

Review

Immunology and skin cancer

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Abstract

Skin cancer represents the most frequent type of human malignancy. Skin poses an important immunologic role, therefore also the correlation between skin cancer development and immunologic mechanisms are intensely studied. These aspects are of the utmost importance in patients requiring immunosuppressive therapy as transplant recipients or immunologic disorders. Cancer development after organ transplantation is the result of intense intercommunication between immunological and non-immunological factors. Non-immunologic risk factors like individual predisposition, sun and environmental exposure are a contributing part to the skin neoplasia incidence. In addition, continuous exposure to immunosuppressive medication is closely linked to the development of the new malignancy. A similar situation is encountered in autoimmune diseases, those patients having an increased risk of skin cancer, especially squamous cell carcinoma. Immunotherapy shows promising results and encourages further studies in this direction. Also, an important aspect is to support preventive strategies in patients with high risk of skin cancer development.

Keywords: *skin cancer; immune response; immunosuppressant therapy; transplant; autoimmune disease*

Introduction

Skin cancer represents the most frequent type of human malignancy. The tumors with keratinocytic origin (non-melanoma)-Basal Cell Carcinoma (BCC) and Squamous Cell Carcinoma (SCC) are the most common types, having for example in United States an annual incidence of more than 4 million cases [1, 2]. With their increasing incidence, those malignancies affect in US more people than all other types of cancer together, representing a significant problem for the public health system [3]. Therefore, a rigorous understanding of skin cancer mechanisms is

mandatory to develop adequate preventive and therapeutic strategies with efficient allocation of medical resources.

Recently, an increased preoccupation in international research focuses on study the implication of immune system in etiology and evolution of skin cancer in order to develop new therapeutic options [2].

Skin Cancer Classification

Multiple skin cancer entities have been described, depending on the tumor cells of origin, as we can see in Table 1 (Skin tumors classification according to World Health Organization WHO, 2018) [4, 5].

Non-melanoma cutaneous cancer comprises around 30% of all malignancy cases with an annual incidence in continuous rising [6]. The most frequent type of skin cancer (75-80% of cases) and also the most common of all cancers in humans is

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represented by the basal cell carcinoma. The anatomic regions usually affected by BCC are the head and neck (70-80%), followed by the

trunk (approximately 25%) and perineum region [7].

Table 1. Skin tumors classification

Type of tumor relating to origin	Representative tumors
Keratinocytic/Epidermal (Non-melanoma)	Basal cell carcinoma Squamous cell carcinoma Squamous cell carcinoma in situ (Bowen disease) Merkel cell carcinoma
Melanocytic	Malignant melanoma
Adnexal	Malignant tumours with eccrine and apocrine differentiation Malignant tumours with follicular differentiation Sebaceous carcinoma
Lympho-hematologic	Mycosis fungoides CD30+ T-cell lymphoproliferative disorders Skin T-cell leukaemia/lymphomas (primary or secondary) Skin B-cell lymphomas (primary or secondary) T-lymphoblastic and B-lymphoblastic leukaemia Blastic plasmacytoid dendritic cell neoplasm Skin determination in myeloid leukaemia
Neural	Malignant peripheral nerve sheath tumour
Soft tissue	Liposarcoma Fibroblastic, myofibroblastic and fibrohistiocytic malignant tumours Leiomyosarcoma Skin angiosarcoma Kaposi sarcoma
Uncertain differentiation	Pleomorphic dermal sarcoma Epithelioid sarcoma Myxo-fibrosarcoma Dermal clear cell sarcoma Ewing sarcoma
Inherited syndromes	Familial melanoma Gorlin syndrome (Naevoid basal cell carcinoma syndrome) Skin cancers on <i>Xeroderma pigmentosum</i> Muir-Torre syndrome

The second most common skin cancer type, after BCC, is squamous cell carcinoma, with around one million annual cases in US. This type of cancer may develop on healthy tissue or on previous specific conditions like actinic keratosis or an old burn scar (Marjolin ulcer). Risk factors associated with SCC development are: UV radiation exposure, light skin patients, elderly, male gender, chronic lesions, radiation therapy, presence of oncogenic viruses like HPV, environmental exposures (arsenic) and immunosuppression [6, 8, 9]. It is a known fact that immune-suppressive treatments, physical or pharmacological, determine an increased risk of malignancies compared to general population, suggesting the involvement of

immune system alterations in skin cancer development and progression [10].

Malignant melanoma is recognized as the most lethal type of skin cancer, bearing a significant burden for health system. Unlike other malignancies, melanoma affects younger, socially active patients with a median diagnostic age of 57 years. Both genetic and environmental factors are associated with cutaneous melanoma development. Despite ongoing research for promoting new therapeutic strategies, for patients with advanced disease the prognosis remains poor [11].

In general population, the least frequent types of skin cancer are cutaneous lymphoma,

Kaposi sarcoma, Merkel cell carcinoma, skin adnexal tumors and skin sarcoma [12].

Merkel cell carcinoma-a neuroendocrine epidermal tumor- is a rare but very aggressive type of skin cancer with a very high recurrence risk and metastasizing potential, with higher incidence in the past decades. It is related to Merkel cell polyomavirus in the majority of cases, but also other risk factors as advanced age, UV exposure and immunosuppressant therapy were mentioned [13].

Immunological mechanisms involved in skin cancer

It is certain fact that skin represents a key player of the immune system. During the last five decades, researchers analyzed the immunologic pathways involving cutaneous components. Four immunologic models were described, synthetised in Table 2 [14, 15].

Table 2. Skin immunologic models

Immunologic model	Year of introduction	Concept Description
SALT(Skin-associated lymphoid tissues)	1983	- skin immune surveillance is based on interactions between keratinocytes, Langerhans cells, the presence of lymph nodes and immunocompetent lymphocytes
SIS(Skin immune system)	1986	- includes all components of the normal skin involved in complex immune responses - ensure both cellular and humoral responses
DMU(Dermal microvascular unit)	1989	- situated in small vassels of papillary dermis - includes all components of immune reactivity
DIS(Dermal immune system)	1993	- involved fibroblasts which interacts with epidermal components - includes humoral and cellular components

Table 3. Skin immunologic constituents Adapted by permission from Springer Nature: Bos JD, Luiten RM. Skin Immune System. In: Stockfleth E, Ulrich C. (Eds) Skin Cancer after Organ Transplantation. Cancer Treatment and Research, vol 146. Springer, Boston, MA, 2009; License Number: 4424231400954.

	SALT	SIS	DMU	DIS
Coagulation/fibrinolysis system	-	+	-	-
Complement factors	-	+	-	-
Cytokine network	-	+	-	+
Dermal T lymphocytes	-	+	+	+
Eicosanoids	-	+	-	-
Epidermal T lymphocytes	+	+	-	-
Fibroblasts	-	-	-	+
Free radicals	-	+	-	-
Granulocytes	-	+	-	-
Keratinocytes	+	+	-	-
Langerhans' cells	+	+	-	-
Lymphatic endothelial cells	+	+	-	-
Mast cells	-	+	+	+
Monocytes/macrophages	-	+	+	+
Neuropeptides	-	+	-	+
Secretory immunoglobulins	-	+	-	-
Skin draining lymph nodes	+	-	-	-
Tissue dendritic cells	-	+	+	+
Vascular endothelial cells	+	+	+	+



The concept of cancer immunosurveillance was introduced by Burnet in 1957 and served as a starting point for the more recent cancer immunoediting approach. Through cancer immunoediting the immune

system interacts with developing tumors, sculpting them as an ongoing process including three phases: elimination phase, equilibrium and escape phase, illustrated further in Figure 1 [2, 16, 17].

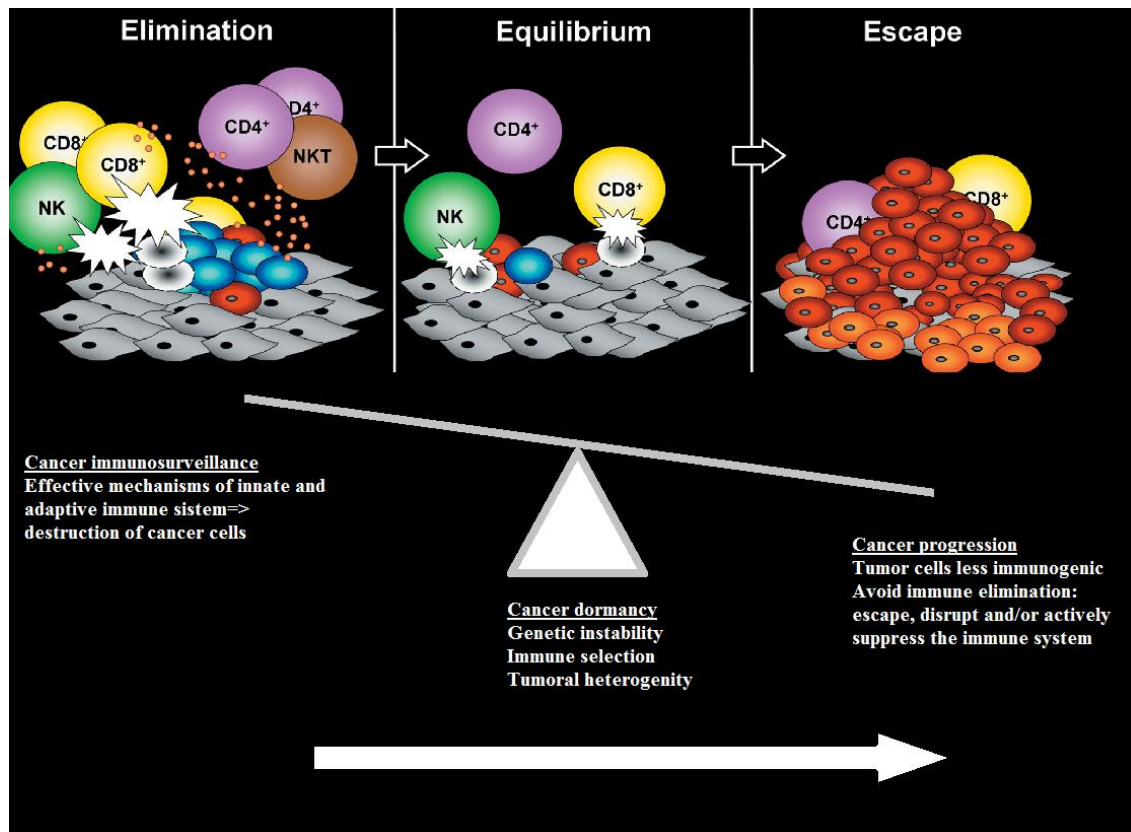


Fig. 1. Phases of cancer immunoediting. Adapted by permission from Springer Nature: Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol* 2002; 3 (11):991-8. License Number: 4427771257332

Clinical implications

Skin cancers in transplant patients

In the last decades the field of organ transplantation developed significantly due to the improvements of surgical protocols and also more efficient immunosuppressive therapies [18].

Annual reports available on Global Observatory on Donation and Transplantation (GODT) for year of 2015 presents the following data: a total of 126,670 organs were transplanted in 2014, from which two thirds (84,347) were renal transplant, 22% were liver transplants and the rest of 11.5% included heart, lung, pancreas and small bowel transplant [19].

A recent therapeutic entity is represented by the vascularized composite allotransplantation, including non-vital allograft transplantation like upper and lower limbs, face, larynx and trachea, abdominal wall, penis and uterus transplantation. Those procedures are not life-saving like solid organ transplant and they are performed for functional reconstruction and improvement in quality of life of patients with complex soft tissue defects and specific lost functions, impossible to restore with conventional therapeutic strategies [20, 21].

The limitation on an even more extensive use of transplantation procedures as standard therapeutic options for a large panel of diseases is represented by the immunological

considerations. Lifelong immunosuppression exposes the transplant patients to severe complications including systemic disorders (cardiovascular, renal, diabetes mellitus), infections and malignancies. Cancers developed in transplant patients are often more aggressive in comparison with general population [22, 23].

Carcinogenesis in transplant patients recognizes an association between immunological and non-immunological risk factors. Non-immunological cancer risk factors encountered in general population (gender, advanced age, smoking, sun and radiation exposure, environmental exposure) interacts with cumulative effects of immunosuppressant therapy [24].

Researchers showed also that there are particular viral infections that are clearly connected to specific types of cancer. The following associations have been noted: human herpes virus 8 and Kaposi's sarcoma, human papilloma virus (HPV) and epithelial cancers (skin and non-skin carcinoma). The mechanism of these viral infections consists of the ability of controlling cell cycle and division, escape from apoptosis, supporting transformation and cell-growth. Persistent immunosuppression is the most important risk factor for viral infections-linked malignancies [24, 25].

The geographic regions are also a very important factor in determining the type and frequency of neoplasia, creating a wide variance. Therefore, the variables between geographic provenience consist in the following: skin phototype, sun exposure and viral infections prevalence. The association between sun exposure and skin malignancies is present in both the general population as well as in post-transplant patients and it is very frequent in Australia and in the fair-skinned Caucasians and very rare in the Asiatic population [23, 24].

Skin cancers represent the most common malignancies associated with transplantation, affecting more than half of the white race transplanted patients, observing an increasing incidence parallel with immunosuppressive therapy duration; more than 90% of those skin

tumors include squamous and basal cell carcinomas [23, 26].

Each solid organ expresses different immunogenicity when it is allotransplanted, for example heart transplant recipients need higher immunosuppression level comparing with other organs [23]. Liver is considered an immune privileged organ, even clinical transplant tolerance with no need for immunosuppressant therapy being reported in some patients [27].

Unlike solid organs, vascularized composite allografts (VCA) contain histological heterogeneous tissues (skin, muscle, tendons, fat, bone, nerves, blood vessels, lymph nodes) expressing different levels of immunogenicity. The immunosuppressive regimes are similar with kidney transplant, with triple therapy including Tacrolimus, Mycophenolate mofetil (MMF) and corticosteroids [28, 29].

Recent findings in VCA field promoted the concept of "split rejection": the various components of the allograft may reject in distinct moment and intensity, suggesting a continuous need for immunologic monitoring of the graft in order to apply a prompt therapy [30].

Immunologic instability with multiple rejection episodes, inappropriately treated, lead to chronic rejection with risk of graft loss and also difficulties in treatment of successive rejection episodes. Aggressive immune-suppressive regimens administered for protecting the allograft increase considerably the risk of complications including malignancies [30-32].

Definitely, continuous exposure to immunosuppressive medication is closely linked to the development of the new malignancies in transplanted patients, each type of immunosuppressant having a different risk in cancer development as we can see in Table 4 [33].

The most frequent association with skin cancers that has been observed is exposure to a high regimen of cyclosporin A or exposure to a combination of cyclosporine A and azathioprine (both recognized as group I carcinogens) [34].

Table 4. Interaction between immunosuppressant medication and skin cancer

Immunosuppressive agent	Mechanism of action	Skin cancer involvement
Glucocorticoids (Prednisolone)	Blocks: IL-1,-2,-3,-4,-6; TNF- α ; Interferon- γ . Inhibits: phospholipase A2; arachidonic acid cascade	No evidence of directly carcinogenic side effect
Calcineurin inhibitor (Cyclosporin)	T-cell signaling inhibition	<p>↑ risk of keratinocyte skin cancer</p> <p>Cyclosporine + Azathioprine = ↑ risk in transplanted patients for skin malignancy</p> <p>High prevalence of cutaneous dysplasia</p> <p>Mutagenic effect–deficient repair of damaged DNA; p53 mutations</p> <p>Promote cancer progression (cell culture and animal studies)</p>
Azathioprine	Immunosuppressive effect – adding 6-TG into DNA Deficient activated T-cell pathways signaling Further ↑ of DNA oxidative stress after UVA exposure	Carcinogenic and immunosuppressive potential =>cutaneous cell carcinoma
mTor Inhibitors/Proliferation Signal Inhibitors (Rapamycin – Sirolimus)	Inhibition of mTor pathway Altered protein synthesis	<p>↓ the incidence of non-melanoma skin cancer risk in transplant recipients</p> <p>Induced remission of non-melanoma skin cancer in renal transplant patients</p>

Skin cancers in autoimmune diseases

Lupus erythematosus, dermatomyositis, scleroderma and Sjögren syndrome are the most frequent autoimmune connective tissue diseases [35]. The main causes for the connection between the autoimmune connective tissue diseases and tumors, that could increase the probability of developing skin cancer, imply the damaged immune system, immunosuppressant therapy persistent skin inflammation, higher predisposition to viral infections, as well as additional causes like smoking, ultraviolet radiation exposure, white race and advanced age [35].

The most prevalent skin tumor in lupus erythematosus is squamous cell carcinoma, and a few cases of melanoma and basal cell carcinoma have been outlined. SCC is considered also a complication of discoid lupus erythematosus, with an estimated range from 2.3% to 3.3% [35, 36].

Scleroderma is also an autoimmune condition associated with higher risk of malignancy. Patients presenting the diffuse cutaneous form of systemic sclerosis,

increased age and female gender have increased malignancy risk [37, 38].

In scleroderma, the most frequent cutaneous malignancy is squamous cell carcinoma, in patients with systemic disease or particularly in cases of pansclerotic morphea, when SCC presents recurrences and resistance to treatment. The cancer risk is attributed to chronic ulcers, persistent inflammation, abnormal scarring, and immunosuppressant treatment. The most frequent sites of squamous cell carcinoma associated to scleroderma are legs, feet and scalp [35, 38].

Dermatomyositis is a systemic chronic autoimmune disease, with multifactorial etiology, but also it was observed as a paraneoplastic phenomenon. Requiring lifelong immunosuppression, dermatomyositis increases the patient malignancy risk. Association with malignant melanoma was reported in the metastatic stages and association of dermatomyositis as paraneoplastic phenomenon in melanoma patients determines a very poor prognosis [35, 39].



Sjögren's syndrome patients also have high cancer incidence. In a study reported by Lazarus et al. on 112 patients suffering by primary Sjögren's syndrome, lymphoma was the most frequent malignancy, followed by breast cancer and melanoma [40, 41].

A few cases were mentioned in the literature regarding occurrence of primary cutaneous lymphomas in patients with Sjögren's syndrome, including B and T cell lymphomas and cutaneous IgGk plasmacytoma [35].

A study conducted by Leung et al. showed an enhanced risk of non-melanoma skin cancer in patients on long-term immunosuppressive therapy for autoimmune hepatitis [42].

Also, strong associations were observed between psoriasis and T-cell lymphomas, Kaposi sarcoma and ulcerative colitis, sarcoma with Graves disease, rheumatoid arthritis with Merkel cell carcinoma [43].

Nitsan et al. reported a case of Mycosis fungoides development on face and left trunk in a 53 years old woman treated for her relapsing-remitting multiple sclerosis with Fingolimod-a sphingosine-1-phosphate (S1P) receptor modulator [44].

Summarizing, patients with autoimmune disorders have an increased risk of developing cutaneous neoplasia, especially squamous cell carcinoma [35].

Avoiding sun exposure, screening and monitoring of skin lesions in autoimmune disorders represent the means for guiding optimal skin cancer screening strategy, but further studies are needed in this direction [42].

Immunotherapy for skin cancer

The first scientific proof of using immunotherapy for cancer dates back from 1891, when William Coley placed into inoperable tumors streptococcal bacteria to induce an immune response [45, 46].

After years in which this therapeutic option was viewed with disbelief, the 1990s brought new insights regarding cancer immunotherapy. Immunogenic cancer antigens were detected, which encouraged the idea of immune system implication, moreover activated dendritic cells

are able to induce specific tumor T-cell in order to limit melanoma metastasis [47-49].

From all skin cancers, melanoma has the privilege to be the most studied in terms of immunotherapy. IFN and IL-2 have been used intensively as adjuvant for advanced melanoma, but unfortunately disease-free survival is still a hard goal to achieve [50-52].

Another study found that sentinel node metastasis and ulcerated form of melanoma benefit the most from IFN- α -2b treatment [53]. High doses of IL-2 (HD IL-2) had moderate results, with mild benefit for metastatic melanoma. Due to the side effects and quality of life impairment, HD IL-2 alone failed to impose the medical practice [54]. Association between IL-2 and chemotherapeutic agents as cisplatin or temozolomide led to development of biochemotherapy, also with low overall response rate [55].

By blocking the CTLA-4 receptors from T-cells using specific antibodies (Anti-CTLA-4 antibody- Ipilimumab) it will enhance proliferation of tumor-specific T-cells. Ipilimumab increased the median overall survival which led to the approval by several countries [56, 57].

The concept of using vaccines for melanoma treatment was also investigated, but some Phase III trials failed to prove any benefits in the study group [58, 59].

Nowadays a significant attention is pointed to personalized medicine and the study of melanoma is not an exception from this fact. Adoptive T-cell therapy means that lymphodepleted patients will benefit from their own processed (amplified/expressed specific antigen receptors) lymphocytes. In some recent clinical trials, the overall clinical response rate was 30%, but patients experienced autoimmune side effects [60, 61].

In the field of non-melanoma skin cancer immunotherapy, Imiquimod is the first synthetic agent of immune-response modifier with best clinical outcome. It binds dendritic cell receptors (TLR7, TLR8) and promotes secretion of a wide variety of cytokines. Furthermore, Imiquimod is able to give a positive feedback on NK cells, B lymphocytes and Langerhans cells [62]. It can be used topically in treatment of superficial BCC, small-nodular BCC and in situ SCC [63].



Imiquimod is the most successful example of immunotherapeutic agent, especially for inoperable cases or patient concerned with cosmetic result of surgery [64].

Promoting prevention strategies

Promoting prevention strategies regarding skin cancer development is a major goal when dealing with immunosuppressed patients.

Tapering of immunosuppressant doses, prevention of viral infections and early diagnosis through regular and adequate screening programs before and after transplantation may help decrease the risk of malignancy after transplantation [65].

The sun exposure is a main factor in tumor development and we saw that squamous cell carcinoma is the most frequent cancer in association with organ transplant or autoimmune diseases. Therefore, patients have to avoid sun exposure as much as possible, use lotions with high level of sun-protection factor, wear adequate clothing (large hats or umbrella, long sleeves, long trousers) when performing outdoor working [23].

According to Tunçer Vural et al., immunosuppressed patients (like solid organ transplant recipients) are strongly advised by medical care providers to make regular visits (once or twice a year) for dermatologic examination and education for skin cancers and sun exposure prevention measures, improving their attitude toward the aforementioned factors [66].

Wu et al. have shown that self-examinations and dermatologist-performed skin exam of the whole body together with sun protection education can decrease skin cancer morbidity and mortality in solid organ

transplant recipients but further longitudinal trials are needed in order to understand the impact of interventions on cutaneous malignancy, morbidity and to optimize the results of the treatment of transplant recipients [67].

Early recognition and ablation of premalignant tumors also help in preventing skin cancers [23].

Conclusions

Important clinical evidence attests the implication of immune system in development and further evolution of skin cancer. Patient conditions requiring prolonged immunosuppressant therapy like transplant recipients or autoimmune diseases determine an increased malignancy risk, skin cancer (especially non-melanoma tumors: squamous and basal cell carcinomas) being a frequent occurrence in those patients. It is important to understand the relative risk and to identify the causes of the high risk in tumor development in order to decrease the effects of malignancies on the morbidity and mortality in immunosuppressed patients.

Interaction immune system-skin cancer was the base for introducing immunotherapy in the therapeutic panel with good clinical results. Promoting skin cancer preventive strategies represent an important element and life-long follow-up of the patients is mandatory.

Competing interests

The authors declare that they have no competing interests.

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