



## MINI REVIEW

# The Role of CD57+ T-Lymphocytes in the Increased Frequency and Aggressiveness of Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients

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## Introduction

Organ transplant recipients (OTR) have 100-fold increased risk for cutaneous squamous cell carcinoma (cSCC) compared to the general population. Modified immune surveillance mechanisms may contribute to the perceived differences in incidence, clinical behavior and increased aggressiveness of cSCC in OTR. It could also provide some insight into the pathogenesis of cSCC in various disorders characterized by low immunity such as HIV, hematological malignancies and immune-mediated inflammatory disorders. In a recently published study, immunological senescence resulting from an increased expression of CD57+ T-cells in the peripheral blood was found to be associated with a higher risk of cSCC in OTR and may serve as a valuable tool in predicting a future skin cancer risk in those patients [1]. Immunocompetent individuals (ICP) and OTRs frequently show an intense peritumoral inflammatory cell infiltrate [2]. However, the inflammation is thought to be different, both qualitatively and quantitatively between these two populations. A subset of the lymphocytic inflammatory infiltrate, the CD57, is routinely used to identify terminally differentiated 'senescent' cells characterized by a reduced ability to proliferate and by a modified function. This lymphocyte subset has been linked to various malignancies in the past [3].

## Discussion

Skin cancers are the most common malignancies in organ transplant recipients. Cutaneous SCC occur 4

times more frequently than BCC in OTR, while the reverse is noted in ICP [4]. Significant morbidity and mortality are associated with cSCC in OTR resulting from their multiplicity and their potentially aggressive clinical outcome. As a result, they constitute a major health burden in this patient population [5]. The pathogenesis of cSCC in OTR is multifactorial and includes: The mutagenic effects of ultraviolet (UV) radiation, altered immune surveillance mechanisms, host genetic susceptibility factors, the direct carcinogenic effects of immunosuppressive drugs and increased susceptibility to oncogenic viruses, such as human papillomaviruses. Exposure to UV radiation results in a typical UV signature mutation in cSCC of OTR which involves tumor suppressor genes as well as activate several oncogenes. The specific tumor suppressor genes commonly involved are: TP53, Notch1/2 and CDKN2A, which are similar to the genetic alterations frequently observed in cSCC of ICP, suggesting no consistent differences in host genetic susceptibility factors between cSCC in OTR and ICP [1].

Immunosuppression is believed to be a major contributing factor for metastasis in cSCC of OTR, as these tumors are more likely to be associated with aggressive clinico-pathological features than is seen in cSCC of ICP [5]. The Dysregulated immune system of the host and tumor microenvironment has also been suggested to contribute to the early development and the progressive course of cSCC in immunocompromised patients. Histological evaluation of the lymphocytic infiltrate present in cSCC showed that T lymphocytes are the major constituent cells of the

inflammatory infiltrate present in and around the tumor, they compromise 60% to 90% of the entire lymphocytic population [6]. However, Previous studies suggested differences in the density of the peritumoral inflammatory cell infiltrates and the specific lymphocyte subsets present between cSCC of OTR and ICP. OTRs showed a decrease in CD3+ T-lymphocyte and CD8+ cytotoxic T-lymphocyte population in their cSCC. A reduced FOXP3+ regulatory T-lymphocyte population in cSCC of OTR was also observed. Additionally, the CD123+ plasmacytoid dendritic cells were found to increase proportionally in the progression from intraepithelial to invasive cSCC in ICP but were diminished in all cSCC of OTRs [2].

The CD57 antigen (HNK-1, LEU-7 or L2) is a 100-115 kD terminally sulfated carbohydrate surface molecule that is present on human natural killer cells (NK), CD4 and CD8 T-cells in their late stages of differentiation. It possesses both memory-like features and powerful effector functions. However, the accumulation of CD57+CD4+ T-cell subset occurs at a lower level than does the CD57+CD8+ subset. Accordingly, the focus of medical research was on examining the function of the CD57+ T-cell subset specifically expressed by the CD8+ T-cell population [3]. Terminally-differentiated CD57+CD8+ T-cells in the peripheral blood of healthy individuals are characterized by a loss of expression of CD27 and CD28 [7]. They indicate a reduced proliferative capacity of these cells and altered effector function. However, Senescent CD57+CD8+ T-cells can still display a high cytotoxic potential with a robust expression of granzyme, granulysin, and perforin. They also maintain the ability to secrete certain cytokines such as TNF- $\alpha$  and IFN- $\gamma$  upon stimulation with an antigen. CD57+ T-lymphocytes were also shown to increase during normal aging, chronic infections and certain autoimmune diseases, as chronic antigen stimulation results in the accumulation of senescent and terminally differentiated T cells [8]. Consequently, the expression of the CD57+ T lymphocytes in the peripheral blood and tissues have been used as a prognostic marker indicating an adverse clinical outcome in chronic infections such as HIV, hepatitis and tuberculosis as well as in human aging, autoimmune disorders and various malignancies [3].

Studies have consistently shown that the presence of senescent CD57+ CD8+ T-cells in the peripheral blood is associated with a poor survival in patients with certain malignancies such as: Renal cell carcinoma, metastatic melanoma, gastric carcinoma, and bladder malignancy. Although the CD57 subset of circulating CD8+ T-lymphocytes are responsible for almost all the cytotoxic potential of CD8+ T-lymphocytes, these CD57+ T-cells do not seem to prevent the growth of malignant cells and may compete with the host immune system for resources such as cytokines and nutrients, further ameliorating

host defense mechanisms against tumor antigens. In a flow cytometric analysis of CD8 tumor-infiltrating lymphocytes isolated from resected melanoma metastasis, Richard C. Wu, *et al.* reported that a significant number of tumor infiltrating lymphocytes consisted of CD8+CD57+ T-cells. They concluded that CD8+ T-cells differentiation seems to be inhibited in the tumor infiltrating lymphocytes of metastatic melanoma and associated with the appearance of a late terminally differentiated cytotoxic T-cell lymphocyte subset with an effector memory function, the CD57. They hypothesized that the appearance of this unique CD57 subset maybe in part related to immunosuppressive factors, such as TGF- $\beta$ 1, with the resultant inhibition of the CD8+ T-cell differentiation [7]. Another study evaluated the presence of a tumor infiltrating CD57 cells derived from natural killer cells in primary squamous cell lung carcinoma and found that the survival was significantly better in patients with the increased proportion of these cells [9]. Furthermore, the prognostic significance of CD57+ T lymphocytes in the peripheral blood of patients with malignancy was supported by a study on advanced gastric cancer patients which showed that an increased proportion of CD57+ T cells in the peripheral blood indicates a poor prognosis manifesting as a shorter survival period after surgery in patients with advanced gastric carcinomas [10]. Increased levels of CD8+ CD57+ T-cell lymphocytes in peripheral blood were observed in patients with bladder carcinoma suffering from recurrent disease. CD8+ CD57+ T-cell lymphocyte proportion was therefore regarded as a prognostic marker for the recurrence-free interval in addition to the other parameters, such as the age of the patient, history of prior recurrence and number of tumors in nonmuscle-invasive bladder carcinoma treated with transurethral resection and intravesical IL-2 [11]. Levels of CD4+ CD57+ T cells that display a characteristic cytokine profile with the increased expression of IFN $\gamma$  and reduced IL2 and IL4 were also found to be distinctly elevated in the nodular lymphocyte predominant variant of Hodgkin's Lymphoma compared to their tonsillar counterpart [12].

## Conclusion

By understanding the immunological mechanisms of cSCC in OTR, strategies for future prevention and early recognition of these tumors can be implemented. The potential role of CD57+ T cells in cutaneous malignancies is not fully understood. Further study is needed to explain how CD57+ T-cells present in and around malignant cells differ from those encountered during normal aging or chronic infections. This is achieved by detailed exploration of the possible differences in metabolism, gene expression and function of CD57+ T-cells in these disorders. Structural modulation of senescent CD57+ T-cells may lead to the development of cancer immunotherapy that spe-

cifically targets this population of lymphocyte subset, therefore disrupting the immunological mechanisms driving cancer development and evolution [3].

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