Interleukin-22 and Cyclosporine in Aggressive Cutaneous Squamous Cell Carcinoma

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KEYWORDS

• Squamous cell carcinoma • Cyclosporine • IL-22 • Organ transplant recipient
• Transplant-associated squamous cell carcinoma • Immunosuppression
• Nonmelanoma skin cancer

KEY POINTS

- Cutaneous squamous cell carcinoma (SCC) is frequently curable, but causes significant morbidity and mortality, particularly in immune-suppressed organ transplant recipients.
- The SCC tumor microenvironment is rich and composed of multiple subsets of immune cells that exert antitumor and protumor effects.
- Interleukin (IL)-22 and its receptor are highly expressed in SCC and more so in transplant-associated SCC.
- IL-22 mediates SCC proliferation; an effect that is potentiated by cyclosporine.
- IL-22 blockade results in decreased SCC burden in a murine model system in vivo and may represent a therapeutic target.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is the second most common human malignancy, with more than 700,000 cases expected in 2016.[1–4] Although typically curable by excision with clear margins, SCC can behave aggressively and metastasize to local lymph nodes despite treatment.[5–7] Cutaneous SCC is characterized by the malignant proliferation of keratinocytes that typically occurs on sun-damaged skin and tends to develop within areas of noninvasive actinic keratosis (AK). Progression from AK to SCC is thought to occur as a result of ultraviolet (UV)-induced mutations in proto-oncogene genes, with as few as 2 mutations being sufficient to drive SCC development.[8,9] Additional factors from the tumor microenvironment likely influence SCC progression.

THE TUMOR MICROENVIRONMENT OF SQUAMOUS CELL CARCINOMA

Gene expression profiling of invasive SCC has revealed the presence of a large inflammatory response.[10] On a broad level, immune cells are thought to play a role in the antitumor response. These immune cells include Langerhans cells

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Abbreviations and acronyms

AK	Actinic keratosis
APC	Antigen-presenting cell
CSA	Cyclosporine A
DC	Dendritic cells
IL	Interleukin
iNOS	Inducible nitric oxide synthase
LC	Langerhans cell
mTOR	AKT-mammalian target of rapamycin
NFAT	Nuclear factor of activated T cells
NK	Natural killer cell
OTR	Organ transplant recipient
MMP	Matrix metalloproteinase
SCC	Squamous cell carcinoma
STAT	Signal transduced and activator of transcription
TAM	Tumor-associated macrophage
TNF	Tumor necrosis factor
Treg	Regulatory T cell
TSCC	Transplant-associated squamous cell carcinoma
VEGF	Vascular endothelial growth factor

(LCs), dermal dendritic cells (DCs), CD4+ and CD8+ T cells, T regulatory cells (Treg), macrophages, and natural killer (NK) cells. For SCC, some cell types typically implicated in tumor eradication, NK, B cells, and monocytes, are rarely detected surrounding and infiltrating tumors.[11] However, CD4+ and CD8+ T cells, DCs, and tumor-associated macrophages (TAMs) are often found infiltrating SCC tumors (**Fig. 1**).[11,12] These cells are thought to stunt malignancy and promote regression of primary tumors, but in the context of SCC some of these cell types may be functionally impaired or may exert protumor effects.

T cells are a significant component of the SCC microenvironment.[13–17] Gene expression profiling has shown that T-cell activity is decreased in SCC, as shown by downregulation of activation maker CD69 and impaired secretion of granzyme B and inducible nitric oxide synthase (iNOS).[10] In addition, myeloid-derived suppressor cells are present in SCC and function to impair T cell–mediated immunity by secreting nitric oxide in the tumor microenvironment. The consequence of this is dampening E-selectin expression on epithelial cells and impairment of T-cell entry into tumors.[18] In contrast, human T cells have been reported to secrete interleukin (IL)-24 in response to antigen stimulation, secretion of which has been shown to increase matrix metalloproteinase (MMP)-7 gene expression by SCC cells in culture, potentially contributing to SCC invasion.[19,20] Antibody blocking of SCC cells with MMP-7–specific antibody has been shown to significantly delay SCC migration.[19]

Antigen-presenting cells (APCs) in the skin include epidermal LCs and dermal myeloid DCs. Myeloid DCs from SCC do not stimulate T-cell proliferation, even when cultured in the presence of maturation promoting cytokines such as IL-1β, IL-6, tumor necrosis factor alpha (TNFα) and prostaglandin E2.[21] These data might indicate a significant gap in defense against SCC. This possibility is further supported by the presence of IL-10 and transforming growth factor beta (TGFβ) in the SCC microenvironment and expression of CD200 receptor by SCC-associated DCs.[21,22] Each of these has been shown to decrease DC-mediated T-cell responses.[23] LCs, located in the epidermal layer, should be the first APCs to encounter SCC tumor antigens generated by transformed keratinocytes. These cells are primarily found in tissues adjacent to and including the interface with the tumor.[24] Moreover, LCs from SCC have been shown to stimulate CD4+ and CD8+ T-cell proliferation at rates higher than those from normal skin eliciting a type 1 T-cell response.[24] In addition, they express higher levels of LC maturation markers, CD40, CD80, CD83, and CD86. This finding might indicate an antitumor role for LCs in human SCC. In contrast, diphtheria toxin depletion of LCs in mice decreases ultraviolet B (UVB)–induced SCC tumor growth.[25] These data suggest that LC responses somehow contribute to SCC tumor growth. LCs from SCC have been reported to express immune-activating signal transducer and activator of transcription (STAT) 4, IL-15, and CD80, and immune tolerizing CD200 genes.[24] Therefore, it is possible that LCs can have protumor roles in the context of SCC, despite their ability to elicit T-cell responses.

An abundance of TAMs are found surrounding as well as penetrating SCC.[26] TAMs may play a dual role in the tumor microenvironment, because they maintain the potential to eradicate tumor cells but have been shown to promote tumor growth. TAMs in the SCC microenvironment have been shown to be classically activated M1 marker, alternatively activated M2 marker, or biactivated M1 and M2 marker expressing (**Fig. 2**).[27,28] M1 activation is driven through the type 1 T helper (Th1) cytokine interferon gamma (IFNγ),[27,29] whereas M2 activation occurs as a result of type 2 T helper (Th2) cytokines, which include IL-10, IL-13, and IL-4.[29] Although M1 macrophage responses are thought to prevent tumor growth, the predominant subtype found in SCC tumors are M2 macrophages, which have lower antigen-processing capacity.[30] In addition, they have been shown to negatively correlate with tumor growth and