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Roles of the Immune System in Skin Cancer

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Abstract

Over the past several decades, there has been increasing interest in understanding the roles of the immune system in the development and progression of cancer. The importance of the immune system in human skin cancer has been long recognised based primarily upon the increased incidence of skin cancers in organ transplant recipients and mechanisms of ultraviolet light-mediated immunomodulation. In this review, we integrate multiple lines of evidence highlighting the roles of the immune system in skin cancer. First, we discuss the concepts of cancer immunosurveillance and immunoediting as they might relate to human skin cancers. We then describe the clinical and molecular mechanisms of skin cancer development and progression in the contexts of therapeutic immunosuppression in organ transplant recipients, viral oncogenesis, and ultraviolet light-induced immunomodulation with a primary focus on basal cell carcinoma and squamous cell carcinoma. The clinical evidence supporting expanding roles for immunotherapy is also described. Finally, we discuss recent research examining the functions of particular immune cell subsets in skin cancer and how they might contribute to both anti-tumour and pro-tumour effects. A better understanding of the biological mechanisms of cancer immunosurveillance holds the promise of enabling better therapies.

INTRODUCTION

Skin cancer is the most common class of human malignancies. The most common types are the two major non-melanoma skin cancers (NMSC) of keratinocytic origin: basal cell (BCC) and squamous cell carcinoma (SCC). In the United States alone, more than 3 million cases of BCC and SCC are estimated to occur annually[1,2] with the total direct and indirect costs exceed $2 billion dollars annually[3]. In this review, we discuss theoretical frameworks and clinical and molecular evidence for how the immune system is involved in the pathogenesis, progression, and persistence of skin cancers, particularly NMSC.

CANCER IMMUNOSURVEILLANCE

In 1909, Paul Ehrlich first suggested that the immune system could be protective against cancer[4]. Around the same time, William Coley laid the foundation for cancer immunotherapy by describing patients who experienced spontaneous tumour regression after developing post-surgical infections, notably erysipelas[5]. Subsequently, Coley administered *Serratia marrascens* and *Streptococcus pyogenes* to elicit tumour regression; however,

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studies were not well-controlled and interest faded with the rise of chemotherapy and radiation[6].

In the 1950s, the original immunosurveillance theory of Burnet and Thomas was bolstered by the finding that syngeneic mice rejected tumours upon secondary challenge and could be vaccinated[7]. This suggested that the immune system could recognise tumour-specific antigens and acquire anti-tumour immunity. The term "cancer immunoediting" as advanced by Robert Schreiber and colleagues has been used to emphasise that the immune system continuously sculpts tumours[8] (Fig. 1). Immunodeficient mice lacking lymphocytes and components of interferon signaling such as *IFN-γ* and *Stat1* are more susceptible to carcinogen-induced and spontaneous primary tumours[9,10]. These findings, combined with the identification of tumour antigens in experimental cancer models and in humans, provide a basis for the activation of innate and adaptive immune systems in anti-tumour responses[11]. To test the immunogenicity of tumours arising in immunocompetent versus immunodeficient mice, they were isolated and re-introduced into naïve wild-type mice, whereupon it was found that those tumours arising in immunodeficient mice were more immunogenic (more likely to be rejected) than those arising in immunocompetent mice[9,12]. Thus it was postulated that tumours are continuously "edited" by the intact immune system in three stages such that immunogenic tumour cells are progressively eliminated, effectively selecting for cells more likely to be able to evade the immune response (Fig. 1).

In the **elimination** phase, innate and adaptive arms of the immune system are able to destroy cancer cells, and has yet to be definitively demonstrated. If the tumour is not completely eliminated, an **equilibrium** can develop in which the immune system and tumour interact to yield alterations in both cell populations. Evidence for tumour dormancy is largely indirect from reports of decades-long latencies in recurrent primary cancers or metastases in patients (discussed below), but it has also been reported in carcinogen-induced sarcomas in mice in which acute antibody-mediated depletion of immune function resulted in outgrowth of previously occult tumour cells[13]. In the **escape** phase, tumour cells become less immunogenic, adapt to evade the immune response, and/or actively immunosuppress the host[8]. This likely results from a combination of factors including the presence of immunosuppressive leukocyte subsets and the suppression of tumour antigen presentation through downregulation of antigen processing or MHC class I expression[14].

Though definitive evidence for these stages is still emerging in humans, there are some lines of evidence suggesting that this a useful conceptual framework for cancer immunosurveillance. The composition and quantity of intratumoural immune infiltrates has prognostic value in multiple tumour types[15–17]. Spontaneous anti-tumour responses occur in patients sometimes resulting in paraneoplastic neurologic disorders, and there is an increased risk of multiple tumour types including skin cancer in immunosuppressed individuals. The immunoediting framework may also apply to the development of skin cancer, because of the typically long latencies and the apparent spontaneous resolution of pre-neoplastic lesions such as actinic keratoses, but these specific phases have yet to be delineated *in-vivo*.

CLINICAL STUDIES LINKING IMMUNOSUPPRESSION WITH SKIN CANCER

Pharmacological Immunosuppression

The impact of immunosuppressive therapy on cutaneous cancer development has been studied most comprehensively in solid organ transplant recipients (OTRs). Although immunosuppression is necessary for preventing transplant rejection, these lifelong treatments promote carcinogenesis. Skin cancer is the most common, comprising 40% of post-transplant malignancies[18], 90% of which are BCC and SCC[19]. In kidney recipients, 15

to 40% will develop skin cancers within the first 10 years, and as many as 82% do so after 20 years[20,21]. The most common skin cancers among OTRs are (in decreasing order of frequency) SCC, BCC, Kaposi's sarcoma (KS), melanoma, and Merkel cell carcinoma (MCC) Table I)[22]. In large series, there is an estimated 65 to 250 fold increased incidence of cutaneous SCC and a 10 fold increased incidence of BCC in renal transplant recipients (RTRs) versus immunocompetent populations, and the risk is higher in men[23–26]. Skin cancers are also more aggressive in OTRs[27–29], with a 3-year disease specific survival of 56%[30,31] and a metastasis rate of 7% compared to 0.25% in the general population[32]. Cutaneous cancer incidence may correspond to the degree of immunosuppression[20,25,33], correlating with lower CD4 counts[34], and the reduction of immunosuppression reduces the rate of initial and subsequent skin cancers[33,35].

A modest risk of skin cancer in haematopoietic cell transplantation (HCT) recipients may be attributed not only to radiation, but also to altered immune function and immunosuppression. Aberrant cutaneous immune responses in lymphoid malignancies are probably best understood in the context of chronic lymphocytic leukaemia (CLL), the most common leukaemia, in which pseudolymphomatous reactions to otherwise innocuous stimuli such as insect bites are well described[36]. CLL patients have an 8-fold increased risk for NMSC[37,38], are 7 to 14 times more likely to suffer recurrences from SCC and BCC, respectively, following Mohs surgery[39,40], and are more likely to develop and die of metastatic SCC[41]. NMSCs can be densely infiltrated by neoplastic B-cells, and this is proposed to compromise anti-tumour T-cell responses[42,43].

There are other contexts in which HCT patients are predisposed to skin cancers. The positive correlation between chronic graft versus host disease (GVHD) and NMSC, especially SCC[44–48], may be due to GVHD prophylaxis as well as to chronic inflammation[44–48]. Retrospective analyses have also found an increased risk of SCC in this patient population with azathioprine therapy, especially when combined with cyclosporine and steroids[49,50].

The degree of risk conferred by particular drugs and their mechanisms of action remains an active area of research. Calcineurin inhibitors (CNIs), such as cyclosporine and tacrolimus, are among the drugs most strongly linked to skin cancer development. The risk of SCC is increased with cyclosporine use in psoriasis patients exposed to UVA radiation[51]. In RTRs, cyclosporine promotes cutaneous carcinogenesis in a dose-dependent manner[33,52]. CNIs inhibit Langerhans cells,[53,54] dermal dendritic cells (DC)[55,56], and T-cell signaling and proliferation, and cyclosporine directly promotes tumour development[57–59]. Inhibition of calcineurin enhances carcinoma development in mouse models, and correlative evidence in human SCC implicates induction of *ATF3* and bypass of senescence[59,60]. Tacrolimus is increasingly used for OTRs due to a favourable side effect profile as compared to cyclosporine in some settings.[61] With respect to NMSC, studies have either shown a trend towards reduction in risk with tacrolimus as compared to cyclosporine particularly at early time points[62–64], or no significant difference[65].

Azathioprine is associated with increased skin cancer risk, particularly for SCC, which may partly be due to increased photosensitization and UVA-mediated mutagenesis through direct incorporation of the metabolite 6-thioguanine into DNA[52,66,67]. Increased numbers of *p53*-mutant foci were found in the skin of azathioprine-treated RTRs, and corresponded to decreased DNA repair activity in treated keratinocytes[68]. Inflammatory bowel disease patients have a modest increase in NMSC that is especially pronounced with chronic thiopurine (azathioprine/6-mercaptopurine) use[69]. Many trials in OTRs evaluate combination regimens making it difficult to discern the individual contributions of azathioprine[70]; however there is data suggesting that the dose-dependent risk of SCC associated with azathioprine use is significantly higher than that associated with

cyclosporine or corticosteroid use[71]. Many trials trials show a significantly elevated risk of NMSC with azathioprine and a relative protective effect of mycophenolate mofetil (MMF)[72–75] with up to 27% relative risk reduction[74], though at least one trial shows no significant difference[65]. MMF has also been associated with an elevated risk of BCC in heart transplant recipients[76]. MMF is also an antimetabolite, inhibiting *de novo* purine biosynthesis through inhibition of inosine monophosphate dehydrogenase[77]. However, it does not appear to have the photosensitizing or mutagenic properties of azathioprine, perhaps explaining the lower relative risk of malignancy with this drug[78].

Recently, the mammalian target of rapamycin (mTOR) inhibitors, which include sirolimus (rapamycin), temsirolimus, and everolimus, have elicited significant interest because they have direct anti-tumour properties. Temsirolimus and everolimus are used to treat renal cell carcinoma[79]. Originally, sirolimus was found to be immunosuppressive by inhibiting the ability of T-cells to proliferate in response to interleukin (IL)-2[80,81]. The target of this group of drugs, mTOR, is a multifunctional protein kinase that regulates protein translation[82–84], survival, cell growth, and cell proliferation[85–87] in response to growth factors through its two main targets 4E-BP1 and S6K1[79,88]. mTOR activity can promote cell motility through regulation of actin reorganization and adhesion[88], and promote secretion of angiogenic factors such as VEGF-A/C by tumour cells thus accounting for the ability of mTOR inhibitors to suppress metastasis[89–91]. In retrospective analyses, RTRs[92] who received sirolimus/everolimus without cyclosporine, or sirolimus maintenance therapy after early cyclosporine withdrawal, had reduced numbers of *de novo* skin malignancies, and some patients experienced regression of skin cancers such as KS, sebaceous carcinomas, and SCC that were present prior to initiation of mTOR inhibitor therapy[93–98]. De Fijter and colleagues described 53 RTRs from 8 European centres who developed NMSC, but after conversion from a CNI to an mTOR inhibitor, 37 of them underwent remission. Although 15 relapsed, there was no correlation with drug levels and some continued to receive low-dose CNIs[98]. Most studies suggest that mTOR inhibitors are an important alternative to CNIs and that the intrinsic anti-tumour activities of these drugs may be particularly useful in the transplant setting.

Biologic therapies are increasingly used for autoimmune conditions including rheumatoid arthritis, psoriasis, and Crohn's disease because they are effective and steroid-sparing. Infliximab, adalimumab, and golimumab are monoclonal antibodies that target tumour necrosis factor (TNF)-α, and ustekinumab is one that targets the p40 subunit of IL12 and IL23[99,100]. Etanercept functions as a decoy receptor for TNF-α, and alefacept binds CD2 on T-cells, preventing their interaction with antigen presenting cells and promoting apoptosis. The majority of these drugs directly target pro-inflammatory mediators whereas alefacept targets a critically important cellular interaction necessary for promotion of local inflammation[101]. Several case and cohort studies suggest that infliximab, etanercept, and adalimumab are associated with rapid development of NMSC, especially SCC[69,102–107], and that etanercept and adalimumab are associated with resurgence of latent metastatic melanoma[108]. This connection may be related to disruption of cancer immunosurveillance and polarization of the immune response towards a Th2 cytokine profile, which is less able to control tumour growth[109,110]. A recent meta-analysis of randomised controlled trials of anti-TNF-α biologics for psoriasis indicated that there is no statistically significant increased risk of malignancy; however it is likely that the collective experience with these drugs in large trials is insufficient to assess this risk accurately, and there are likely to be different risk profiles in other patient populations such as those with rheumatoid arthritis[111].

Other commonly used immunosuppressants also affect skin cancer risk though they are much less extensively studied. Oral glucocorticoid use is correlated with an up to 2 to 3 fold

increase in NMSC[112–114]. Buchbinder and colleagues identified a 3 fold increase in melanoma among rheumatoid arthritis patients treated with methotrexate[115].

Inadvertent transplantation of occult melanoma to OTRs is the most common cause of donor-derived malignancy to result in metastasis[116,117]. It makes up 28% of metastatic donor-transmitted cancers,[118] occurs 6 months to 16 years after the surgery, and is associated with a less than 5% overall five-year survival rate[118–121]. This extended dormancy may be explained by a prolonged equilibrium phase. In one study of donor-derived metastatic melanoma, 11 of 16 patients died but 4 showed complete remission after nephrectomy and cessation of immunosuppression[118]. Similarly, a deceleration of NMSC was observed in RTRs who discontinued immunosuppressants[122]. This suggests that the host immune system can enforce long-term tumour dormancy and destroy an immunogenic cancer once competence has been restored.

Ultraviolet (UV)-Induced Immunosuppression

UV radiation, particularly UVB (290–320nm), is considered the most important environmental risk factor for skin cancer (Fig. 2). Chronic exposure causes actinic keratoses and SCC, while intermittent high-dose exposure correlates more with risk for BCC and melanoma[123]. In addition to facilitating mutagenesis through induction of DNA photoproducts, UV exposure has dramatic effects on immune function. In the foundational experiments of photoimmunology, Margaret Kripke and colleagues demonstrated the antigenicity and immunogenicity of UV-induced skin cancers by showing that these tumors are rejected by syngeneic hosts but not by syngeneic hosts exposed to UVB radiation[124,125]. This exposure induced “suppressor T cells” that could specifically inhibit the ability of syngeneic mice to reject UV-induced but not other types of transplanted tumours[126]. It is now known that these “suppressor T cells” are either NKT cells [127] or regulatory T-cells (Tregs; discussed below) depending on the context, and these cells dampen immune responses *in-vivo* [128]. In UV-induced skin cancer models, chronic irradiation at one site could accelerate UV-induced tumour development at distinct, previously-shielded sites consistent with the systemic immunosuppression demonstrated by Kripke and colleagues[129].

Though most experiments detailing UV-mediated immunosuppression have been performed in animal models,[130] exposure in humans has been found to inhibit delayed-type (DTH)[131–133] and contact hypersensitivity reactions (CHS)[134–137]. In both contexts, UV-mediated immunosuppression can be local and systemic. For example, CHS can be suppressed if the sensitiser is applied to a previously irradiated site; however at 3 to 4 mean erythemal doses of UVB, elicitation can be significantly suppressed even if sensitisers are applied to distant non-irradiated sites[134,138]. DTH measure antigen-specific responses following vaccination. In reported human studies, UV exposure was given after exposure or infection[139], and like CHS, suppression of elicitation reactions occurs at both local and distant unirradiated sites[133,140]. Interestingly, UVB-mediated suppression of CHS positively correlates with a prior history of skin cancer[141], and UV-induced immunosuppression is enhanced in males which may explain the increased incidence and risk of mortality in skin cancers in men[142].

The mechanistic basis for UV-induced immunosuppression is likely to overlap significantly for local and systemic effects. Local effects include the depletion and downregulation of Langerhans cell antigen-presenting capacity[143,144]. UV exposure also stimulates keratinocytes and macrophages to produce cytokines such as IL-10, which is important for systemic immunosuppression[144,145]. The chromophores that are thought to be most important for UV radiation are DNA, membrane lipids, and trans-urocanic acid (trans-UCA) which is isomerised to cis-UCA. The resultant combination of DNA damage, generation of reactive oxygen species, and cytokines conspires to mutagenise epidermal cells and create

an immunosuppressive environment that favours tumour formation and progression (Fig. 2)[146–148].

Viral Etiologies

Studies have demonstrated an increased incidence of certain viral-associated cancers in immunosuppressed populations secondary to virus reactivation.[149] Viral infection is important in the pathogenesis of certain variants of SCC[150,151], KS[152], and MCC.

Human papillomavirus (HPV) can be found in almost all skin samples tested, including in neonates[153]. High-risk α-HPVs are known to cause cervical, periungual, and anogenital carcinomas[151,154]. However, high-risk HPV serotypes that express the oncogenic E6 and E7 variants that abrogate p53 and retinoblastoma (pRB) protein family function, respectively, are not reproducibly found in cutaneous SCC[155,156], and, in contrast to anogenital SCC or cervical carcinoma due to high-risk α-HPV, HPV gene expression is not present in human cutaneous SCC[157] indicating that HPV is not required for maintenance of SCC. Although this does not formally exclude a role for HPV in the initiation of sporadic SCC, for example by synergizing with UV-induced DNA damage or apoptosis[156,158–161], the high incidence of *INK4A* and *p53* inactivation in SCC suggests that the best established oncogenic activities of HPV proteins may not be relevant[155].

MCC, a highly aggressive cancer, was recently found to express Merkel cell polyomavirus (MCPyV) gene products[162]. The risk of MCC is increased in the immunosuppressed (Table I)[163], and MCPyV genes are present more often in NMSC of OTRs as compared to immunocompetent patients, particularly those with Bowen's disease and BCC.[164] In immunocompetent hosts, the virus is present in over 60% of normal skin samples[165,166], 30% of BCC, and 15% of SCC[164,167]. MCPyV DNA is integrated into MCC tumour cell genomes, and expression of a mutated viral large T-antigen that is capable of inhibiting pRB is found in MCC tumour tissues[168,169]. In addition, this expression is required for the survival and proliferation of MCC cell lines[170]. This evidence collectively suggests that MCPyV is critically important in the pathogenesis of MCC, although the precise molecular mechanisms remain to be elucidated. Recently, two articles show that high-titer virus-specific antibody responses and denser intratumoural CD8+_T-cell correlate with improved prognosis[15,171], suggesting that MCPyV is also immunogenic and that MCC may be amenable to immunotherapy.

IMMUNOTHERAPY

Immunotherapy for skin cancer has been most extensively studied in melanoma. Immune agonists such as systemic IFN-α-2b and high-dose IL-2 have both been used as adjuvants for late-stage melanoma with modestly increased disease-free survival in a small proportion of patients[172,173]. Because melanomas express specific antigens such as Mart1 and gp100 that elicit T-cell responses, there has been sustained interest in vaccine-based and adoptive T-cell immunotherapies. Many systemic immunotherapies now combine vaccination against these antigens or chemotherapy with adoptive T-cell immunotherapy for which at least 19 trials are currently open around the world[174]. In these methods, lymphocytes are extracted from melanomas or peripheral blood, stimulated and expanded *ex-vivo*, and then re-introduced back into the patient. In some methods, T-cells are genetically engineered to have specificity for particular antigens[175,176]. Though some long-lasting remissions have been reported and initial response rates have been as high as 72%[177], it has been difficult to predict responses in patients.

Recently, ipilimumab, a humanised antibody against the inhibitory T-cell receptor CTLA-4, was shown to extend overall survival in unresectable Stage III/IV melanoma from an

average of 6.4 months with gp100 vaccine alone to 10 months with ipilimumab alone or in combination with gp100 vaccine[178]. CTLA-4 normally suppresses the activity of T-cells after initial T-cell receptor engagement in order to limit immune responses and to prevent autoimmunity[179–181]. It was soon shown that CTLA-4 blockade could enhance anti-tumour immune responses in combination with vaccines, resection, and chemotherapy[182–186]. In accordance with this function, multiple biomarker studies indicate that ipilimumab enhances T-cell responses as measured by increased numbers of activated effector CD4 and CD8 T-cells[187,188]. In the near future there will be multiple studies examining combinations of ipilimumab with chemotherapy, radiation, and other immunotherapies[189].

For other skin cancers such as NMSC, topical or local immunomodulatory has been used. Imiquimod is clinically effective against superficial primary skin tumours and cutaneous metastases[190], including BCC, Bowen's disease, erythroplasia de Queyrat, and lentigo maligna[191]. Imiquimod activates Toll-like receptor (TLR) 7 on plasmacytoid DCs, causing the NF-κβ-dependent secretion of pro-inflammatory cytokines such as IFN-γ and the chemokines CXCR3, CXCL10, CXCL11, and CCL8 that collectively regulate lymphocyte trafficking[192–194]. This results in further activation of antigen-presenting cells and enhancement of Th1 and cytotoxic CD8+ T-cell responses[194–196]. Imiquimod also antagonises adenosine receptor signaling pathways, thereby suppressing the regulatory arm of the immune response, which normally functions to limit inflammation[197]. In SCC, imiquimod decreases the number of peritumoural regulatory T cells (Tregs) recruited, the amount of IL-10 and transforming growth factor (TGF)-β produced, and it restores vascular E-selectin expression[198]. E-selectin is a cell adhesion protein important for the extravasation of inflammatory cells, and may be important for enabling anti-tumour responses. Although these mechanisms have not been as extensively studied in actinic keratosis and superficial BCC, short-term clearance following imiquimod treatment has been demonstrated[199–201] suggesting that in some circumstances, recruitment of an appropriate inflammatory response can result in tumour clearance. Intralesional IFN-α-2b, another immune agonist, also has activity against BCC and SCC[202,203].

WOUND HEALING AND CHRONIC INFLAMMATION

Though we have emphasised how the immune system may control tumour progression, a link between inflammation and carcinogenesis has also been established. Virchow posited a connection between wound healing and cancer when he demonstrated the resemblance between tumour stroma and granulation tissue[204]. The microenvironments of healing tissue and invasive tumours are very similar: both are characterised by inflammation and are rich in growth factors, chemotactic and angiogenic factors, and migrating cells[205]. Chronic inflammation may also promote cancers, as suggested by associations between inflammatory bowel disease and colorectal carcinoma, gastroesophageal reflux disease and esophageal adenocarcinoma, and chronic skin wounds and Marjolin's ulcers. In small series and reviews of case reports, Marjolin's ulcers, carcinomas that arise in sites of chronic wounds are more aggressive with rates of metastasis over 20%[206]. This is true in series describing carcinomas in leg ulcers[207–209], ulcerated leprosy lesions[210], scar carcinomas[211,212], and burns (the most common presentation of Marjolin's ulcers)[206], though rates of SCC in burn sites are not significantly increased[213,214]. These associations could result from increased mutagenesis, facilitated by elevated free radicals and continuous cell proliferation in the setting of chronic inflammatory stress[215]. It has been suggested that aggressive management to close wounds quickly may largely forestall development of carcinomas in these areas[206]. Importantly, the correlation between chronic inflammation and cancer is not always seen. The prominent chronic inflammation seen in psoriasis has not been consistently linked to increased skin cancer rates, even after immunosuppression and elevated UV exposure secondary to treatment[216].

THE ROLES OF IMMUNE CELL SUBSETS IN NON-MELANOMA SKIN CANCER

Initial characterisation of peritumoural infiltrates in cutaneous SCC showed that there are polyclonal CD3+ αβ T-cells present, only a minority of which are CD8+[217]. Multiple series have indicated that peritumoural inflammatory infiltrates are more cellular in immunocompetent individuals as compared to immunosuppressed ones[218,219]. Increased tumour-related immune responses are associated with improved prognosis in MCC[15,171], and increased density of tumoural T-cell infiltrates is associated with improved prognosis in melanoma[16,17]. Mechanistic studies aimed at understanding how these cells function in the tumour microenvironment have been reported primarily in NMSC.

A subset of the “suppressor T-cells” identified by Kripke and colleagues that suppress the rejection of UV-induced tumours are now considered to be Tregs. Tregs are now known to be critical for maintaining tolerance to self-antigens and are ideal candidate culprits in enforcing tolerance to tumours by perhaps suppressing otherwise effective anti-tumour immune responses.[220–222]. The lineage-specific transcription factor and marker *FOXP3* is required for the maintenance and function of Tregs, which are believed to suppress immune function by elaborating IL10 and TGF-β, competing with effector T-cells for IL2, and inhibiting antigen presentation by DC[223]. Increased numbers of Tregs are linked to a worse prognosis in breast, ovarian, pancreatic, and hepatocellular carcinomas[224–228], and have been identified in BCC[229], SCC[198,230], and primary and metastatic melanomas[231–233]. In addition, vitamin D3 and immunosuppressants such as dexamethasone and sirolimus can induce differentiation of naive T-helper cells into Tregs[234,235]. Up to 50% of T cells in SCC isolates are reported to be FOXP3+ Tregs[198], and one study found that Tregs increase in number with the progression of pre-cancerous actinic keratoses to established SCC[236]. A rise in the percentage of Tregs was also seen in the progression of benign nevi to atypical nevi to radial growth phase melanomas[231]. The risk of SCC in RTRs is modified by peripheral blood immune phenotype, as those with elevated FOXP3+CD4+:CD8+ T-cell ratios appear to be at greater risk[237]. However, others have reported that perineoplastic inflammatory infiltrates in SCC of OTRs have a significant reduction in Tregs and TGF-β when compared to those of non-transplant populations[219,238]. However, important caveats to these sometimes contradictory studies are that Treg numbers are not always compared to those of other T-cell subsets such as cytotoxic killer cells (their relative abundance might be more relevant), that *FOXP3* can be transiently expressed by activated non-Treg T-cells, and that the actual function of Tregs in the tumour microenvironment is not known.

Before T-cells can be activated, they must be presented their cognate antigen. DCs fulfill this function as professional antigen-presenting cells and induce lymphocyte activation and proliferation; however, they can also inhibit immune responses depending on their degree of differentiation[239]. BCC infiltrates contain elevated numbers of immature CD11c+ myeloid DCs, suggesting a suppressive immune environment, since immature DCs are thought to cause T-cell anergy instead of activation[229]. In SCC, tumoural myeloid DCs were less able to stimulate allogeneic T-cell proliferation in a mixed-lymphocyte reaction than those isolated from normal skin, also suggesting functional compromise. Increased expression of IL-10 and TGF-β around the tumour tissue was proposed as the mechanism for this deficiency[240]. Finally, plasmacytoid DCs are potent inducers of IFN-α and are present in cutaneous peritumoural tissue as well as tumours treated with imiquimod[194,241,242]. These cells are reduced in SCC from OTRs as compared to those from immunocompetent individuals[219]. However, their exact role in tumour modulation is still unknown.

As with dendritic cells, tumour-associated macrophages (TAM) may play significant roles in both tumour progression and suppression. The presence of TAMs in BCC correlates with

increased invasion, microvessel density, and COX-2 expression, properties that are linked to more aggressive cancers[243]. In SCC, TAMs are heterogeneously activated with markers that suggest both pro-tumour and anti-tumour activities[244], and also appear responsible for vascular endothelial growth factor-C-induced lymphangiogenesis[245].

This recent work characterising the often complex and contradictory roles of specific immune cells in NMSC has started to shed light on how immune cells can both control and promote tumourigenesis and progression (Fig. 3). It is only through advances in cell culturing and isolation techniques that such work is even possible now. The directed manipulation of the immune system to control cancer will require this type of detailed knowledge so that interventions may be rationally designed based upon our understanding of how immune cells interact with cancer cells.

CONCLUSIONS

Significant clinical evidence implicates the immune system in the development, progression, and destruction of skin cancers. However, active cancer immunosurveillance, particularly by adaptive immune cells, is not universally accepted. In clinical experience, established tumours very rarely spontaneously regress, though it is impossible to know how many of these events occur undetected. Because tumours possess both genetic and non-genetic heterogeneity, there may be differential outgrowth of particular subclones but it is unknown how this might relate to immunoediting[14]. Although it has been argued that many tumours do not exhibit inflammation[14], infiltrates are frequently observed in skin cancers[16,198,246], even those in which there is no secondary ulceration or infection.

The elevated risk of skin cancers in therapeutically immunosuppressed individuals is well-established, but recent discoveries indicate direct tumour-promoting effects of certain drugs, such as cyclosporine on SCC development. UV radiation appears to have dual effects in mutagenesis and immune suppression as well. Although the natural course of tumour-immune interactions remains incompletely understood, ongoing studies will surely aid in improving cancer immunotherapy.

What's known

- The importance of the immune system in human skin cancer has been recognised based upon the increased incidence of skin cancers in organ transplant recipients and ultraviolet (UV) light-mediated immunomodulation.
- Studies primarily in mice have demonstrated roles for specific immune cell subsets such as lymphocytes and macrophages in promoting and inhibiting tumour formation.
- Studies in mice have identified mediators of UV-mediated immunomodulation.

What's new

- Recent research identifies specific mediators of immune modulation following exposure to ultraviolet light, immunosuppressants, and immune activators in humans.
- Calcineurin inhibitors are now known to directly affect human keratinocytes likely synergizing with immunosuppressive effects to promote cancer.

- Functions of specific immune cell subsets such as tumoural macrophages and regulatory T-cells in human skin cancers have been shown to both promote and inhibit tumour progression.

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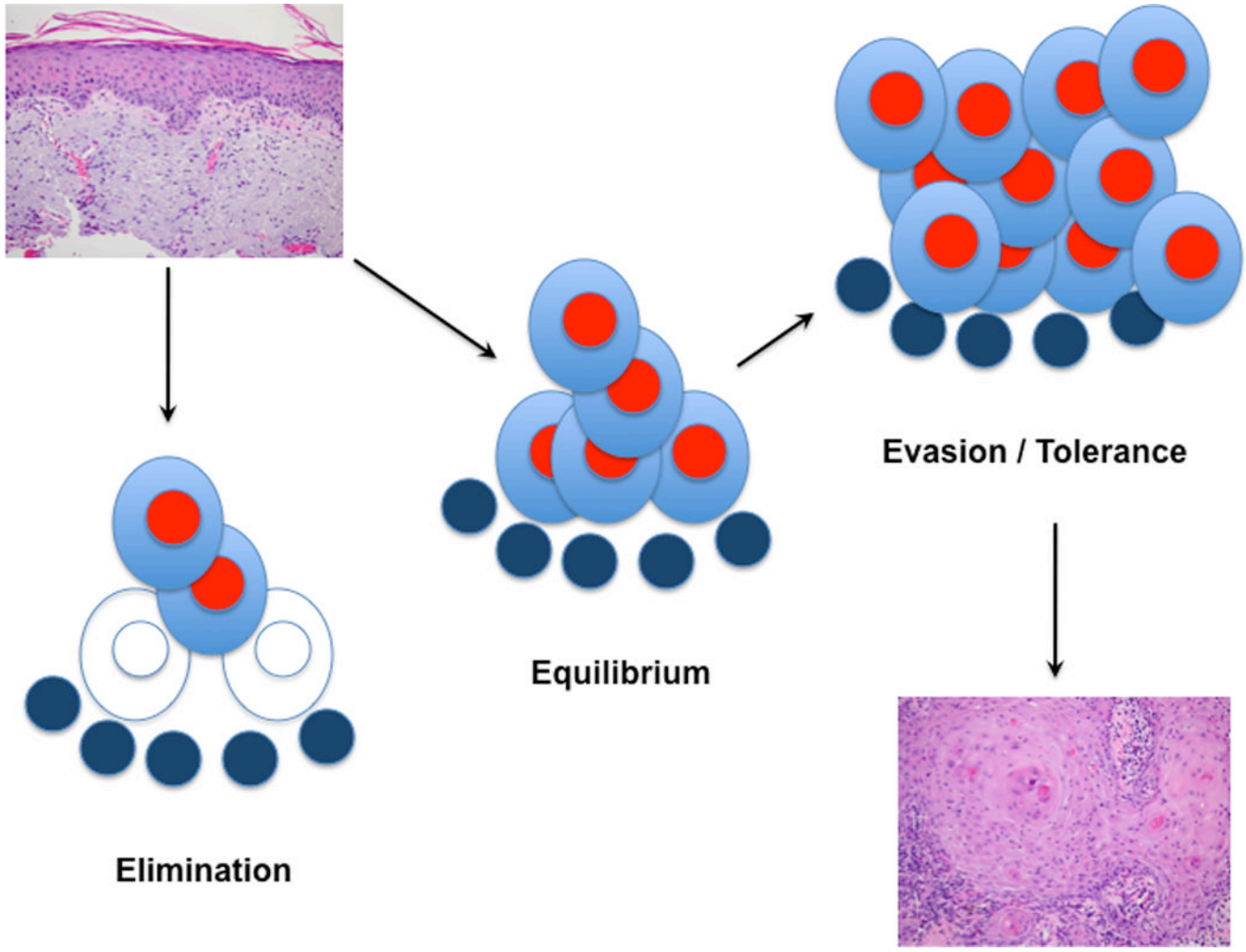

Figure 1. A Paradigm of Cancer Immunosurveillance

Initially, there are pre-cancerous lesions, such as the illustrated actinic keratosis (upper left), in which elimination may occur due to the killing of altered cells by elements of the immune system. Alternatively, a stage of equilibrium may result where tumour cells and immune cells interact during a period of stable tumour size. During this period, immune cells may select to more aggressive and/or less immunogenic tumour variants. Eventually, perhaps as a result of this process, the tumour expands and continues to grow despite the presence of an immune response. This continued growth can be observed in invasive squamous cell carcinoma which typically does not spontaneously regress (lower right).

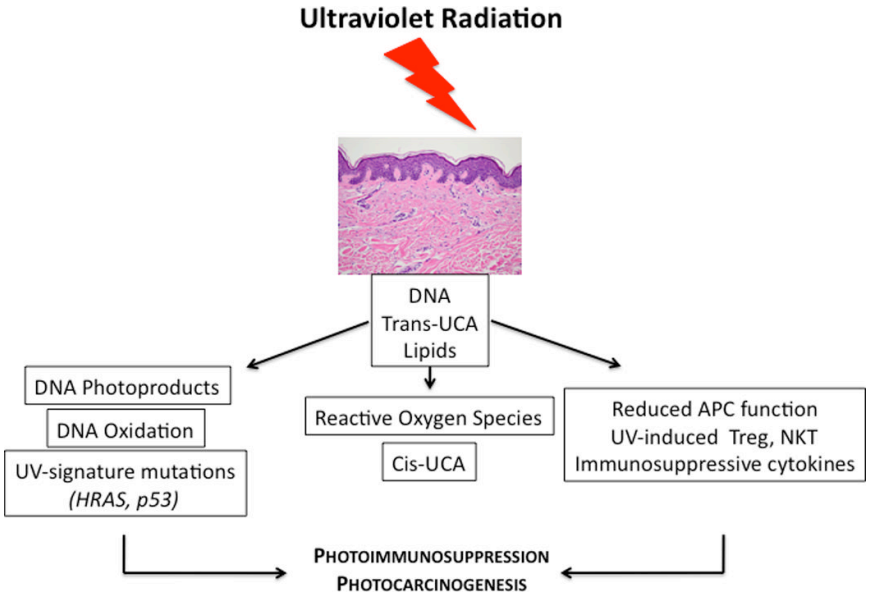

Figure 2. Mechanisms of Ultraviolet (UV)-Induced Immunomodulation and Carcinogenesis

UV radiation is absorbed by DNA, trans-UCA, and membrane lipids. This results in multiple effects on DNA (left column), generation of various chemical species (middle column), and changes in various cellular compartments (right column). The production of DNA photoproducts, cis-UCA, reactive oxygen species, and active vitamin D produces a range of additional biological mediators that ultimately result in enhanced DNA damage, DNA mutagenesis, decreased DNA repair, and immunosuppression. These factors conspire to induce carcinogenesis.

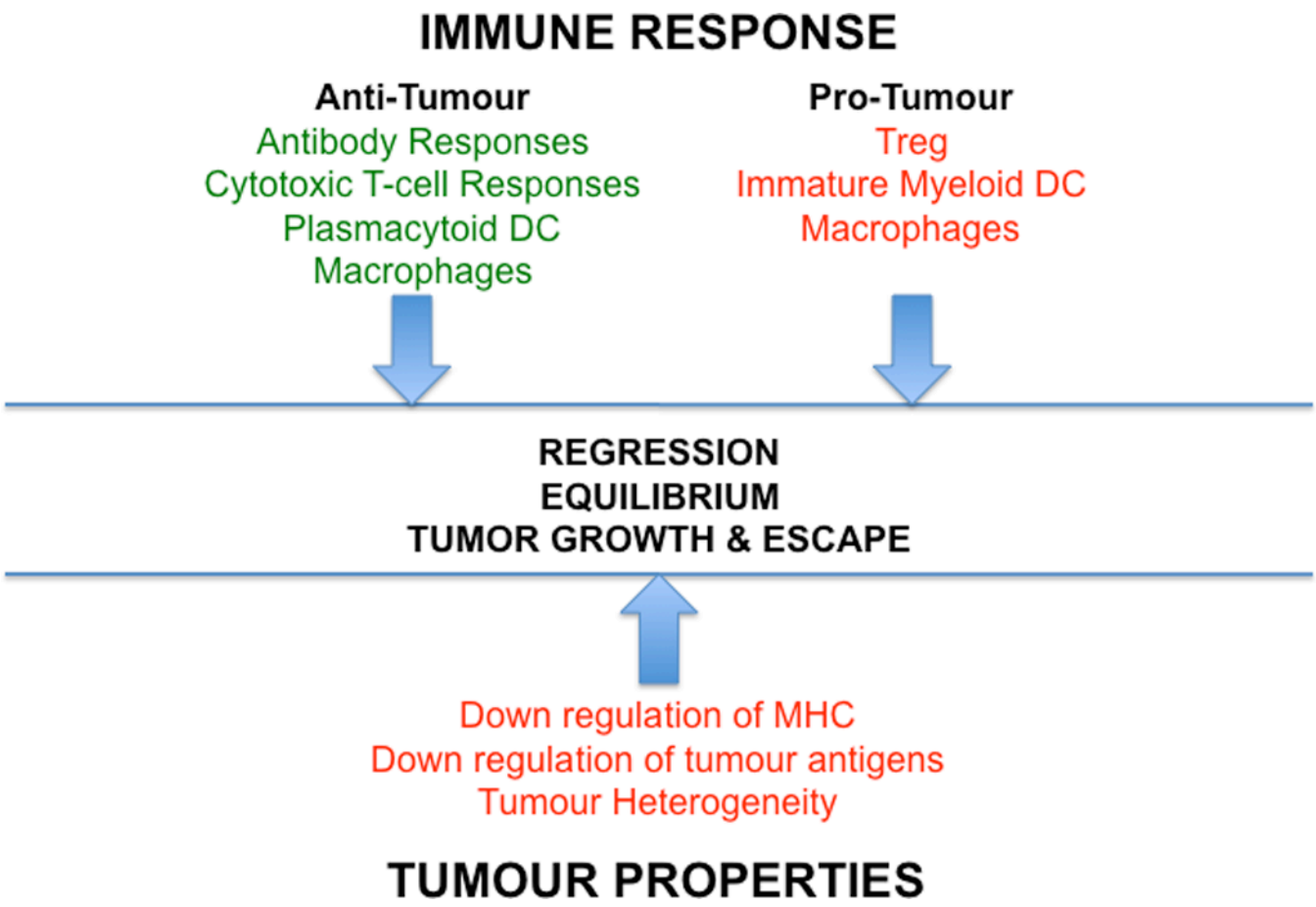

Figure 3. Multiple Cancer-Immune Interactions Occur in Skin Cancer

Antigen-specific and non-specific interactions characterise the immune response to cancer as well as tumour-intrinsic adaptations. Those thought to favour tumour development are highlighted in red and those that favour tumour elimination are highlighted in green. The combination of these interactions ultimately dictate the outcome in terms of tumour regression, equilibrium or progression. Lymphocyte responses can be antigen-specific or non-specific. T-cells, macrophages, and DCs can have pro- and anti-tumour effects. Tumour cells may adapt as well by downregulating MHC class I and processing and expression of tumour antigens, and may acquire new mutations or exhibit heterogeneous immunogenicity, enabling immune escape.

Table I

Population-based standardised incidence ratios in cutaneous malignancies in organ transplant recipients

Skin cancer	Standardised Incidence Ratio
Squamous cell carcinoma	
Cutaneous	65 to 250 fold[23–26]
Lip	20 to 45 fold[25,26]
Basal cell carcinoma	10 fold[24]
Malignant melanoma	0 to 8 fold[25,26,62,247–249]
Kaposi sarcoma	80 to 200 fold[25,247]
Merkel cell carcinoma	70 fold[163]