The etiology and pathogenesis of squamous and basal cell carcinoma

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Abstract

Basal cell carcinoma (BCC) is the most frequently encountered human malignant tumor. Squamous cell carcinoma (SCC), also common, has a more aggressive biological behavior. Ultraviolet radiation (UR) is the most important epidemiological carcinogenic factor in the evolution of BCC and SCC. Low phototype patients have a higher incidence of these tumors, which occur, mainly in exposed areas. Childhood sun exposition could be important. The carcinogenic potential of UR is experimentally confirmed. Other kinds of radiation, chemical substances and viruses could also be implicated in the aetiopathogenesis. These associations are not yet fully understood. It seems there is not a sole mechanism which causes a normally differentiated keratinocyte to transform into a malignant cell, with the potential for local invasion and distant metastases. The way this change occurs still remains almost unknown.

Key words: Basal cell carcinoma, Squamous cell carcinoma, aetiopathogenesis, ultraviolet radiation.

Introduction

Basal cell carcinoma (BCC) is the most common malignant neoplasm affecting humans. Although it usually does not metastasize, it is capable of growing locally in extensive form, causing significant cosmetic and functional damage, and even leading to death. Squamous-cell carcinoma (SCC), which is four times less frequent, has more aggressive behavior and is less dependent of the epithelium where it develops.

Our knowledge about these neoplasms derives from epidemiological studies, and is supported by animal experiments and, in some cases, investigation on human skin.

The factors involved in their etiology can usefully be classified as extrinsic and intrinsic. Among the extrinsic factors, ultraviolet radiation seems to play an important role. Other types of radiation, chemical substances and viruses may also, in some cases, act as triggers.

The pathogenesis of these neoplasms is complex and is not entirely known, but it seems to depend on a combination of several independent events in each cell.

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Etiology

Extrinsic factors

Ultraviolet radiation. Ultraviolet radiation (UVR) is, from an epidemiological point of view, the most important extrinsic factor in the carcinogenesis of human SCC and BCC.

The skin is a non-homogeneous and complex element on optics, which makes it rigorously difficult to predict its behavior when submitted to a non-ionizing radiation.[1] Nevertheless, the data that establishes a relationship between BCC and SCC, and radiation is important and varied, either epidemiological or experimental in nature.

For individuals with the same phototype, the incidence of these neoplasms increases as the distance from equator decreases.[2] The exposed parts of the body - head, neck, backs of the hands - are the most affected regions.[3] The history of exposure, professional or otherwise, correlates to increased incidence.[4] Phototype 1 and 2 individuals, who are less protected as they have less melanin, are the most affected by these neoplasms.[5,6] Paradoxically, some isolated studies, particularly in Australia, show a significant incidence of BCC in less exposed parts of the body,[7] which indicates that BCC are not always related to exposure to the sun. Recent epidemiological data considers exposure in children and exposure within the last ten years as the most determining factor.[8]

Animal experiments show that UVRB is carcinogenic per se,[9] and UVRA not only potentiates UVRB

but can also be carcinogenic.[10] Nevertheless, regarding SCC, a linear relationship with does seems to exist; for BCC, there is a dose saturation effect.[11] In this context, it is interesting to note that rats develop BCC at low exposure, and SCC at high exposure.

In mice, UVRB decreases the number of Langerhans cells and increases the number of suppressor T cells,[12] results in less rejection of transplants and higher incidence of neoplasms.[13] The same is true for high exposure to UVRA or associated with photoactive pigments.

In humans, UVRB damages Langerhans cells[14] and reduces the capacity of dinitrochlorobenzene capacity.[15]

Patients subject to PUVA (psoralen followed by UVRA) in the USA show a higher incidence of BCC and SCC[16] in some regions such as the genitals, being thirty times higher than in non-exposed patients; however, the same concept does not apply in Europe. This fact is not unrelated to the different forms of application of this therapy, which is for long periods in sessions in the USA - and it is speculated that this fact limits the elimination of cells with altered DNA by enabling, through recovery, cells that otherwise would be eliminated. Higher total cumulative dose is another possible explanation.

Ionizing radiation (X, gamma, grenz). Epidemiologically less important than UVR, this radiation may affect restricted groups of patients or professionals from several fields, including medicine. Since the studies conducted by Frieber at the beginning of the century, x radiation has been considered an etiological factor of BCC and SCC. Today, we know that the total cumulative dose is the decisive factor.[17] The latent period ranges from six to thirty years,[18] with shorter periods corresponding to individuals irradiated during childhood by meningoblastoma. Exposure to other ionizing radiations (gamma, grenz, etc.), although rare, can also cause neoplasms.

Virus. The association of some human neoplasms with some viruses (HB, EB, HTLV, HIV, HPV) is well documented.[19] There is an association of between the human papillomavirus 16 and 18 and cervix, penis and periungual SCC,[20] and it has been reported for other types of HPV in a less consensual manner.[21] For other types of SCC, convincing data is non-existent.[22]

There is no association between virus and BCC.

Chemical substances. The relationship between a chemical substance and a neoplasm was established for the first time by Sir Percivall Pott in the 18th century, when he reported a higher incidence of SCC of the scrotum among chimney sweepers in London, due to some substance in the grime.[23] The substance in question is among an important group of chemical carcinogenic substances - hydrocarbons - to which some professionals handling tar and cutting oil are exposed.

As for hydrocarbons, most of the carcinogens are associated with SCC, but not with BCC. An exception to this rule includes, in experimental carcinogenesis in rats, anthramine and 3-methylcholanthrene, and in humans, arsenic, which was reported by Hutchinson over a century ago as a possible carcinogen and documented as being associated with BCC and SCC,[24] which today is known to be dose-dependent.[25] It is interesting that this substance was used in Dermatology for a long time (Fowler's solution).

Tobacco, whether it is smoked or chewed, is associated with SCC of the lips and oral cavity,[26] when only Dermatology is considered.

Several drugs have been involved in the experimental carcinogenesis of SCC, either in topical use (e.g.: nitrogen mustard) or systemic use (e.g.: corticosteroids).

Intrinsic factors

Age, gender and phototype. Advanced age, male, lighter skin tones, which have less pigmentation and burn more easily in the sun, blonde or red hair and blue eyes are characteristics in literature that are commonly related to a higher incidence of BCC and SCC.[5,6]

Genodermatosis. Xeroderma pigmentosum - Patients with this rare autosomal recessive dermatosis experience an enzymatic change in the DNA repair system. As it will be further explained later, dysfunction in the immune system is also seen. Around 42% of these patients up to twenty years of age develop one or more SCC or BCC, with the increase in incidence in SCC being up to 4800 times higher.[27] The average age at onset is eight years, and 97% of the neoplasms occur in exposed regions,[28] well above the 80% figure observed in the general population, which highlights the important role of UVR in the genesis of neoplasms of these patients.

Oculocutaneous albinism - Also an autosomal recessive disease, this condition makes evident the protective role of melanin, since these patients, who

have a poor melanin-synthesis enzyme system, have a higher incidence of early-onset SCC.[27]

Immunosuppression. It is thought to play an important role in SCC and only a modest role in BCC. The knowledge of the role of immunosuppression in cutaneous neoplasms in humans is derived mainly from studies in renal transplant patients. Therefore, it can be safely said that there is a relationship between immunosuppression and azathioprine associated with corticosteroid and higher incidence of SCC.[29] In the case of cyclosporine, the data is less linear and controversy exists.[30] The first SCC develops on average 3 to 7 years after transplant, usually occurring in exposed regions; it has an aggressive biological characteristic and usually occurs in multiple sites.[31] The SCC:BCC ratio is 4:1,[32] representing an inversion of the usual relative frequency.

In rheumatoid arthritis and inflammatory bowel disease, there is a slight increase in the incidence of SCC - up to five times.[33]

In chronic lymphatic leukemia, SCC develops ten to twenty years before the usual average age, and is more aggressive.[34]

In human acquired immunodeficiency syndrome, the association is not clearly demonstrated.[35]

Existing skin pathology. The development of SCC on burn scars[36] or after dermatosis determining fibrosis[37] is a documented fact. Although rarer, the same happens after chronic inflammation in ulcerated areas, fistulas and inflammatory dermatosis.[38]

Actinic keratosis (AK) is the most frequent premalignant lesion in humans, despite the low risk of transformation into SCC. The risk of a patient with multiple AK developing SCC at any point is calculated as 12%.[39] The number of these lesions is a good marker of cumulative UVR for individuals with low phototypes.[40]

In bowenoid papulosis, which has an association with HPV, and whose histology resembles Bowen's disease, the risk of SCC is low, but reported. Erythroplasia of Queyrat and Bowen's disease are, as is known, SCC in situ.

The organoid nevus is a predisposing area for BCC and syringocystadenoma papilliferum, and more rarely keratoacanthoma, SCC and apocrine carcinoma.[41]

The epidermis that covers dermatofibroma is typically acanthotic, with an increase of the basaloid component. Basal cell hyperplasia, BCC-like or BCC can be found in 2% to 8% of the cases.[42] It has been suggested that these changes can develop in response to a mediator produced by the cells in this neoplasm. Some authors relate the increase of aminopeptidase activity,[43] the distance to the epidermis[44] and the abnormal expression of keratin[45] to the mentioned changes. Other authors did not make the same observations.

The papules of the rare unilateral basal cell nevus syndrome with comedones frequently occur with basal cell hyperplasia and, sometimes BCC.[46]

The basal cell nevus syndrome, a rare autosomal dominant condition, with complete penetrance and variable expressivity, in which 60% of patients have new mutations, includes multiple BCC, small papules on the palms of the hands, and bone and dental changes. These patients are highly sensitive to UVR and develop BCC before 20 years of age.[47] A possible suppressor gene may exist on chromosome 9, inactivation of which would be responsible for the development of the syndrome.[48]

In the Bazex syndrome - a dominant disorder characterized by follicular atrophoderma with multiple BCC, hypotrichosis and hypohidrosis - the patients can develop BCC at age 12, particularly in the face.[49]

Pathogenesis

What is known today about the pathogenesis of BCC and SCC is too vast to list here. Nevertheless, some brief notes will be made.

The carcinogenesis pattern that we accept as a possible reality is based on animal experiments, therefore it does not allow generalizations. The induction of epidermal neoplasms by chemical, physical or viral stimulation has been extensively studied. It should be mentioned that different laboratory specimens develop different neoplasms when subjected to the same stimulations. For example, a BCC may develop by chemical carcinogenesis at low doses in rats, but not in mice, which develop only SCC as a malignant epidermal neoplasm. Actinic keratosis does not occur in mice, therefore papilloma and keratoacanthoma are the most common benign cutaneous neoplasms.

On a logical sequential approach, we find four determining processes in the genesis of epidermal neoplasms: individual susceptibility, environmental pressure leading to excessive mutations in the DNA (UVR, HPV, chemical influence), inability to repair DNA and, finally, poor elimination of cells with abnormal DNA.

Individual susceptibility

These neoplasms most frequently affect elder males with phototypes 1 and 2.[5,6] As observed previously, multiple disease and syndromes may determine an increase in individual risk.

Environmental influences can lead to excessive DNA mutations. These influences may be physical (e.g. UVR), chemical (e.g. aromatic hydrocarbons) or biological (e.g. HPV).

From an experimental point of view, malignant epithelial neoplasms derive from three distinct mechanisms: initiation, promotion and progression.

Initiation is the transformation of the normal cell into an initiated cell, which may proliferate with stimulation. It is a consequence of a genetic modification - mutation, rearrangement, deletion, etc. - and it is, therefore, an irreversible phenomenon that occurs after limited or single exposure to a carcinogenic agent or the introduction of mutations (e.g. to the HRAS gene). Among the main agents are UVR, viruses, aromatic hydrocarbons, phenols, dinitropyrene, nitrosamines, urethane and alkylating agents.

Promotion corresponds to controlled cell proliferation from the initiated cell and occurs as a consequence of a gene expression alteration, due to exposure to a promotion agent. Some of these agents can also be initiation agents, for which they are mentioned above. Other agents include benzoyl, phorbol ester, cutting and abrasion. The phenomenon is reversible, provided exposure is suspended.

In progression, a benign neoplasm (papilloma in mice) develops into a carcinoma. The controlled proliferation turns into autonomous proliferation with abnormal differentiation. As occurs in the initiation phase, progression is the result of a change in DNA (but irreversible) and is a rare phenomenon, with chances of development increasing due to exposure to some initiation agents.

For the regions that have been exposed, at least two structural, genetic changes are necessary for the genesis of a cancerous cell. The chances that these will occur in the same cells are determined by the frequency of each of them. When a high number of cells with initial alteration are induced, promotion agents are the main agents determining the probability of genesis of a cancerous cell.

Several genes have been involved in the progression of cutaneous neoplasms. They include suppressor P53 and oncogenes such as neu, fos and the most frequently investigated, Hras.

The Hras gene codifies for p21 protein in the plasma membrane. This protein has a guanosine--triphosphate activity and appears to be important in transduction. The mutant agent of this gene introduced in the epidermal cell determines the formation of benign neoplasms similar to those obtained through exposure to initiation and promotion agents. Nevertheless, transgenic mice with mutant Hras develop papillomas after the application of promotion agents, without experiencing initiation. The deletion of normal Hras or duplication of the mutant frequently occurs during progression; mutations in this gene are often observed in BCC and SCC cells.[50] In benign lesions, the deletion of two normal HRAS alleles is not observed.[51] The fos oncogene has also been related to the conversion.[52]

The mutants of neu and p53 genes appear to be correlated to dysplasia without conversion.

Mice strains that express mutant p53 in the epidermal cell develop a higher number of UVR-induced carcinomas, despite the existence of a normal latent period.[53]

Mutation of gene q21 of chromosome 9, which is common in the basal cell nevus syndrome, also appears to be associated with sporadic BCC.[54]

Local levels of GGT, transin, TGF and cystatine were considered by some authors in the past as good transformation markers, which does not correspond to the reality. Currently, several studies assign this role to the expression of abnormal keratins 13 and 19. Differences between the carcinogenesis of BCC and SCC seem to exist:

In the case of BCC, it appears that promotion does not occur;[55] the normal cell originates the initiated cells that directly evolve to a carcinoma. Besides, association does not exist with HPV[56] and it does not occur in other epithelia.[57]

Inability to repair DNA

This inability exists in multiple pathologies - X. pigmentosum, S. cokayne, trichothiodystrophy, etc -, but increased incidence of cutaneous neoplasms is not a characteristic of all pathologies. In X. pigmentosum, this increased incidence may, in part, be explained by poor cellular immunity, and in particular, a less efficient natural killer activity.

Inability to eliminate abnormal DNA cells - immunosuppression

Several data point to a relevant role of immunosuppression. The extent to which UVR can determine has been explained previously.

In relation to SCC, some studies show lymphocytopenia and a weaker helper/suppressor relation in patients,[60] but the methodology is not always appropriate, since a mandatorily elder population, who are immunodeficient compared to the general population, is used in the comparison. A twenty-fold increase can be observed in the incidence of this neoplasm in renal transplant patients.[32]

In relation to BCC, reduced natural killer activity is reported,[61] as well as reduced ICAM1 expression,[62] reduced cytokine expression at the periphery, reduced neoplasm expression and only 8% of hypersensitivity response to dinitrochlorobenzene. Nevertheless, it is not correct to compare this number to the 60% observed in the general population, as explained above.

Conclusion

From what was possible to include in this brief paper, it is clear that the etiopathogenesis of these neoplasms is far from being entirely understood. A single mechanism responsible for the transformation of a normal differentiated keratinocyte into a malignant cell with invasion and metastization potential does not appear to exist.

UVR seems to be a very important factor in human carcinogenesis, with exposure being a partially controllable factor, which enables the prediction of a positive impact on the changing prevalence of BCC and SCC.

In the short term, a significant understanding could occur in three fields: clarification of the role of the suppressor gene associated with the basal cell nevus syndrome; understanding of the immunopathogenesis of the UVR-mediated susceptibility; determination of the cytokines involved in the dermal-epidermal interaction in cutaneous neoplasms. ■

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