SCC, KA and sun exposed normal skin[4,26]. p53 gene mutation results in loss of protective functions and development of pro-oncogenic functions leading to uncontrolled cell proliferation and disability of cells to undergo apoptosis. Thus, resistance to cell death is a key event in photocarcinogenesis and conversely, elimination of cells containing excessive UV-induced DNA damage is a key step in protecting against skin cancer development. Its critical role in maintaining integrity of human genome is evident, because p53 is the most commonly altered gene in human cancer (around 50% of human cancers) especially in NMSC[3,25,26] and in the majority of others its activity is blocked by increased expression of different inhibitor or decreased activity of co-activators[24]. p53 protein can induce apoptosis through transcriptional and non-transcriptional mechanisms. p53 tumor suppressor protein can influence both major pathways of apoptosis, intrinsic and extrinsic[24,27]. p53 protein regulates apoptosis by disturbing the balance between pro-apoptotic and anti-apoptotic Bcl-2 family proteins, up-regulating the Bak and Bax gene and down-regulating the Bcl-2 gene transcription. p53 also induces apoptosis stimulating transcription of Fas and TRAIL-R genes by binding to their transcriptional activation site[28]. It promotes the redistribution of cytoplasmic Fas to the cell surface. Recent studies have shown that UV-induced formation and »sun burn« cells are mediated by p53 signaling through the Fas death receptor, which rapidly clusters following UVB exposure[19]. Studies on mice models confirmed that FasL-mediated apoptosis is involved in sun-burn cell formation since it is reduced in mice deficient in Fas-L[28].

UVB induces expression of multiple genes in keratinocytes but also activation of pre-synthesized proteins. Recently it has been shown that proapoptotic proteins bak and bax also contribute to apoptosis following UV exposure[30]. These proteins are expressed in healthy keratinocytes[18,20] but are significantly up-regulated following UV exposure[30].

Although, UV exposure induces expression of different genes important for activation of apoptosis, recent studies have shown that UV irradiation also rapidly activates the epidermal growth factor receptor (EGFR) which is highly mitogenic. Activation of EGFR favors keratinocytes proliferation and suppresses apoptosis, leading to epidermal hyperplasia[31].

Other Factors Contributing to Skin Cancer Development

Other factors, besides UV light, significantly contribute to the development of skin cancer especially in those tumors developing in sun non-exposed areas. Newer studies showed the importance of co-carcinogenic effect of Human papilloma viruses (HPV) and UV light mainly through blockage of apoptosis. As mentioned earlier UV light exposure leads to increased expression of p53 and pro-apoptotic bak proteins that can than activate apoptosis or result in cell cycle arrest. In the cells with mutated p53 as in majority of skin cancers, bak protein can activate apoptosis in p53-independent manner. Studies have shown decreased expression of pro-apoptotic proteins bak and bax in skin tumors, such as BCC and SCC, and increased expression in KA[4,18–20]. It has been shown that E6 protein HPV targets bak for degradation decreasing its expression in the cell and blocking UV-light induced apoptosis[19,30] favoring uncontrolled cell proliferation and tumor progression. Decreased bak expression has been shown to correlate with worst tumor differentiation and HPV positivity[4,19,30].

Immunosupression, especially following transplantation, significantly increases risk for development of skin cancers[32]. Increased incidence of skin cancer in immunosupressed individuals is suggested to be the result of co-carcinogenic effect of UV irradiation, through p53 gene mutation, and HPV[19,30,32]. Significantly higher incidence of different HPV types was detected in SCCs (80% positive tumors) in immunodeficient individuals as compared to imunocompetent patients (30% positive SCCs)[33].

Other physical factors such as irradiation and thermal exposure as well as chemical carcinogens can contribute to skin cancer development[26,34]. Skin cancers also develop more often in chronic skin wound, on the site of chronic trauma, chronic inflammation, degenerative skin changes and different scars[26,35].

UV-induced Immune Suppression Contributes to Skin Cancer Development and Progression

UV irradiation affects skin immune system. The skin contains Langerhans cells that serve as antigen-presenting cells and serve to communicate with T cells. Also, keratinocytes produce several cytokines that have a role in immune recognition in the skin. These cells, together with the regional draining lymph nodes, are labeled »skin-associated lymphoid tissues« (SALT). UV irradiation alters the morphology Langerhans cells, down-regulates the expression of major histocompatibility complex class II antigens on their surface and alters the cell-surface expression of co-stimulatory molecules and intracellular cell adhesion molecule 1. These changes block the initiation of immune response. On the other, the suppressive pathway is activated through formation of suppressor T-cells[36]. Keratinocytes also release various cytokines following UV irradiation, including interleukin 1 (IL-1), IL-4, IL-6, IL-10 and tumor necrosis factor alpha (TNF-a)[36]. It has been shown that IL-10 has a central role in the induction of both local and systemic immunosuppression following UV irradiation. It has been shown that UV irradiation induces suppression of contact hypersensitivity and delayed-type hypersensitivity what could favor development and growth of skin cancer.

Anti-Tumor Immune Response and Tumor Escape Mechanisms in Skin Cancer

Significance of the immune response in the control of cutaneous SCC and KA is evident by increased risk of development of cutaneous SCC in immunosuppressed individuals[32] as well as T-cell infiltration within the lesions of patients with cutaneous SCC and KA[2,22,37,38]. The role of T cells in anti-tumor immunity is well established, however, a tumor progression, often seen in the presence of substantial lymphocyte infiltration, suggests that these T cells are not capable of mounting an effective immune response to control tumor growth[38]. Failure of tumor-infiltrating lymphocytes to intervene and control tumor growth is thought to be associated with signaling dysfunction[38], spontaneous apoptosis of circulating[37–39] and tumor-infiltrating T lymphocytes[22,38].

The immune system exerts its anti-tumor surveillance and regression mainly through cell death induced by cytotoxic CD8+ T lymphocytes (CTLs) and natural killer (NK) cells supported by CD4+ T cells[40,41]. CTLs can kill tumor cells and mediate tumor regression *in vivo* through two distinct molecular mechanisms: one through direct exocytosis of granules containing granzyme B and perforin, and the other based on the binding of the CD95 (Fas) receptor on target cells[40,41]. Although it has been suggested that in some tumors the FasL/Fas pathway is important for optimal tumor regression[40], tumor cells are capable of developing different escape mechanisms in order to overcome their sensitivity to apoptotic signals[41]. CTLs may circumvent tumor resistance to Fas/FasL-induced death via granzyme-mediated apoptosis[42].

In the granzyme-mediated pathway, secreted lytic protein perforin is believed to produce pores in the target cell's membrane and granzymes penetrate targeted cell through these pores consequently inducing apoptosis[41,42]. Other authors suggest that granzyme B, serine protease, can be internalized into target cells independently of perforin by receptor-mediated endocytosis[36]. Once delivered to the cytoplasm, granzyme B can induce apoptosis in a few different pathways but it mainly utilizes mitochondrial pathway[41]. Also granzyme B can bypass mitochondria and cytochrome c release, by direct activation of effector caspases and direct damage of non-nuclear structures, such as mitochondria, in caspase-independent pathways[41,43]. Ability of granzyme B to bypass caspase cascade and to activate apoptotic pathway at multiple entry points is important, because of tumors capability to develop different selective defects in the intracellular signaling and caspase cascade leading to their resistance to apoptotic stimuli[41]. It has been shown that granzyme B/perforin pathway can kill tumor cells *in vitro* and is able to induce apoptosis in multiple-drug-resistant and death-receptor resistant cell lines[44], although some studies suggested that tumors can resist granzyme-mediated killing through overexpression of the protease inhibitor PI-9/SPI-6 (serpin) [45].

Tumor cells are capable of developing different escape mechanisms in order to overcome their sensitivity to apoptotic signals[41]. SCC can escape Fas/FasL mediated killing by down-regulating Fas expression on the cell surface[21], and mediate killing of infiltrating T lymphocytes by expressing FasL on their surface[38,40,43,46]. On the other hand KAs have been shown to consistently express high levels of Fas at the interface with the inflammatory cells, being susceptible to T-cell mediated apoptosis contributing to tumor regression[21].

Recent studies suggested significance of the intensity of inflammatory infiltrate, the number of cytotoxic CD8+ T cells and increased cytotoxic activity as determined by granzyme B expression in skin tumors growth and regression control[6,47]. Granzyme B expression has been found to be significantly increased in KAs as compared with SCCs and was suggested to contribute to KA regression[6]. Even though CD8+ cytotoxic T lymphocytes appear to be critical for causing tumor regression, it has been suggested that the quantity of these cells alone is not sufficient[38].

Accumulating evidence suggests that T lymphocytes infiltrating human neoplasms are functionally defective, incompletely activated or anergic. Recent studies suggest that tumor regression and anti-tumor protective response depends mainly on immune response mediated by cytotoxic CD8+ T lymphocytes supported by CD4+ T cells producing IFN-gamma[33]. T helper type 1 (Th1) $CD4^+$ anti-tumor T cell secreting IFN-gamma appears crucial to the optimal induction and maintenance of durable anti-tumor CTL responses *in vivo* and may serve to recruit these effector cells into the tumor microenvironment via delayed-type hypersensitivity responses[48]. In contrast, T helper type 2 (Th2) or T helper type 3 (Th3) $CD4^+$ T cell responses may subvert Th1-type cell-mediated immunity, providing a microenvironment conducive to disease progression. Studies on melanoma model have detected a gradual shift of initial Th0-type, mixed Th1-/Th2-type $CD4^+$ T cell response to Th2-type dominated responses with progressive tumor growth[49]. It has been shown that tumor infiltrating lymphocytes in patients with spontaneous and therapeutically induced regressing lesions appear to be characterized by dominant Th1-type responses to mitogens, whereas tumor infiltrating lymphocytes from patients with progressing lesions have been reported to exhibit functionally dominant Th2-type (IL-4, IL-5) and/or Th3-/Tr-type (IL-10, TGF-ß1) $CD4^+$ T cell responses[50].

Apoptosis of tumor infiltrating T lymphocytes observed *in situ* was suggested to be related to expression of FasL and perhaps other death-related molecules on the tumor cell surface since immunostaining indicated that FasL+ tumors were often infiltrated by Fas+ lymphocytes, many showing evidence of apoptosis[22,37,38]. Apoptosis of tumor infiltrating T cells can result in decreased T cell density favoring tumor progression[22,37,38]. Previously described presence of the unusual CD3+ CD4-CD8- phenotype attributed to apoptosis[51] of tumor infiltrating lymphocytes in strong FasL expressing tumors, such as SCC and BCC[23], has been detected in rare cases of KAs and majority of SCCs[38].

Role of Telomerase in Skin Cancer

Telomeres are specialized structures at the ends of eukaryotic chromosomes that play a central role in chromosome protection, positioning and replication. Telomerase is a ribonucleoprotein reverse transcriptase that synthesizes telomeric DNA onto chromosomal ends protecting chromosomes from degradation. As the normal cell divides, there is a corresponding shortening of telomeres, thus acting as mitotic clock by which cells count their divisions. Finally, chromosomes reach a critical length at which cell division ceases, senescence begins, and the cell ultimately undergoes apoptosis or cell death[52,53]. Telomerase activity presents a critical step in tumorigenesis because it overcomes the limitations of catastrophic telomere loss and is actually present in more than 80% of human cancer including skin cancers[53,54,55]. Telomerase activity is detectable in germline cells, somatic cells during fetal development, germinal centers of lymph nodes, regenerative epithelium of the gastrointestinal tract, proliferative endometrium, the bulge region of hair follicles, and stem cells of epidermis[56–59]. Studies have shown that sun-damaged skin has a higher telomerase activity than sun-protected areas, although much less than that detected in non-melanoma and melanoma skin tumors, suggesting that environmental factors may modulate telomerase expression[60]. Increased telomerase activity has been suggested to correlate with the progression of benign melanocytic through dysplastic lesion to malignant melanoma[55]. The significant role of telomerase in skin cancer development and progression is evident in significantly higher activity detected in SCC as compared to KA[61].

Future Challenges and Directions

In the past thirty years since first description of apoptosis, intense studies acquired significant understanding of the molecular controls and biochemical processes involved in programmed sell death in healthy skin and various skin diseases. The role of keratinocyte apoptosis is better understood in epidermal development. Further studies should be directed toward unraveling completely the details of apoptotic control in normal skin and further understanding of factors resulting in apoptotic disbalance and disease. Also, there is a need for further research to study the molecular mechanisms involved in tumor regression, spontaneous and therapy induced. The new knowledge should be used in development of new apoptosis-based therapeutics, directed toward protection of keratinocytes, in diseases characterized by intense cell death, or enhancement of apoptosis, in diseases characterized by impaired cell death. Although a wide range of inflammatory and hyperkeratotic diseases might be treated with apoptosis-based therapies, there appears to be the greatest interest in developing agents for cancers therapy.

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APOPTOZA U NASTANKU I REGRESIJI TUMORA KOŽE

S A Ž E T A K

Epitelni tumori kože najčešći su tumori bijele populacije i njihova je incidencija u konstantnom porastu u svijetu. Molekularni mehanizmi bitni u regulaciji preživljavanja, apoptoze, zaustavljanja rasta i diferencijacije stanica doprinose kinetici rasta stanica, te imaju središnju ulogu u nastanku, progresiji i regresiji benignih i malignih tumora kože. Neadekvatna funkcija ovih mehanizama može uzrokovati gubitak kontrole proliferacije stanica uz posljedični razvoj tumora inaktivacijom tumor-supresorskih gena ili aktivacijom onkogena. Imunološki mehanizmi, također, imaju bitnu ulogu u procesu progresije i regresije tumora. U radu su sažeto prikazana osnovna zbivanja bitna u etiopatogenezi, razvoju, progresiji, te ponekad spontanoj regresiji tumora kože. Dodatne studije potrebne su kako bi se u potpunosti razjasnio kompleksan proces programirane smrti stanice u zdravom tkivu i utvrdili čimbenici koji uzrokuju poremećaje ovog procesa i maligni rast stanica.