Regulation of Apoptotic and Necroptotic Cell Death in Skin Cancer

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Abstract

Cell death is defined by different factors ranging from default in functional properties, changes in morphological appearance and loss in immunological characteristics among so many others. These are brought about by accidental and programmed processes of cell death. Apoptosis, and the more recently discovered necroptosis, are two avenues of programmed cell death. Cancer cells survive by evading these two programs, driven by oncogenes and tumor suppressor genes.

A vast knowledge and advancement on the regulation of apoptosis and necrosis is needed for a functional approach in pathological condition. In the last decade, researches have revealed that novel therapies against melanoma have allowed for a prolonged survival rate of malignant melanoma while not allowing for a cure because of its aggressiveness and death resistance.

In this review, the implications and insights into the signaling networks involved in the regulation of programmed cell death for the diagnosis or treatment of skin cancer will be brought to foresight.

INTRODUCTION

Melanomas are malignant neoplasms arising from melanocytes, which originate from the neural crest cells [1]. Although primary melanoma develops occasionally in other organs, the most common site of involvement is the skin. The other organs are (eye, oral and nasal mucosa, vulval and anorectal mucosa, other gastrointestinal mucosa and the central nervous system). Malignant melanoma is the third most common skin malignancy. It comprises of only 3 to 5% of all cutaneous malignancies [2]. Melanomas are a major cause of premature death from cancer. Recognized associated risk factors include personal or family history of melanoma, large numbers of naevi and/or dysplastic naevi, giant congenital melanocytic naevi, fair complexion, a tendency to sunburn, solar-damaged skin, a history of non-melanoma skin cancer, and immunodeficiency [3].

Cell death represents a key physiological process that is critical for maintaining tissue homeostasis, since a tight balance between cell growth on one side and cell death on the other side is pivotal for various functions in our body [4]. Since there exist a variety of subroutines which finally can lead to cell death in mammalian cells. In addition, these processes and mechanisms are evolutionary highly conserved across species, ranging from yeast, flies, and worms to mammals and humans, underscoring the importance of these basic cellular mechanisms for multicellular organisms. As far as programmed cell death is concerned, distinct modes can be distinguished [5]. Among them, apoptosis has been identified decades ago and has since then been characterized in numerous studies [6]. Programmed cell death is defined as regulated cell death mediated by an intracellular program. Apoptosis was originally thought to be the only form of programmed cell death. However, in the last decade, programmed cell death has expanded to include autophagy and a form of necrosis termed necroptosis (programmed necrosis). Programmed cell death, especially apoptosis and necroptosis, are natural barriers that restrict malignant cells from surviving and disseminating. However, cancer cells have evolved various strategies to evade programmed cell death by generating genetic mutations or epigenetic modifications in the key modulators of programmed cell death pathways [7]. Besides apoptosis, necroptosis has more recently been discovered as another form of regulated cell death. Necroptosis plays a crucial role during normal development and has also been implicated in the pathogenesis of a variety of human diseases. The control of necroptosis by defined signal transduction pathways offers the opportunity to target this cellular process for therapeutic purposes. For example, in cancer necroptosis is often impaired during tumorigenesis and can be engaged by targeted pharmacological approaches. Therefore, in

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this review, the summary of the implications and insights into the signaling networks involved in the regulation of programmed cell death for the diagnosis or treatment of skin cancer will be brought to foresight.

UVs

The center of this confusion is the sun’s ultraviolet A (long-wave) and ultraviolet B (shortwave) rays. Our understanding of exactly what kinds of damage each causes to the skin, and how best to protect ourselves, seems to shift every year as new research comes out. For example, it was once thought that only UVB was of concern, but we keep learning more and more about the damage caused by UVA [8].

UV radiation is one of the electromagnetic spectrum that reaches the earth from the sun (Figure 1) [9]. It has wavelengths shorter than visible light, making it invisible to the naked eye. These wavelengths are classified as UVA, UVB, or UVC, with UVA the longest of the three at 320-400 nanometers (nm, or billionths of a meter). UVA is further divided into two wave ranges, UVA I, which measures 340-400 nanometers (nm, or billionths of a meter), and UVA II which extends from 320-340 nanometers. UVB ranges from 290 to 320 nm. With even shorter rays, most UVC is absorbed by the ozone layer and does not reach the earth.

Both UVA and UVB, however, penetrate the atmosphere and play an important role in conditions such as premature skin aging, eye damage (including cataracts), and skin cancers (Figure 2) [10]. They also suppress the immune system, reducing your ability to fight off these and other maladies [11].

By damaging the skin’s cellular DNA, excessive UV radiation produces genetic mutations that can lead to skin cancer [12]. The U.S. Department of Health and Human Services and the World Health Organization have identified UV as a proven human carcinogen [13]. UV radiation is considered the main cause of non-melanoma skin cancers (NMSC), including basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [14].

UVA rays account for up to 95 percent of the UV radiation reaching the Earth’s surface [14]. Although they are less intense than UVB, UVA rays are 30 to 50 times more prevalent [15]. They are present with relatively equal intensity during all daylight hours throughout the year, and can penetrate clouds and glass.

UVB, the chief cause of skin reddening and sunburn, tends to damage the skin’s more superficial epidermal layers. It plays a key role in the development of skin cancer and a contributory role in tanning and photo aging. Its intensity varies by season, location, and time of day. The most significant amount of UBV hits the U.S. between 10 AM and 4 PM from April to October. However, UVB rays can burn and damage your skin year-round, especially at high altitudes and on reflective surfaces such as snow or ice, which bounce back up to 80 percent of the rays so that they hit the skin twice. UVB rays do not significantly penetrate glass.

SKIN CANCER

There are three most common types of human skin cancers: basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and malignant melanoma. In all of skin cancers, malignant melanoma is the most aggressive and fatal form. With the low overall 5-year survival rate, incidence of malignant melanoma continues to increase worldwide [16].

In 2012, it was reported that skin melanoma was the 19th most incident type of cancer in the world (232,000 new cases) and the seventh in the EU-27 (82,000 new cases) accounting for 2% the total number of cancer [17,18]. The fundamental knowledge and understanding of carcinogenesis of the skin due to the trend of occurrence can greatly help in the discovery of effective therapies against skin cancer.

The majority of melanomas (70%) arise de novo in normal skin [19]. A smaller percentage (30%) arises within a pre-existing acquired naevus or a congenital naevus [19]. Under the normal condition, melanocytes produce melanin which is then transferred to neighboring keratinocytes to protect skin from ultraviolet radiation (UV)-caused damage. Abnormal melanocytes resulted from mutations initially develop into pigmented lesions and further transform into dysplastic nevi [20]. Uncontrollably melanocytes of dysplastic nevi lead to an in situ melanoma that is mostly confined to the epidermis, which is referred as radial
growth phase (RGP) of melanoma. If RGR melanoma is not treated immediately, it acquires the metastatic potential during the vertical growth phase (VGP) to invade to dermis and further lung, bone or brain [21]. Rapid division and impaired ability to undergo programmed cell death in response to a wide range of external stimuli allow melanomas a selective advantage for progression and metastasis as well as their notorious resistance to therapy. Typical features of normal and tumour cells offer us with extensive comprehension of melanoma and improvements for melanoma treatments and therapies without injuring normal cells.

**RISK FACTORS FOR MELANOMA**

**Environmental factors**

Sun exposure, as the main source of UV rays, is the major environmental risk factor for melanoma. UVB (280-320 nm) is proposed to be the most carcinogenic waveband, which can be absorbed by nucleic acids and proteins respectively. UVB radiation mainly leads to C-T or CC-TT transitions and minor C-A and G-T transversions as genetic mutations. Although, melanocyte stem cells generate mature melanocytes that produce melanin, which absorbs ultraviolet (UV) light to prevent DNA damage and gives skin and hair their distinctive colors [22], persistent exposure to UVR also increased DNA damaged lesions and mutations and led to premature aging or carcinogenesis of the skin [23]. In addition to UV rays exposure, contact with environmental carcinogenetic chemicals, including polycyclic aromatic hydrocarbons, benzene, polychlorinated biphenyls and chromium, is able to induce melanoma. Production of reactive oxygen species (ROS), endocrine disruption and immune suppression are also regarded as the potential inducer for melanoma [24-26].

**Host factors**

This refer to pigmentation characteristics of nevi, eyes, skin, hair, colors and also the ability to tan and propensity to burn on individual basis. An analysis of 10 cases controlled studies supported that both fair skin and degree of freckling were associated with increased risk of developing melanoma [27]. In brief, incidences of melanoma are reversely correlated with extent of skin pigmentation.

**Germline genetic factors**

Familial history of melanoma is an alternative useful predictor for melanoma incidence. Sharing the certain germline genetic alterations is the main reason for the occurrence of melanoma in a family setting. Familial genetic linkage studies have identified CDKN2A and CDK4 as high-penetrance susceptibility genes for melanoma. Germline mutations of these genes render an increasing risk of melanoma occurrences [28-31]. With the development of gene screening techniques, the discovery germline genetic mutations of melanoma will help the early prediction and effective treatment for melanoma.

**PROGRAMMED CELL DEATH IN CANCER**

Apoptosis represents one of the best characterized modes of cell death that is highly conserved throughout evolution and involved in the regulation of various physiological conditions (Figure 3). In addition, there is a huge body of evidence demonstrating that deregulation of apoptosis contributes to various human diseases [4]. For example, too little apoptosis can promote tumor formation and progression and also plays a critical role in conferring treatment resistance [33]. Necroptosis has recently been identified as a regulated, caspase-independent mode of cell death. In contrast to necrosis that represents an accidental form of cell death, necroptosis is classified as a programmed form of necrosis that is often engaged under conditions of insufficient caspase activation [34]. Recently, necroptosis has been reported as an alternative cell death program that is triggered in apoptosis-resistant acute leukemia cells that lack FADD or caspase-8, [4] indicating that necroptosis may provide a new approach to overcome apoptosis resistance. Autophagic cell death is characterized by the dependence on autophagy genes for its execution along with typical morphological features such as cytoplasmic vacuolization [35].

Death receptors are part of the superfamily of tumor necrosis factor (TNF) receptors, a large family of transmembrane receptors that exhibit a broad spectrum of biological activities, including the control of programmed cell death and immune functions [36]. As far as the induction of cell death is concerned, two death receptor systems have been best characterized, i.e., the CD95 (APO-1/Fas) system and the TNF-related apoptosis-inducing ligand (TRAIL) receptor system. Both receptor systems comprise transmembrane cell surface receptors that harbor the intracellular death domain and a cysteine-rich extracellular domain that serves for binding of cognate ligands [37].

![Figure 3](image3.png) Types of cell death and their morphological hallmarks. Diagrammatic classification of different types of cell death. PCD: Programmed Cell Death. Morphological features of a) a healthy cell, b) a necrotic cell, c) an apoptotic cell and d) an autophagic cell. (Electron micrograph pictures adapted from Kroemer et al. [32].)
TRAIL has been shown to be involved in the regulation of immune-regulatory functions and immune surveillance of tumors and metastasis. Results derived from studies using TRAIL knockout mice have shown that TRAIL exerts a crucial role in tumor immune surveillance [31,38]. Of note, lack of TRAIL or its receptors was shown to be associated with increased susceptibility to tumor metastasis compared to wild-type animals [31,38]. Furthermore, TRAIL expression on NK cells was reported to restrain metastatic spread of tumor cells [39].

In addition, the TRAIL system has been implicated in the regulation of carcinogenesis. To this end, it was shown that carcinogenesis triggered cancer formation was increased in mice lacking the TRAIL-R or in the presence of antagonistic TRAIL-R antibodies [31]. These studies imply that the TRAIL-R/ligand system plays an important role in the regulation of tumor immune surveillance during both tumor formation and progression. Thus, resistance to TRAIL-induced apoptosis may favor tumor immune escape [36] (Figure 4).

**APOTOPSIS**

Apoptosis was first used to describe a form of cell death morphologically distinct from necrosis [41]. Apoptosis is understood to be a regulated energy-dependent process mediated via cysteine-dependent aspartate-directed enzymes called caspases [42]. Apoptosis is a homeostatic process that balances cell numbers and plays a crucial role in several physiological processes including embryogenesis to shape morphological structures such as fingers, in the establishment of functional synaptic connections in the nervous system, in development of the immune response to remove self-reactive lymphocytes and at the termination of the immune response to remove antigen-specific lymphocytes. Also, it is used to rid the body of cells in various pathological conditions such as removal of cancerous cells, infected cells or cells damaged by noxious agents [43].

**MOLECULAR COMPONENTS AND SIGNALING PATHWAYS OF APOPTOSIS**

In the cytoplasm of the cell, apoptosis is mediated through caspases as pro-enzymes and when activated initiate a proteolytic cascade that results in apoptosis of the cell [44]. There are three activation pathways that can initiate apoptosis: the extrinsic (death receptor) pathway, the intrinsic (mitochondrial) pathway and the granzyme pathway (Figure 5). There are about 14 known caspases which are divided into initiator and effector caspases. Initiator caspases, caspases 8, 9 and 10, are triggered by either the extrinsic, intrinsic or granzyme pathway, respectively. All three pathways converge on caspase 3, which activates effector caspases 6 and 7 that lead to apoptosis. A major target of effector caspases is poly-ADP-ribose polymerase (PARP) which is involved in DNA repair, cell survival, proliferation and differentiation [46].

**DEFECTS IN CELL DEATH PATHWAYS IN HUMAN CANCERS**

A hallmark of human cancers is their tendency to evade programmed cell death, since the ability to resist the induction of cell death provides a survival advantage to malignant cells [47]. On theoretical grounds, resistance to programmed cell death can be caused by loss of expression or function of proapoptotic molecules and/or by aberrantly high expression levels of proteins that inhibit programmed cell death [42].

**MECHANISMS OF RESISTANCE TO CELL DEATH**

Death receptor-induced apoptosis may be blocked by downregulation of surface expression levels of death receptors,
including CD95 and TRAIL-Rs [47]. Also, mutational inactivation of death receptors can contribute to the resistance to death receptor-mediated apoptosis [48]. In addition, the chromosomal region on chromosome 8p which harbors the genetic localization of both agonistic TRAIL-Rs is frequently inactivated in human cancers via loss of heterozygosity (LOH) [49]. In addition to mutational inactivation of death receptors, epigenetic events can also contribute to silencing of death receptor expression levels. CD95 as well as TRAIL-Rs have been reported to be among the targets of epigenetic silencing via hypermethylation of CpG island-rich regions of the promoters of CD95 or TRAIL-Rs [50]. Besides death receptors, also the initiator caspase caspase-8 is often epigenetically inactivated in human cancers, which similarly confers resistance to receptor-mediated apoptosis [51].

Furthermore, death receptor-mediated apoptosis can be impaired by a splice variant of caspase-8, i.e., caspase-8L. This caspase-8 variant is produced via alternative splicing and blocks death receptor-induced apoptosis in a dominant-negative manner. Death receptor-triggered programmed cell death can also be blocked via aberrant up regulation of anti apoptotic proteins.

Over expression of the anti apoptotic Bcl-2 proteins such as Bcl-2, Bcl-XL, and Mcl-1 frequently occurs in human malignancies, whereas the proapoptotic family members are downregulated or inactivated. For example, somatic mutations of the Bax gene have been reported in colon carcinoma or hematological malignancies [52].

IAP proteins represent another family of antiapoptotic proteins that negatively regulate signal transduction to programmed cell death. IAP proteins are expressed at high levels in various human cancers and have been correlated with resistance to cell death and poor prognosis. Among the IAP proteins, it is in particular X-linked inhibitor of apoptosis protein (XIAP) that blocks signaling to programmed cell death by binding to and inhibiting caspases such as caspase-3, -7, and -9 [53].

**ALTERNATIVE TO CANCER INDUCED CELL DEATH**

Fulda [33] affirmed that caspase-8 represents a key component of the death receptor pathway which is frequently silenced in human cancers; therefore, restoration of caspase-8 expression provides an alternative approach to restore defective cell death programs. Programmed cell death, are natural barriers that restrict malignant cells from surviving and disseminating. However, cancer cells evolve various strategies to evade programmed cell death by generating genetic mutations or epigenetic modifications in the key modulators of programmed cell death pathways [6]. Programmed cell death in vivo involves the complex interaction between apoptosis, autophagy, and necroptosis. Different types of mechanisms may co-exist and interact with each other within a cell. The decision taken by a cell to undergo apoptosis, autophagy, or necroptosis is regulated by various factors, including the energy/ATP levels, the extent of damage or stress, and the presence of inhibitors of specific pathways [54] (Figure 6).

![Signaling Pathways of Apoptosis](image)

**Figure 5** Signaling Pathways of Apoptosis.
Apoptosis is induced through either the extrinsic pathway (A), intrinsic pathway (B) or the granzyme pathway (C). Activation of initiator caspases 8 and 9 (Casp 8, Casp 9), leads to apoptotic cell death through activation of Caspase 3 (Casp3) and subsequent activation of effector caspases 6 and 7 (Casp 6, Casp 7). The extrinsic pathway (A) is initiated via extracellular molecules, FasL and TNF α, which bind to TNFR family members, Fas and TNFR respectively which activate Casp8 (green lines). The intrinsic pathway (B) is initiated by stress, UV irradiation and inflammation which act on the mitochondria through the pro-apoptotic Bcl-2 family members, such as Bax, resulting in the blockage of the anti-apoptotic activity of Bcl-2 (red lines). As a result, Cytochrome c is released into the cytoplasm and activates Casp9 through APAF-1 (green lines). Casp8 may also trigger the intrinsic pathway through activation of Bid, which inhibits the anti-apoptotic activity of Bcl-2. The granzyme pathway (C) is activated via cytotoxic T cells (CTLs) that introduce granzyme molecules into the target cells via secretion of perforin, which through a multimerization process forms a pore in the cell membrane allowing granzyme into the target cell. Granzymes cleave multiple caspases, including Caspase 10 [45].
Figure 6 Interaction between different types of programmed cell death and cancer metastasis.

Disseminating metastatic cells must face many unfavorable conditions, including detachment from the ECM, attack by immune cells, hypoxia or a growth factor-lacking environment, that cause increased cellular ROS production and DNA damage and insufficient energy status. Low levels of death signals stimulate apoptosis, whereas high levels of death signals often result in necroptosis. Due to the activity of the apoptosis (anoikis) and necroptosis machineries, most metastatic cells from the primary tumor cannot successfully macrometastasize. Compared with apoptosis and necroptosis, autophagy appears to be fairly capricious, as on one hand, autophagy greatly improves the fitness of metastatic cells under stressful conditions to counteract apoptosis and necroptosis, but on the other hand, autophagy reduces metastasis by restricting tumor necrosis and by precluding inflammatory immune cell infiltration. Additionally, excess autophagy induces the death of metastasizing cells [6].

Signaling necroptosis may involve metabolic alterations (mitochondria-associated processes and the overproduction of ROS) which may damage different macromolecules as well as DNA, contributing to the execution of necroptosis [55]. Furthermore, calcium-mediated activation of calcium-regulated enzymes such as calpain can contribute to the destruction of cellular components, for example by promoting permeabilization of lysosomal membrane and the release of lysosomal enzymes into the cytosol. Moreover, sphingomyelinases have been described to be activated during the execution phase of necroptosis and may promote necroptosis by enhancing the generation of sphingosine as a second messenger that contributes to lysosomal membrane permeabilization. In addition, the RIP1/RIP3 necrosome may promote activation of the stress kinase JNK which can contribute to necroptosis by altering the iron storage compartment. Mitochondria-associated alterations during necroptosis can also alter cellular levels of adenosine 5'-triphosphate (ATP). Accordingly, many examples of necroptotic cell death are eventually associated with a bioenergetic breakdown of the cells with profound drop of intracellular ATP pools. It is important to note that the final consequences of necrotic cell death can be distinguished from apoptotic cell death, as the plasma membrane typically ruptures, resulting in the release of the intracellular content into the microenvironment, for example danger-associated molecular patterns (DAMPs). This in turn leads to inflammatory and immunogenic responses to the dying cell. Furthermore, MLKL has been identified as a substrate that is phosphorylated by RIP3 and shown to play an important role in the transduction of the necroptotic signal to cell death. Accordingly, knockdown of MLKL was shown to retard the onset of TNFα-mediated necroptosis. In addition to MLKL, PGAM5L has also been reported to become phosphorylated upon activation of RIP3. PGAM5L then interacts with PGAM5S on the mitochondrial membrane to initiate the dephosphorylation of DRP1, a mitochondrial fission regulator, which leads to mitochondrial fission and mitochondrial fragmentation [56].

In many circumstances, inhibition of caspase activity, one of the hallmarks of apoptosis, has been shown to enhance rather than inhibit necroptosis, since caspase activity negatively regulates necroptosis by cleaving RIP1 and RIP3, two key components of necroptosis signaling. Since apoptosis is frequently impaired in human cancers, engagement of necroptosis as an alternative mode of programmed cell death opens new opportunities to kill cancer cells, even in treatment-resistant forms of cancer. The challenge will be to selectively initiate necroptosis in tumor cells by pharmacological means, while sparing normal, non-malignant cells. In addition, novel tools are required for specific detection of necroptosis in tissue or tumor samples. Further elucidation of necroptosis signaling pathways and their regulators will likely further advance the development of diagnostic and therapeutic strategies to exploit this form of programmed cell death for the diagnosis and treatment of human diseases [57].
Fulda reported that Programmed cell death is an intrinsic cellular program that regulates various physiological processes and is typically disturbed in human cancers. Since the efficacy of current cancer therapies critically relies on the engagement of this cell intrinsic program, defects in programmed cell death form the basis for treatment resistance. This implies that defective cell death signaling pathways can dampen the efficacy of cancer immunotherapies. Therefore, further insights into the regulation of programmed cell death in cancer cells are expected to pave new avenues for the development of more effective treatment approaches based on the modulation of the immune systems in cancer patients. One example is the combination of cellular immunotherapy approaches together with molecular strategies. Thus, incorporation of the advances in cell death research in the concepts of cancer immunotherapies will likely boost this important field in the near future [58].

POSSIBLE DIAGNOSIS/TREATMENT OPTIONS SURROUNDING NECROPTOSIS INDUCTION IN MELANOMA/SKIN CANCER

The treatment depends on the stage. Generally, if the melanoma is thin then a small operation to cut out the tumour (the biopsy or wide local excision described above) is usually all the treatment that is needed. Deeper melanoma requires larger operation which may include removing the local lymph glands (nodes). Additional treatment may be applied depending on the spread of cancer and the symptoms. This may include: Chemotherapy (The use anti-cancer medicines to kill cancer cells or to stop cancer cells from multiplying), radiotherapy (The use high-energy beams of radiation which are focused on cancerous tissue). This kills cancer cells, or stops the cells from multiplying), and immunotherapy (This aims to boost the immune system to help to fight cancer) (Figure 7).

CONCLUSION

A hallmark of human cancers is their tendency to evade programmed cell death, since the ability to resist the induction of cell death provides a survival advantage to malignant cells. On theoretical grounds, resistance to programmed cell death can be caused by loss of expression or function of proapoptotic molecules and/or by aberrantly high expression levels of proteins that inhibit programmed cell death. Programmed cell death is an intrinsic cellular program that regulates various physiological processes and is typically disturbed in human cancers. Since the efficacy of current cancer therapies critically relies on the engagement of this cell intrinsic program, defects in programmed cell death form the basis for treatment resistance. This implies that defective cell death signaling pathways can dampen the efficacy of cancer immunotherapies. In this review, we summarized how apoptosis and necroptosis are regulated in skin cancer based on the current literature. However, many issues remain to be clarified.

The more understanding of the specific roles, mechanisms, and regulations in apoptosis and necroptosis and their interaction with skin cancer, the better therapeutic strategies can be developed for skin cancer treatment.

FUTURE DIRECTIONS

Regulation to apoptosis is multi-factorial involving the interaction of various signaling pathways at multiple levels. Therefore, the use of single pathway targeted agents to commit cancer cells to undergo apoptosis is not a feasible strategy. Hence, this requires a careful selection of treatment strategies that are based on a comprehensive understanding of the biological networks involved in regulation.

Figure 7 A diagram illustrating the Necroptotic cancer therapy [59].
SIGNIFICANCE STATEMENT

This review has revealed possible regulations of apoptotic and necroptotic cell death in skin cancer which could open new insight to better therapeutic strategies for skin cancer treatment.

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