Chapter

Genes That Can Cause Cancer

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Abstract

Recently, it has become apparent that the pathogenesis of cancer is closely connected with aberrantly regulated apoptotic cell death and the resulting deregulation of cell proliferation. The loss of equilibrium between cell proliferation and cell death in a tissue may play a crucial role in tumor formation. In fact, the initiation of uncontrolled apoptosis in a tissue may serve as the trigger for carcinogenesis. Various laboratory studies on animals and certain human data are suggestive that tumor formation requires at least two discrete events to take place in response to a carcinogen according to this apoptotic model of carcinogenesis. The first involves an elevation of apoptosis in a particular tissue due to a genetic predisposition, stress, or mutation. The second confers resistance to apoptosis in that same tissue resulting in the formation of an abnormal growth due to a dysregulation of cell number homeostasis. The apoptotic response of each individual to any given carcinogenic or other environmental stimulus is determined by their unique double set of genes inherited from both parents. The singular genetic traits and biochemistry of each individual are attributable solely to this unique combination of genes and their specific regulation. A general example of genetic regulation, gene dose, and control is provided by β-thalassemia point mutations in the beta-globin gene, which confer a blood disease mainly in Mediterranean populations. This mutation (heterozygous and homozygous, at one or both genetic loci) can cause a hereditary red blood cell anemia. Specific examples in relation to cancer predisposition include various genetic models such as the elevated levels of skin cancer among those with certain polymorphisms or inherited mutations in their DNA repair genes like those associated with the disorder, Xeroderma pigmentosum (XP); the high rate of skin cancer observed in albinos with little or no melanin; and the high incidence of lymphomas occurring in patients with the inherited disorder, ataxia-telangiectasia (AT). The mutations associated with each of these conditions can result in an elevated level of apoptosis in the target tissues, either constitutively or in response to particular carcinogens such as UV rays, and can be linked to the initiation of cancer in those specific tissues.

Keywords: apoptosis, carcinogenesis, albinism, β-thalassemia, Xeroderma pigmentosum, trichothiodystrophy, DNA repair polymorphisms, DNA repair defect ataxia-telangiectasia

1. Current models of carcinogenesis

Classically, experimental carcinogenesis is a complex, multistage process including initiation, promotion, and malignant progression in which the failure of DNA repair mechanisms and the subsequent clonal expansion of damaged cells play a pivotal role. However, more recently, it has become apparent that the pathogenesis

of cancer is closely connected with aberrantly regulated apoptotic cell death and the resulting deregulation of cell proliferation [1, 2].

The Ames assay as a universal test for carcinogenicity was based on the classical model of carcinogenesis involving the failure of DNA repair mechanisms and the subsequent clonal expansion of mutated cells. However, mutagenicity in bacterial strains is not always an indicator of carcinogenicity since many carcinogens are not mutagenic [5]. Although this may be one feasible mechanism of carcinogenesis in laboratory models, it does not adequately fit many existing systems of carcinogenesis which are increasingly connected with aberrantly regulated apoptotic cell death and the resulting deregulation of cell proliferation. Evidence for the role of apoptotic dysregulation in carcinogenesis comes from several sources involving epidemiological, histological, and comparative animal studies in different target organs. A number of human and mouse models also support a correlation between an initial elevation in apoptosis and subsequent tumorigenesis in various tissues as in the case of the human skin cancer model [6].

Logically, in the initial stages of carcinogenesis, the most important factor to consider may be that of "time." Gene-specific mutations are known to occur randomly over a long period of time, sometimes spanning several generations according to Darwinian doctrine. There simply may not be enough time even over the life-span of a single organism to produce a specific mutation, and it seems less likely that a specific mutation to initiate carcinogenesis could happen in response to a particular carcinogen. Even according to Lamarck's alternate theory of "acquired characteristics" in which altered genetic characteristics acquired over a length of time by a parent may be passed on to the next generation, it is a stretch at best. However, if following exposure to a carcinogen, which causes the generation of free radicals and DNA damage, the occurrence of a specific mutation becomes more likely; this likelihood is still greater at a later point in time. In effect, a specific mutation would be more likely to occur at a later stage of carcinogenesis than during an earlier one. According to the two-stage model of tumor formation (see **Diagram 2**), while an epigenetic change is more likely to occur in the first step of carcinogenesis, a genetic mutation is more likely to occur in the second step of carcinogenesis merely as a function of probability [7].

2. An apoptotic model of carcinogenesis

"Apoptosis" (*falling leaves* in Greek) specifically refers to one particular mode of cell death which is responsible for the elimination of potentially deleterious, mutated cells in multicellular organisms. Inducers of apoptosis include intracellular and extracellular stimuli such as DNA damage, oxidative stress, cell cycle disruption, hypoxia, detachment from surrounding tissue, and loss of trophic signaling [8]. Apoptosis is regulated through at least two well-recognized pathways, both involving caspase activation. The first of these is called the "intrinsic pathway" and is mediated through mitochondrial release of cytochrome c, while the second is known as the "extrinsic pathway" and is mediated through cell surface death receptors, such as the receptor for tumor necrosis factor (TNF) [9, 10]. More recently, a caspase-independent apoptotic pathway has also been gaining some prominence in apoptosis studies [11].

Apoptosis is involved in the homeostasis of cell number in tissues, and although, increased cell proliferation is necessary, it is certainly not sufficient for cell transformation to take place. Normally, in multicellular organisms, a dynamic equilibrium exists between cell birth and cell death to maintain constant cell numbers throughout adult life. This homeostasis depends on an integrated balance between

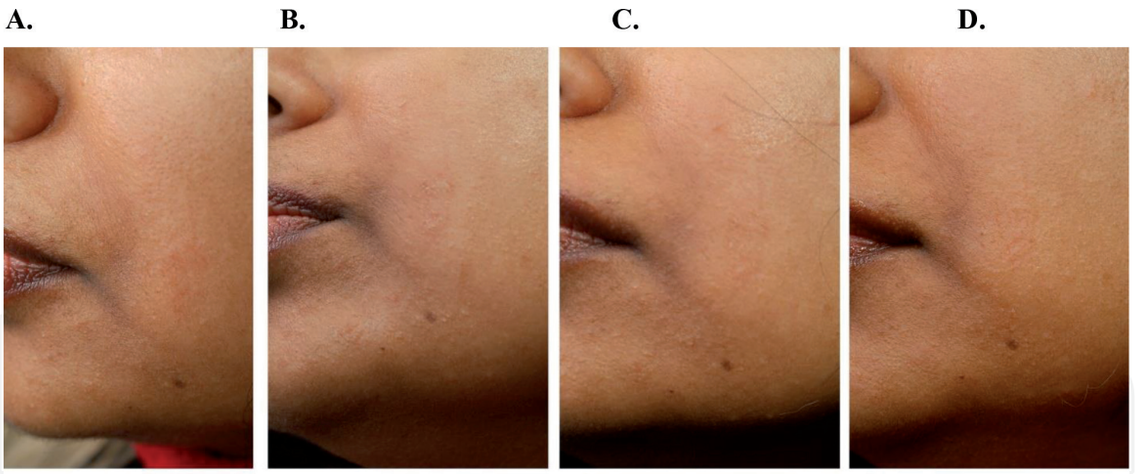

Figure 1.
The human sunburn cycle. (A) 48 h, redness & inflammation; (B) 96 h, new tissue formation; apoptosis (onset); (C) 120 h, apoptosis; (D) 168 h, apoptosis (end). The natural human sunburn cycle (without the use of any sun lotions or sunscreens) is approximately 1 week in length (7 days) from start to finish. Macroscopically, it consists of three phases including Inflammation, New Tissue Formation, and Apoptosis (visible peeling). The inflammatory phase consists of redness and inflammation commencing 20–30 minutes from the time of initial sun exposure. It spans grossly 2–3 days but can last up to 5 or 6 days depending upon UV intensity. New tissue formation is stimulated some time after initial exposure, and it is complete within 1 week. In the last apoptotic phase, the top layer of dead skin cells sloughs off to reveal a new tissue layer beneath. This process follows on from the inflammatory phase and is complete approximately 7 days following sun exposure. (The photos below are based on an initial exposure time of 20–30 min at a Canadian beach in February.)

apoptosis and mitosis such that these two activities are counterbalanced and equivalent. This homeostatic balance may contribute a critical defense mechanism of the cell to various genotoxic agents such as carcinogens [3].

The increased proliferation in some preneoplastic lesions is often accompanied by a parallel increase in apoptosis. A permanent loss in homeostatic equilibrium between cell proliferation and death may be a critical determinant in the transition to tumorigenesis. Support for this comes from the islet B cells of a multistage mouse model of carcinogenesis in which the incidence of apoptosis increased in parallel with increasing proliferation during tumor promotion, while malignancy was associated with a dramatic drop in apoptotic rate without a corresponding decrease in proliferation rate [4]. Also, in the natural human skin cancer model (*not* involving the application of inflammatory skin irritants or tumor promoters found in various suntan oils), there is always a fresh layer of new epidermis underlying the peeling or apoptosing cells as part of the normal human sunburn cycle in response to sunlight (see **Figure 1** and **Diagram 1**) [12]. Tumor formation only seems to occur once the cancer cells display constitutively activated apoptosis and become resistant to apoptosis while continuing to proliferate. In fact, acquired resistance to apoptosis appears to be a pivotal event in immortalization and the transition to malignancy [3, 13].

Various laboratory studies on animals and certain human data are suggestive that tumor formation requires at least two discrete events to take place in response to a carcinogen according to the apoptotic model of carcinogenesis. The first involves an elevation of apoptosis in a particular tissue due to a genetic predisposition, stress, or mutation in response to a carcinogen. The second confers resistance to apoptosis in that same tissue resulting in the formation of an abnormal growth due to a dysregulation of cell number homeostasis (see **Diagram 2**). Moreover, there is some evidence to suggest that both these events can be reversible when treated with a selective apoptotic agent (see **Diagram 3**), and, hence, they may be either genetic or epigenetic in nature [6].

In this context, uncontrolled apoptosis has been directly linked to carcinogenesis. Scientific animal studies have shown that simply increasing the basal frequency

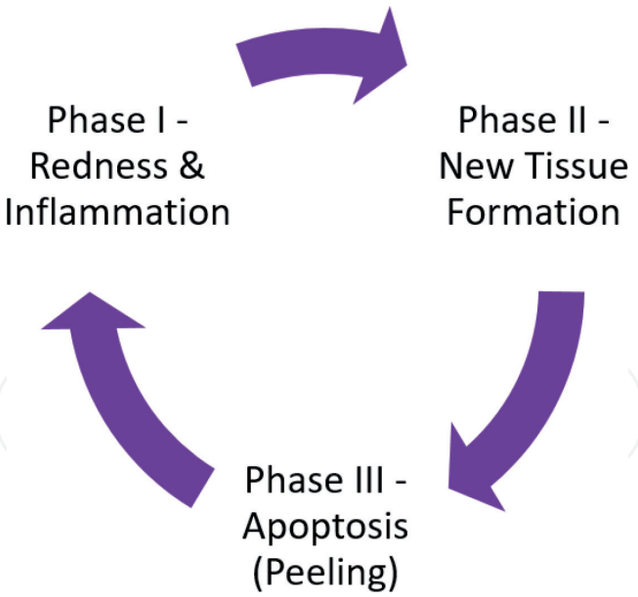

Diagram 1.
The human sunburn cycle. If this cycle continues unchecked in a specific exposed area on the body, it may result in skin cancer.

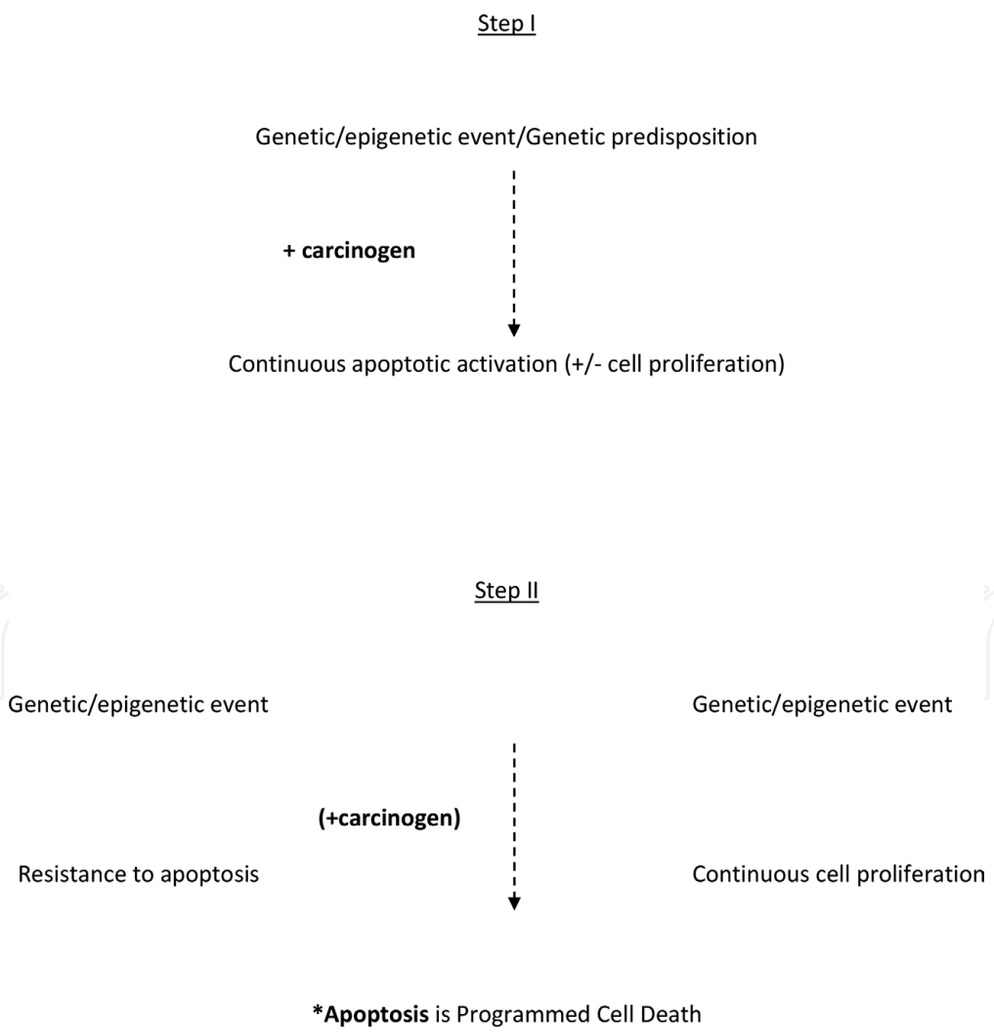

Diagram 2.
Two-stage model of tumor formation (expanded version). Apoptosis is programmed cell death.

of apoptosis in murine skin cells can be linked to the development of squamous cell carcinomas in transgenic mice [14]. In fact, the proliferation rate in certain tissues like nerve cells is so slow or negligible that simply an elevation of apoptosis would

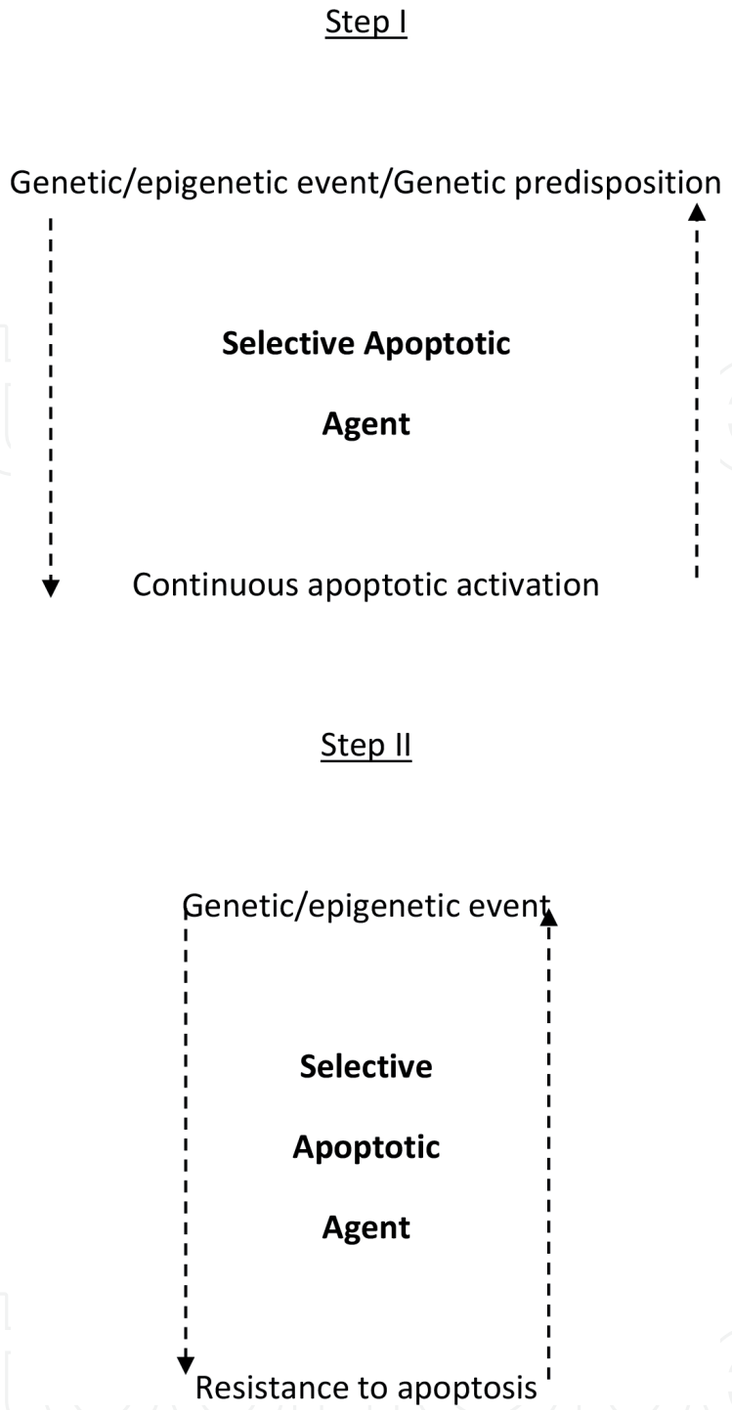

Diagram 3.
Two-stage model of tumor formation and action of selective apoptotic agent.

be sufficient to disrupt the balance between cell birth and death in the brain or nervous system even prior to the second step in the two-stage model of carcinogenesis connected with resistance to apoptosis and tumor formation.

Thus, according to this new model, the stimulation of apoptotic mechanisms becomes an important focus of study and key determinant of carcinogenic potential for any particular carcinogen being studied [15].

3. An example of gene regulation

The apoptotic response of each individual to any given carcinogenic or other environmental stimulus is determined by their unique double set of genes inherited from their parents. The singular genetic traits and biochemistry of each individual

are attributable solely to this unique combination of genes and their specific regulation. A general example of genetic regulation, gene dose, and control is provided by β-thalassemia mutations in the beta-globin gene, which confer a blood disease mainly in Mediterranean populations.

4. β-Thalassemia

Beta-thalassemias are a group of hereditary blood disorders affecting the synthesis of beta hemoglobin chains, and the results range from severe anemias requiring regular blood transfusions to asymptomatic individuals [16]. There are three main forms of the disease: thalassemia major, the most severe form with early presentation; thalassemia intermedia, a moderate form with clinical symptoms that present later in life; and, thalassemia minor, the least severe and asymptomatic form, which can cause moderate anemia. Frequency of this disease is 1 in 10,000 in the European Union and 1 in 100,000 throughout the rest of the world. Beta-thalassemias are caused mainly by point mutations and more rarely by deletions in the beta-globin gene on chromosome 11 leading to reduced or absent synthesis of beta hemoglobin chains. The transmission of this genetic trait is usually autosomal recessive, but dominant mutations also exist.

In developing countries where diagnosis of thalassemia major can be delayed, clinically, children may display growth retardation, pallor, jaundice, poor musculature, leg ulcers, and skeletal changes among other symptoms. In developed countries where blood transfusions may be implemented sooner, patients can develop iron overload-related issues including endocrine complications, dilated myocardiopathy, liver fibrosis, and cirrhosis. The main clinical features of thalassemia intermedia patients are hypertrophy of erythroid marrow and related complications, gallstones, painful leg ulcers, and an increased predisposition to thrombosis. Thalassemia minor is not associated with any clinical symptoms except mild or moderate anemia in certain cases.

The a- and b-globin genes are expressed exclusively in erythroid cells and only during defined periods of development to ensure the correct balance of a- and b-globin chains which form the tetramer of various hemoglobins at different stages. Such tight control of these multigene clusters requires several levels of regulation [17]. This is dependent on regulatory regions of DNA lying in proximity or at great distances from the globin genes. The latter are characterized by several DNase I hypersensitive sites and form the locus control region (LCR). The former and latter sequences exert stimulatory, inhibitory, or more complex activities by interacting with transcription factors that bridge these DNA regions to the RNA polymerase machinery of the cell. Also, LCR can make physical contact with active downstream globin genes by forming a chromatin structure called the active chromatin hub (ACH) in a process termed chromatin looping [18].

The coding sequences of globin genes are generally found within three exons, separated by two introns. Each gene has 5′ promoter sequences, 5′ and 3′ untranslated regions, and a downstream enhancer, in the case of the b-globin gene, which is approximately 600–900 base pairs 3′ of the poly(A) site [19].

GATA transcription factors bind the consensus sequence WGATAR, which is present in the flanking regions of most erythroid-specific genes. Conserved GATA sites are located in each of the hypersensitive sites of both alpha- and beta-globin gene clusters. GATA-1 and GATA-2 transcription factors are coexpressed in erythroid cells and are important for the regulation of erythroid globin genes, in particular for the modulation of embryonic and fetal hemoglobins [20].

β-Thalassemia is mainly caused by non-deletional defects of the b-globin gene, mostly single base substitutions. More than 180 mutations have been identified and classified as beta + or beta 0 depending on whether they reduce or abolish b-globin chain production, respectively. These mutants can be categorized as (1) nonsense or frameshift mutations which produce premature terminations, (2) RNA processing mutants which disrupt splicing and interfere with RNA cleavage or polyadenylation, (3) transcriptional mutants which disrupt the function of the promoter, and (4) mutations in the initiation codon or Cap site [21].

For example, thalassemia intermedia (homozygous and heterozygous forms) can be caused by mutations in the promoter region (CACCC or TATA box) of the beta-globin gene and have been reported in a Spanish population [19]. Nuclear proteins related to SP1 and GT-1 factors bind to a CACCC box sequence in the human beta-globin enhancer adjacent to the erythroid-specific factor NFE-1 and ubiquitous CP1. These same proteins bind to the proximal, but not distal, CACCC box in the human beta-globin promoter. A CG mutation in the promoter CACCC box known to cause beta-thalassemia greatly decreases protein binding. Similarly, the same effect is produced when this mutation is introduced into the enhancer CACCC box [22].

A study in Germany with nonimmigrant German populations found that roughly two-thirds of thalassemia minor cases appear to be caused by Mediterranean mutations (61%), while approximately a third of cases may have originated as a result of local mutations such as the one that affects position −2 of the intron 1 splice acceptor site (IVSI-129 A-G) and a deletion of a single G in codon 15/16 (FS 15/16 ΔG). The former finding suggests introduction due to migration from the Mediterranean region [23]. Similarly, while common mutations causing β-thalassemia major and minor occur in populations from northern, western, and eastern India, rare and even novel mutations may occur in some of these populations. In one Indian study, DNA sequencing of LCR HS2, 3, and 4 core sequences revealed a polymorphism, an A-G, in the palindromic sequence, TGGGGACCCCA, of LCR HS4 [24]. So, once again, the G allele could be a new evolutionary mutation in the Indian population, while the other mutations may have been introduced via migration, for example, as a result of intermarriages documented to have occurred in the frontier provinces during the Indo-Greek and Scythian periods of Indian history [25–27].

Thus, the multiple levels of gene regulation as illustrated in this example of the b-globin genes make up a highly and finely tuned system to determine subtle differences in gene expression between individuals resulting in varied production of b-globin chains. Such small differences or genetic polymorphisms are the reason for the genetic susceptibility of certain individuals to specific diseases. Similarly, in the human skin cancer model, the melanin pigment is the natural sunscreen of the human body, and the body protects itself from solar radiation by increasing melanin production. The UV A and UV B components of sunlight can trigger the human sunburn cycle involving three phases including cell death or apoptosis, repeatedly, in susceptible individuals (see **Table 1**), and this can result in skin cancer. Melanin ranges in color from red and yellow (pheomelanin) to brown and black (eumelanin) with the latter being the most effective [28]. However, certain individuals have less melanin than others and are not able to produce enough melanin to fulfill this function resulting in sunburn. In fact, it is possible and worth noting that certain forms of medical conditions such as actinic prurigo and cheilitis prevalent among some Native American populations [29] may actually be misdiagnosed cases of human sunburn. Notably, the pinkish or reddish hue of Native Americans (originally called "Red Indians" by the paler European settlers), a heightened degree of photosensitivity, and regular peeling of the epidermis upon exposure to sunlight all suggest a

0–1 h (Initial exposure)	Redness and inflammation
24 h (Day 1)	Redness and inflammation; pain
48 h (Day 2)	Redness and inflammation peak; pain
72 h (Day 3)	Minor peeling; less redness and inflammation
96 h (Day 4)	Major peeling
120 h (Day 5)	Minor peeling; itching
140 h (Day 6)	Minor peeling; itching
168 h (Day 7)	Recovery; visible new tissue

No use of sun preparations, sunscreen, or suntan lotion.
Approximately a 1-week/7-day cycle without the use of any sun preparations.

Table 1.
The human sunburn cycle.

I	Inflammation	0–72 h
II	New tissue formation	24–168 h
III	Apoptosis	36–168 h

This table is based on an initial exposure of 20–30 min at noon at the beach.
[These data are based on a set of experiments conducted at Ambleside Beach in West Vancouver (British Columbia), Canada, in February 2010.]

Table 2.
The three phases of sunburn.

lack of melanin in their skins. Since an elevation of apoptotic levels in mammalian skin cells has been linked to carcinogenesis, such patients predisposed to peeling require "apoptosis protection factor" (also called "tumor protection factor," previously) in their sunscreens as opposed to "sun protection factor," which mainly provides protection against redness and inflammation. Unfortunately, skin cancer statistics are not widely available for any Native American populations of North America at present (**Table 2**).

5. Examples of genes that can control apoptosis

Specific examples in relation to cancer predisposition include various genetic models such as the elevated levels of skin cancer among those with certain polymorphisms or inherited mutations in their DNA repair genes like those associated with the disorder, Xeroderma pigmentosum (XP); the high rate of skin cancer observed in albinos with little or no melanin; and the high incidence of lymphomas occurring in patients with the inherited disorder, ataxia-telangiectasia (AT). The mutations associated with each of these conditions can result in an elevated level of apoptosis in the target tissues, either constitutively or in response to particular carcinogens such as UV rays, and can be linked to the initiation of cancer in those specific tissues.

6. DNA repair defects and DNA repair polymorphisms

Mutations in the XPD helicase component of the transcription factor TFIIH, which is involved in basal transcription and DNA repair, can result in the diverse symptoms associated with both Xeroderma pigmentosum (XP) and

trichothiodystrophy (TTD). Aside from the traditional mutations and deletions in the b-globin gene that induce β-thalassemia, it is interesting that specific mutations in XPD that cause TTD can also result in reduced expression of the b-globin gene, in addition to a number of other general clinical features. TTD is an autosomal recessive disorder characterized by brittle nails, brittle hair, short stature, mental retardation, ichthyotic skin, and, often, photosensitivity [30]. Photosensitive TTD patients tend to be deficient in nucleotide excision repair (NER) of UV-induced DNA damage and, in this aspect, resemble XP patients. XP is also an autosomal recessive disease that provides a useful cancer model and is characterized by extreme sensitivity of the skin to sunlight resulting in sunburn, sunlight-induced pigmentation changes in the skin, and a very high frequency of skin cancers in sun-exposed areas including basal or squamous cell carcinomas and melanomas. However, TTD patients display neither pigmentation changes nor skin cancers [31]. The explanation for this difference appears to lie in the fact that XPD has two functions and XP may be caused by mutations that only affect its role in NER, whereas TTD may be caused by mutations that affect its general transcriptional role as a subunit of the transcription factor TFIIH. In TTD patients, de novo synthesis of the components of TFIIH is thought to compensate for this deficiency in most cells, so there is little evidence for deficient transcription of many genes in TTD except for b-globin in humans [30]. Reduced repair of cyclobutane pyrimidine dimers (CPD), which do not seem to be cytotoxic on their own, is observed in TTD as well [32, 33]. By contrast, in XP*A* cells, entirely deficient in the repair of the two major UV-induced lesions, CPDs and (6–4) photoproducts, UV exposure results in cell death [34]. Moreover, 65% of the melanomas in patients with Xeroderma pigmentosum occur on areas that are routinely exposed to the sun like the face, head, or neck [35].

Epidemiological studies have also shown that homozygous genetic polymorphisms in DNA repair proteins resulting in sunburn, and a history of repeated painful sunburn are more correlated with a higher risk for squamous cell carcinoma than the wild-type or heterozygotes [36, 37]. In addition, variants within other DNA repair genes involved in double-stranded DNA repair triggered by UV damage have been found to be associated with the development of malignant melanoma [38]. Moreover, many cancers ranging from acute myeloid leukemia and follicular lymphoma to breast cancer have been associated with specific polymorphisms in DNA repair enzymes resulting in their reduced efficiency to cope with cellular DNA damage [39–41]. The inability to cope efficiently with DNA damage often results in cell death or apoptosis.

7. Albinism

There are a number of genetic models for skin cancer in humans. One such model is also provided by albinos, who are deficient in melanin production (melanin is the pigment that protects against UV radiation and apoptotic sunburn). Albinos are typically characterized by pink skin, pink eyes, and white hair resulting from mutations in genes involved in melanin biosynthesis [42]. As a result, they display an increased skin cancer incidence [43]. This finding is confirmed in the albino hairless mouse model which displays a high incidence of UV-induced cutaneous cancers as well [44].

8. Ataxia-telangiectasia

Patients with the inherited disorder ataxia-telangiectasia [AT] provide another human cancer model since they are highly susceptible to certain cancers,

particularly lymphomas [45]. AT is an autosomal recessive disease which is characterized by loss of coordination and telangiectasias, hypersensitivity to ionizing radiation, progressive neuronal degeneration, and immunodeficiency [46]. Interestingly, the genetic mutation in AT patients occurs in and affects a PI 3-kinase associated with DNA damage and has been found to be involved in the apoptotic response to X-irradiation [47, 48].

In addition, a constitutive elevation of IFNβ production has been demonstrated in fibroblasts derived from AT individuals [49]. An elevation of spontaneous apoptosis in AT lymphocytes has also been observed [50] thereby establishing a link between apoptotic potential and an increase in cancer risk. Cytokines like IFNα/β are known to stimulate the transcription of many proapoptotic proteins [51]. The transcriptional activator, NF-κB, which mediates interferon (IFN) production, is constitutively activated in AT cells [52] as well and is apoptotic in certain cell types like lymphocytes [53]. Thus, there is further evidence here to suggest that cancer predisposition may be connected with genetic polymorphisms that can cause uncontrolled apoptosis.

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