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The Immune Microenvironment in Basal Cell Carcinoma

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The immune system plays a key role in the suppression and progression of basal cell carcinoma (BCC). The primary aetiological factor for BCC development is exposure to ultraviolet radiation (UVR) which, particularly in lighter Fitzpatrick skin types, leads to the accumulation of DNA damage. UVR has roles in the generation of an immunosuppressive environment, facilitating cancer progression. Rates of BCC are elevated in immunosuppressed patients, and BCC may undergo spontaneous immune-mediated regression. Histologic and immunohistochemical profiling of BCCs consistently demonstrates the presence of an immune infiltrate and associated immune proteins. Early studies of immune checkpoint inhibitors reveal promising results in BCC. Therefore, the host immune system and tumor responses to it are important in BCC pathogenesis. Understanding these interactions will be beneficial for disease prognostication and therapeutic decisions.

Keywords: Basal cell, Carcinoma, Neoplasms, Skin neoplasms, Tumor-infiltrating lymphocytes

EPIDEMIOLOGY AND CLINICAL FEATURES

Basal cell carcinoma (BCC) is the most common malignancy, and its overall incidence continues to rise[1,2]. Several studies suggest incidence is increasing in Asian populations with lighter Fitzpatrick skin types[3,4]. Overall, the disease is most prevalent in older age groups and men[5]. Skin, hair, and eye phenotype are independent risk factors for the development of BCC, with the disease occurring more frequently in people with lighter skin (i.e. Fitzpatrick skin type I-III), red or blonde hair color, and light eye colour[6-9]. The most common site for BCC, in all ethnicities, is the head and neck[10-13].

Patients typically present with slow-growing lesions (frequently on sun-damaged skin), that may be ulcerated, bleeding, pruritic, or entirely asymptomatic[6]. Pigmented BCC represents 50% to 75% of tumors in Asians; more than 10 times the number observed in Caucasians[10,11,14]. Pigmented BCC is less aggressive. These lesions require fewer Mohs stages for excision, have reduced subclinical infiltration and are associated with less aggressive histologic subtypes[15,16]. Nodular BCC is the most common histological subtype across all ethnicities—representing up to 80% of cases, followed by superficial BCC[10,12,17]. Less frequent histologic subtypes are associated with clinically aggressive behavior and recurrent disease[18]. These include—morpheaform, sclerosing, infiltrative, micronodular, and basosquamous[18]. The presence of perineural invasion is also a high-risk finding[18]. High-risk clinical factors include—location on the head and neck, size ≥2 cm, poorly defined borders, recurrent tumors, and lesions at sites of previous radiation therapy[18].

LYMPHOMA TO LYMPHOPROLIFERATIVE DISORDERS

BCC appears to be chiefly caused by ultraviolet radiation (UVR)[19]. BCC occurs most frequently on sun-exposed sites (i.e. head and neck) and rates are higher in individuals with greater susceptibility to ultraviolet (UV)-induced DNA damage (i.e. lighter Fitzpatrick skin types)[6,7]. BCC is characterized by a typical UV mutation signature, namely C>T transitions occurring at dipyrimidine sites, and sporadic BCC has the highest mutation burden of any malignancy[20,21].

Iatrogenic radiation and arsenic exposure have also been established as causes of BCC[22-24]. Iatrogenic radiation to the head and neck leads to a relative risk for BCC development of 3.6[23]. Arsenic-induced BCC often develops after a long latency period and frequently occurs on non-sun exposed sites[24].

Commonly mutated genes in BCC have been described. Genetic profiling of patients with Basal Cell Naevus Syndrome, who develop multiple BCCs from a young age, identified mutations in the *PTCH1* gene[25,26] which encodes a transmembrane receptor involved in the Hedgehog signaling pathway[27]. Studies of sporadic BCC have mapped driver mutations to *PTCH1* and other components of the Hedgehog pathway including *SMO* and *GLI*[28-30]. Other recurrently mutated driver genes include *TP53* and members of the *RAS* proto-oncogene family[21].

UVR suppresses cutaneous immunity. Early studies by Kripke[31] demonstrated that transplantation of UV-induced tumors into immunocompetent mice resulted in the immune rejection of tumors. Similar transplantation experiments with immunosuppressed or UVB-irradiated mice maintained tumor survival[31]. The induction and elicitation of contact hypersensitivity are suppressed when hapten is applied to a site irradiated by either UVB or UVA radiation[32,33].

There are many mechanisms of UV-mediated immunosuppression. Locally, UVR affects chromophores in the skin, changing the molecular configuration and altering function. Urocanic acid is found predominantly in the stratum corneum[34,35]. It is a chromophore that undergoes UV-mediated conversion from trans-urocanic acid to *cis*-urocanic acid[36]. The roles of these isomers differ. While trans-urocanic acid appears to have a photoprotective role—there is an accumulation of UVB-mediated DNA damage in mice deficient in the enzyme necessary for its production[37]—*cis*-UCA has deleterious effects through its promotion of cutaneous immunosuppression. *Cis*-UCA increases TNFα levels[38]. TNFα traps Langerhans cells within the epidermis, impairing migration to draining lymph nodes and subsequent generation of specific T cells[38]. *Cis*-UCA has roles in promoting mast cell degranulation[39].

UVR promotes the formation of reactive oxygen species, which oxidize esterified fatty acyl residues and create platelet-activating factor-like (PAF-like) ligands[40]. These stimulate the PAF pathway, producing cyclooxygenase (COX) 2 and mast cell activation[41].

Experimental studies have implicated COX2 overexpression in BCC cell lines with increased angiogenesis and resistance to regulated cell death following UVR[42]. Higher expression of COX2 in BCC has been associated with increased invasion and angiogenesis[43].

Nucleotide lesions, specifically UVR-induced cyclobutane pyrimidine dimers (CPDs), may have immunosuppressive properties[44,45]. In mouse models and human skin, repair of CPD lesions by endonucleases facilitated systemic and local hypersensitivity reactions[46,47], prevented erythema and sunburn, and increased production of interferon (IFN)-γ-mediated cell adhesion molecule ICAM-1[46].

Vitamin D (activated by UVR) has roles in immunosuppression[48,49]. When applied topically in high doses, calcitriol, the active form of vitamin D, suppresses delayed-type hypersensitivity reactions[48]. Calcitriol binds dendritic cells and suppresses their maturation[50]. The outcome is a reduced antigen-presenting capability and an increased differentiation of T-regulatory cells[51]. Vitamin D intake has been reported as modestly associated with BCC but not cutaneous squamous cell carcinoma (cSCC) risk[52,53].

IMMUNOSUPPRESSION AND BCC

Immunosuppression is associated with an elevated risk of keratinocyte cancer (KC) development. Organ-transplant recipients (OTRs) are a high-risk group for the development of KC[54]. cSCC incidence in OTRs is up to 250 times that of the general population[55]. BCC incidence is around 10 times that of the general population[55]. This may be explained by the differences in immunogenicity of each tumor. The cumulative dose of immunosuppressive medication in OTRs has a greater effect on cSCC risk than BCC risk[56,57]. Heart/lung and renal transplant recipients have higher KC rates compared to liver transplant recipients[58-60] and the BCC:cSCC in liver transplant patients appears to be closer to that of the general population[60,61]. This may be due to reduced cumulative immunosuppressive doses in liver transplant recipients[60].

Unlike cSCC, there is no strong evidence supporting that BCCs in OTRs display aggressive disease. A study examining 176 cases of BCC from OTRs identified certain features unique to OTR BCCs, including the development of lesions at a significantly younger age, presence of significantly more lesions on extra-cephalic locations, and identification of lesions at unusual sites including genitalia and axillae[62]. A retrospective study

of 69 renal transplant recipients did not identify differences in localization or clinicopathologic presentation of BCCs[63].

LYMPHOMA

Non-Hodgkin lymphoma (NHL) encompasses a group of lymphoproliferative disorders which induce immunosuppression. The neoplastic immune cells alter the expression of cell surface markers, leading to reduced recognition and inhibition of effector cells[64,65]. Locally and systemically B-cell NHL patients have an expansion of $CD14^+$ $HLA\text{-}DR^{low}$ monocytes with immunosuppressive properties and elevated $CD4^+$ $CD25^+$ T-regulatory cells[66,67]. Chronic lymphocytic leukemia (CLL) patients are at an increased risk of developing many cancers[68]. Compared to the general population, the standardized cancer incidence ratio (all cancers) is 2.0 for men and 1.2 for women[68]. Rates of KC (both cSCC and BCC) are elevated in patients with NHL[68-71]. In a recent study, BCC incidence was calculated for CLL and non-CLL-NHL[72]. Both groups demonstrated an elevated incidence of BCC compared to the general population[72], with a greater difference observed in the CLL group[72].

The clinical behavior of KC in NHL patients is more aggressive, and KC is associated with a poorer NHL prognosis[73]. Non-melanoma skin cancer may be a marker of poor prognosis in patients with non-Hodgkin's lymphoma[74]. This relates to both BCC and cSCC. In patients with CLL and BCC managed with Mohs micrographic surgery (MMS), 5-year local recurrence was 22%; 14 times higher than in patients without CLL[75]. Higher post-treatment recurrence rates were identified in another study assessing this population[72].

HUMAN IMMUNODEFICIENCY VIRUS

HIV status has been associated with elevated rates of BCC and cSCC development[76-78]. In one large study HIV, positive individuals had a 2.1-fold increase in BCC[76]. Similar results were identified by Burgi et al.[77]. Crum-Cianflone et al.[79] evaluated incidence rates and risk factors for the development of cutaneous malignancies in 4,490 HIV-infected patients. In HIV-positive individuals, risk factors for the development of BCC, including skin, hair, and eye phenotype, are unchanged from those seen in the general population[79]. In their study, participants developed BCC at a significantly younger age than that observed in the general population[79]. They also noted a raised BCC:cSCC ratio, unlike the converse observed in OTRs where cSCC is the predominant KC. The most common location for BCCs was the head and neck[79].

Studies have not identified an association between lower $CD4^+$ T cell counts and higher viral load with increased risk of BCC[76,77,79,80].

IMMUNE INFILTRATE

T lymphocytes

Early studies consistently demonstrated a predominantly T cell infiltrate in BCC[81-86] (Fig. 1)[85]. These tumor infiltrating lymphocytes (TILS) have various functions and may promote or inhibit tumor survival. Normal skin appears to have a paucity of infiltrating T cells—this includes a lack of CD8 and CD3 expression[87].

A small proportion of BCCs undergo either partial or complete spontaneous regression. Several immunologic differences have been described in this population. $CD3^+$ and $CD4^+$ cells are present in significantly higher numbers in the overlying epidermis of regressing BCC[88]. A case report of a regressing BCC described elevated levels of $CD3^+$, $CD4^+$, $CD8^+$, and TIA-1 (a marker of NK cells) in the immune infiltrate[89]. A case series of periorbital regressing BCC also demonstrated increased infiltration of $CD4^+$ T cells around and into the tumor nests[90]. In addition, the IL-2 receptor, a marker of activated T cells, was elevated in regressing tumors[88,91]. These findings suggest that particular phenotypes of $CD4^+$ expressing T cells may mediate tumor regression[88]. These may likely be Th1 $CD4^+$ T cells—reflected by the cytokine profile of regressing BCCs[91].

$CD4^+$ $CD25^+$ $FOXP3^+$ T-regulatory cells have been detected around BCC tumor aggregates[87].

In facial BCC, nearly half of $CD4^+$ cells were identified as being $CD4^+$ $FOXP3^+$ regulatory T cells[86]. This is in comparison to UV-protected skin which has a paucity of T-regulatory cells[86]. T-regulatory cells have immunosuppressive functions[87]. Elevated expression of CCL22, CCL18, and CCL17, chemokines that attract T-regulatory cells, have also been described in BCC[87].

Kaporis et al.[87] have described elevated levels of $CD8^+$ T cells in BCC compared to normal skin, with high levels of IFN-associated gene interleukin (IL)-12 and IL-23 expression which together promote memory T cells and have anti-tumor properties. Other studies have reported the presence of these cytokines in BCC[92,93]. CD8 expression levels were reduced in

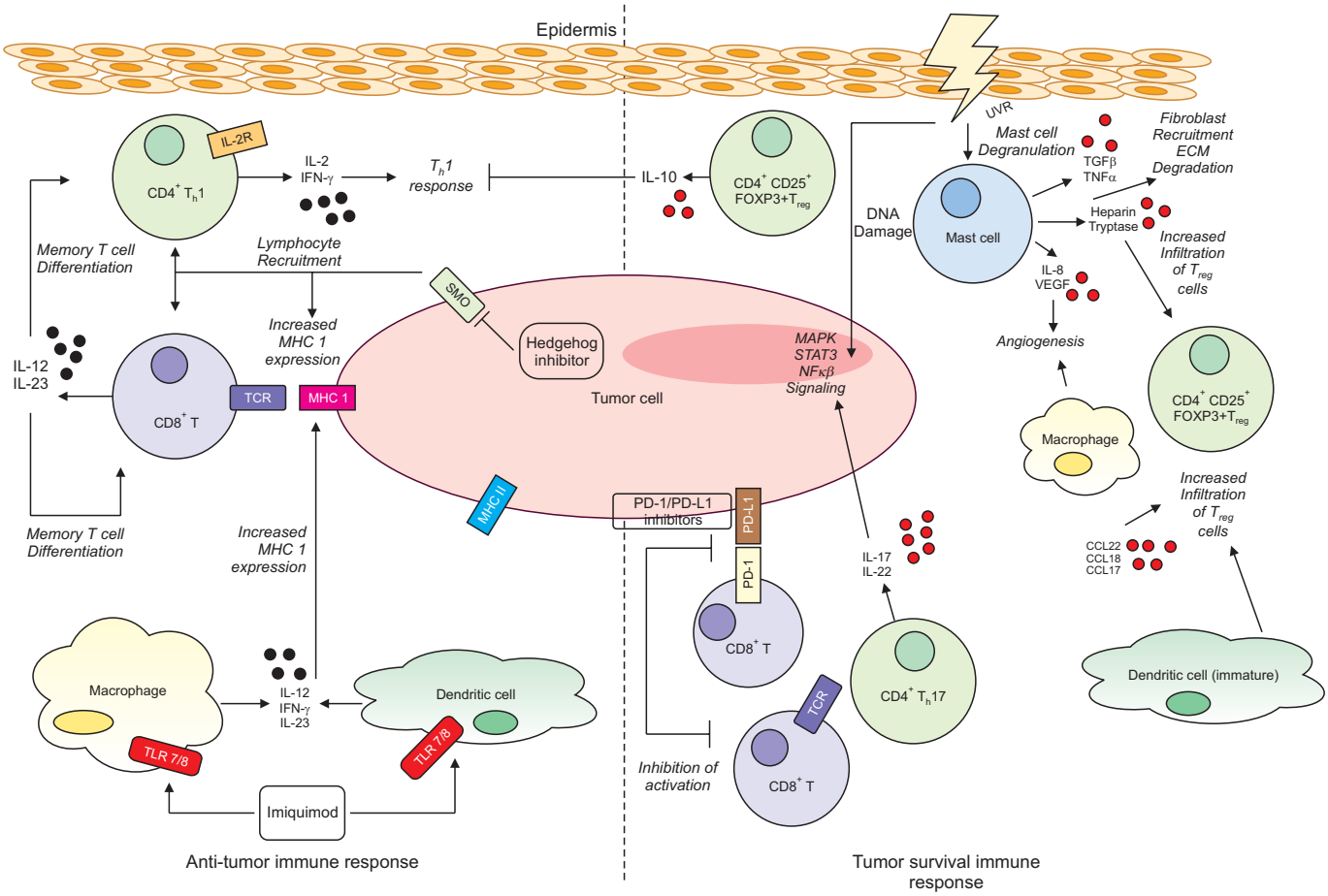

Fig. 1. The immune response (tumor promoting and tumor inhibiting) to basal cell carcinoma (BCC). Tumor promoting: Ultraviolet radiation (UVR) damages DNA leading to mutagenesis. UVR suppresses cutaneous immunity through many mechanisms including promotion of mast cell degradation. Mast cells have roles in angiogenesis through expression of interleukin (IL)-8 and VEGF. Other mast cell mediators include heparin, tryptase, TGFβ and TNFα. These promote a T_h2 environment, induce T-regulatory cells and recruit fibroblasts. $CD4^+$ $FOXP3^+$ T-regulatory cells are found in the immune infiltrate. These cells release suppressive cytokines and inhibit the T_h1 response. IL-17 and IL-22 cytokines promote MAPK, NFκβ and STAT3 signaling. Chemokines CCL17, CCL18, CCL20 and immature dendritic cells have roles in attracting T-regulatory cells. The PD-1/PD-L1 pathway is an immune resistance mechanism promoting apoptosis of effector cells. High levels of PD-1 and PD-L1 are found on tumor cells and immune cells. This interaction is inhibited by immune checkpoint inhibitors. Tumor inhibiting: $CD4^+$ and $CD8^+$ helper T cells are present in the BCC immune infiltrate. These effector cells secrete T_h1 cytokines including IL-2 and interferon (IFN)-γ. IL-12 and IL-23, cytokines involved in the regulation of the T_h1 response, promote memory T cell differentiation and the anti-tumor response. MHC expression is low in BCC. Expression is increased after Imiquimod treatment and Hedgehog Inhibitor treatment. Imiquimod increases levels of the anti-tumor cytokines IL-12 and IFN-γ. Mature dendritic cells have tumor inhibiting roles. Macrophages appear to have conflicting roles in BCC pathogenesis. ECM: extracellular matrix.

primary BCC tumors of patients who then went on to have recurrent disease[94]. In summary, there is relatively sparse knowledge of T cell infiltration in BCC lesions and how they affect clinicopathologic presentation and prognosis.

Mast cells

There is a significant mast cell infiltrate in BCC, especially at the periphery of tumors[85,95-97]. The number of mast cells is inversely proportional to TILs[85], more aggressive tumors have greater mast cell numbers[85,96].

While smoking does not appear to be a risk factor for the development of BCC[98], it is associated with greater peritumoral mast cell numbers, which may explain the higher prevalence of aggressive morpheaform BCC variants in this population[99].

Mast cells express VEGF and IL-8, suggesting that mast cells may have roles in the regulation of the immune cell infiltrate and angiogenesis[95]. Similarly, BCCs with greater microvessel density are more aggressive[100]. Mast cell-deficient

mice inoculated with an aggressive melanoma variant have slower angiogenic responses and reduced rates of metastasis[101].

Mast cell granules contain various substances including histamine, heparin, leukotrienes, prostaglandins, tryptase, TNFα, TGFβ, IL-3, and IL-4[102]. Histamine and TNFα have roles in local and systemic immunosuppression[96,102-104]. Heparin and tryptase are mitogens for fibroblasts and endothelial cells and increase regulatory T cell function[105]. IL-4 levels have been demonstrated to be upregulated in BCC and facilitate a Th2, immunosuppressive environment[87].

Dermal mast cell prevalence is elevated in sun-protected skin of patients with a history of BCC, suggesting increasing mast cell density may be a risk factor for BCC development[106]. The authors proposed that given mast cells are facilitators of cutaneous immunosuppression, higher baseline dermal mast cell density may increase susceptibility for BCC development[106]. Previously, the authors reported that UVB-induced systemic suppression of contact hypersensitivity is determined by dermal mast cell prevalence[107].

Thus, mast cells may promote UVB-mediated immunosuppression, angiogenesis, and extracellular matrix degradation[102]. UVR itself also affects mast cells. UVR-induced mediators including *cis*-urocanic acid and endothelin-1 promote mast cell degranulation[104,108].

Macrophages and dendritic cells

Macrophages and dendritic cells are antigen-presenting cells. They are consistently reported to be present in the BCC immune infiltrate, but to a lesser extent than T cells[81,109].

Macrophages can broadly be classified into two phenotypic subsets, M1 and M2. M1 macrophages have traditionally been viewed to have anti-tumor properties—i.e. phagocytosis of tumor cells, secretion of cytokines promoting cytotoxic lymphocytes within the tumor microenvironment (TME)[110,111]. However, secreted reactive oxidative species also cause tissue damage and promote malignancy[112]. M2 macrophages may release tumor-promoting growth factors and have roles in angiogenesis and cell proliferation[113-115].

Beksaç et al.[94] identified a predominance of M2 macrophages in BCC. They did not identify an association of M2 macrophage level with recurrence[94]. No association was identified between macrophage subtype or amount in recurrent vs non-recurrent BCC in another study[116]. However, contrasting findings have been reported by Tjiu et al.[43], who identified the presence of M2 macrophages in BCC. Higher numbers of these TAMs were significantly associated with more aggressive disease—i.e. greater depth of invasion and higher microvessel density[43]. Exposure of BCC cell lines to M2 macrophages enhances invasion and angiogenesis in vitro[43]. Depletion of dermal dendritic cells, Langerhans cells and M1 macrophages in a PTCH-deficient mouse model resulted in enlargement of BCC lesions[117].

In contrast, nicotinamide (NAM), a KC chemo-preventive agent, results in a significant reduction of $CD68^+$ macrophages (a marker of M1 and M2 cells), but not of the M2-specific marker $CD163^+$, in the tumor infiltrate[118]. Therefore, NAM may selectively deplete M1 macrophages[118]. The authors postulated that this may be one mechanism of its anti-tumor effect[118].

CD1a is a marker of dendritic cells including Langerhans cells[94]. CD1a expression is relatively low in BCC[94]. Lower levels have been identified in primary tumors of patients who developed recurrent disease[94]. In one study, there were fewer CD1a expressing cells in the epidermis adjacent to the tumor versus normal epidermis[87]. Higher levels of Langerhans cells, identified by the S-100 marker, have been associated with less aggressive BCC[119]. Therefore, the presence of mature dendritic cells in the BCC TME may have a protective role.

Dendritic cells lacking markers of maturation (i.e. CD40, CD83, and LAMP) have been described in BCC[87]. These immature dendritic cells may have pro-tumorigenic functions by induction of T cell tolerance and production of suppressive cytokines[87,120,121].

MHC molecules

The significantly elevated rates of cSCC in OTRs compared to BCC may be in part explained by reduced MHC1 levels in BCC, implying that the $CD8^+$ cytotoxic immune response has a lesser role in BCC than in cSCC[122].

If cancer is to survive it must evolve mechanisms to evade the immune response. MHC class 1 molecules are expressed on antigen-presenting cells[123]. They present abnormal peptides synthesized by the cell itself and are presented to $CD8^+$ T cells[123]. BCC has a relative lack of MHC expression[122,124]. Normal human skin constitutively expresses MHC 1[124]. Expression of β2-microglobulin, a component of the MHC 1 molecule, is low in BCC[125]. Lower class 1 antigen expression in BCC is correlated with more aggressive tumors and lack of differentiation status[124]. Treatment with imiquimod increases

MHC 1 expression in BCC[126]. Treatment with hedgehog pathway inhibitors also increases MHC 1 levels and infiltration of $CD8^+$ T cells in BCC[127]. MHC class 2 expression is variable in BCC[85,89] and is more commonly present on infiltrating T cells compared to tumor cells[128,129].

HLA-G is a type of MHC class 1b antigen. Under physiological conditions, it occurs in immune-privileged sites. It has been characterized in some tumors and has immunosuppressive functions[130,131]. In BCC it is expressed on both neoplastic cells and inflammatory cells[132].

Cytokine profile

The dominant cytokine expression profile in most untreated BCCs facilitates local immunosuppression and tumor survival[133]. This suppressive cytokine profile is altered during treatment and in tumors which display spontaneous regression[91,93].

Most studies report that BCC is characterized by the expression of T_h2 cytokines[87,133,134], including IL-4, IL-5, IL-13, and IL-10[132,133]. Compared to cSCC, BCC has significantly higher levels of T_h2 cytokines: IL-4, IL-5, IL-6, and IL-1β[133]. ELISA assay of a BCC cell line demonstrated high levels of IL-10 and IL-4 production[134]. Tumor cell production of suppressive cytokines is a mechanism of tumor survival in BCC; however, anti-tumor cytokines are also present in lesions[87,91]. Head and neck BCC exhibits a more aggressive and treatment-resistive clinical course[133]. Higher numbers of suppressive cytokines are found in head and neck BCC[133].

IL-17, IL-22, and IL-23 are present in higher levels in BCC compared to normal skin[93]. Exposure of BCC cell lines to IL-17 and IL-22 cytokines results in cellular proliferation in vitro[92]. These results were replicated in xenograft tumor mouse models[92]. Prior studies have demonstrated slower tumorigenesis in IL-17 deficient mice[135]. Exposure of BCC cell lines to IL-22 results in increased amount and duration of phosphorylated products within the STAT3 and MAPK pathways[92]. Constitutive p65 phosphorylation, a proxy of NFκβ signaling , was identified following IL-17 exposure[92]. These findings imply that IL-17 and IL-22 play a role in BCC pathogenesis and likely promote tumor survival[92].

IFN-γ is a T_h1 cytokine with roles in promoting T_h1 differentiation[136]. Most studies report low IFN-γ levels in BCC, implying a reduced role for T_h1 mediated immunity[92,134]. Flow cytometry analysis of isolated BCC immune infiltrates demonstrated reduced IFN-γ-positive and $CD8^+$ T cell levels compared to peripheral blood mononuclear cells[92].

Elevated IFN-γ in the tumor infiltrate is associated with regressing tumors[91]. A recent study has described presence of Th1 cytokines in BCC and peritumoral skin, however non-irradiated (by UVR) skin lacked expression of these cytokines[86].

Imiquimod is a standard treatment for superficial BCC. It has both direct and indirect effects on the skin immune system which leads to immune-mediated destruction of neoplastic cells. It binds to toll-like receptor 7/8 on inflammatory cells leading to the release of pro-inflammatory mediators, including IL-12 and IFN-γ, and activation of the cell-mediated immune response pathway[126,137]. It also results in elevation of $CD68^+$ macrophages and plasmacytoid predendritic cell levels in the intra and peritumoral infiltrate[138], and an increase in $CD4^+$ T cells levels and MHC 1 expression[93,126,139]. These findings suggest the immune mechanisms by which imiquimod induces an anti-tumor response.

IMMUNE CHECKPOINT INHIBITORS

The programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) signaling pathway is an adaptive immune resistance mechanism that promotes apoptosis of effector immune cells[140]. In a series of 40 BCC's, 22% of tumors demonstrated PD-L1 expression on tumor cells and 82% demonstrated PD-L1 expression on TILS or macrophages[141]. PD-1 expression was demonstrated on TILS in 100% of cases[141]. 82% of cases with PD-L1 expression on infiltrating immune cells were near a PD-1 expressing cell[141]. Case reports describe mixed, but predominantly favorable, responses to immunotherapy[142-144].

A patient with metastatic BCC demonstrated a favorable response after 14 months of pembrolizumab[143]. Ikeda et al.[142] present a Hedgehog-inhibitor-resistant metastatic BCC treated with nivolumab. A near-complete remission at 4 months was achieved[142]. Amplification of a chromosomal region containing *PDL1/PDL2/JAK2* genes and a high mutation burden was detected[142]. A vismodegib-resistant metastatic BCC attained partial response to a trial PD-1 inhibitor REGN2810[145]. Goodman et al.[146] reported on four patients with locally advanced/metastatic BCC, with three of four demonstrating complete or partial responses to anti-PD-1 therapies. A recent phase 2 trial of the PD-1 antibody cemiplimab demonstrated clinically significant anti-tumor activity in locally advanced and metastatic BCC, with 21% of patients

demonstrating a partial response and 6% of patients demonstrating complete response[147]. In late 2021, the FDA approved cemiplimab for use in locally advanced and metastatic BCC[148].

The role of CTLA4-inhibitors in BCC is poorly characterized. A case report of a locally advanced BCC of the head and neck in a patient with BRAF-negative metastatic melanoma was commenced on ipilimumab with subsequent shrinkage of the BCC[149].

Inoperable or metastatic BCC may be a good candidate for immune checkpoint inhibitors; however, understanding the prognostic role of the immune infiltrate is imperative in the selection of these agents.

CONCLUSION

There are multiple mechanisms by which BCC evades the anti-tumor immune response. UVR facilitates the creation of an immunosuppressive environment. BCC tumors express suppressive cytokines and may downregulate MHC expression on tumor cells. BCC may undergo spontaneous regression and the immune profile of regressing tumors differs from that of progressing tumors. Treatments alter the immune infiltrate and cytokine profile of BCC, promoting an anti-TME.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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