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Review

Cutaneous squamous cell cancer (cSCC) risk and the human leukocyte antigen (HLA) system

Pooja Yesantharao [a], Wei Wang [a], Nilah M. Ioannidis [a], Shadmehr Demehri [b], Alice S. Whittemore [a,*], Maryam M. Asgari [b]

[a] Epidemiology Division, Department of Health Research & Policy, Stanford University, Stanford, CA 94305, USA
[b] Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA

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ABSTRACT

Cutaneous squamous cell carcinoma (cSCC) is the second most common cancer among Caucasians in the United States, with rising incidence over the past decade. Treatment for non-melanoma skin cancer, including cSCC, in the United States was estimated to cost $4.8 billion in 2014. Thus, an understanding of cSCC pathogenesis could have important public health implications. Immune function impacts cSCC risk, given that cSCC incidence rates are substantially higher in patients with compromised immune systems. We report a systematic review of published associations between cSCC risk and the human leukocyte antigen (HLA) system. This review includes studies that analyze germline class I and class II HLA allelic variation as well as HLA cell-surface protein expression levels associated with cSCC risk. We propose biological mechanisms for these HLA-cSCC associations based on known mechanisms of HLA involvement in other diseases. The review suggests that immunity regulates the development of cSCC and that HLA-cSCC associations differ between immunocompetent and immunosuppressed patients. This difference may reflect the presence of viral co-factors that affect tumorigenesis in immunosuppressed patients. Finally, we highlight limitations in the literature on HLA-cSCC associations, and suggest directions for future research aimed at understanding, preventing and treating cSCC.

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Abbreviations: HLA, human leukocyte antigen; cSCC, cutaneous squamous cell carcinoma; HPV, human papillomavirus; UVR, ultraviolet radiation; MHC, major histocompatibility complex; GWAS, genome wide association study; BCC, basal cell carcinoma.

* Corresponding author.
E-mail address: alicesw@stanford.edu (A.S. Whittemore).

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1. Introduction

cSCC is the second most common cancer in the United States [1], particularly affecting Caucasians. cSCCs present as an uncontrolled growth of abnormal keratinocytes, mostly arising on sun-exposed anatomic sites. If left untreated, cSCCs can penetrate underlying tissues and metastasize. cSCC is a major public health concern due to its high incidence and associated medical costs [2]. Risk factors for cSCC can be classified as genetic (family history, pigmentation) and environmental (ultraviolet radiation (UVR), human papillomavirus (HPV) infection, immunosuppression, cigarette smoking) [3].

The immune system impacts cSCC susceptibility and pathogenesis, as evidenced by the substantially higher incidence of cSCC in immunocompromised patients (e.g. solid organ transplant recipients who undergo iatrogenic long-term immunosuppressive therapy and patients infected with human immunodeficiency virus (HIV)) [3,4]. Furthermore, susceptibility to the effects of UVR is known to be genetically determined [3–5]. Variations in immunological makeup of human hosts may influence their ability to recruit immune responses needed to prevent cSCC development [6].

The human leukocyte antigen (HLA) system comprises genes that encode the major histocompatibility complex (MHC) proteins. Variation in the expression pattern of these proteins, which are involved in the presentation of tumor antigens to T lymphocytes, has been implicated in multiple cancers by influencing host defenses against tumorigenesis [6]. Class I HLA genes (A, B, and C) encode proteins expressed on the surface of all nucleated cells, which present intracellular peptides to CD8+ T lymphocytes. Class II HLA genes (DR, DQ, DP, DM, DOA, and DOB) encode proteins expressed only on the surface of antigen-presenting cells, which serve as important restriction elements for the induction and proliferation of CD4+ T lymphocytes.

This paper provides a systematic review of the associations between the HLA system and cSCC risk. It suggests mechanistic explanations for these associations based on known mechanisms of HLA involvement in other diseases, as well as further directions for research. Since the literature on HLA and cSCC risk is restricted to class I and class II HLA genes, we focus on these two classes. Both classes contain highly polymorphic genes, which greatly increases the number of possible interactions with antigenic peptides such as tumor antigens. This allows for effective immune surveillance, as tumor antigens presented by class I and class II HLA proteins activate CD8+ and CD4+ T lymphocytes for antitumor immunity. However, cancer cells are able to evade this normal surveillance, leading to unrestricted growth.

We review studies that address associations between cSCC risk and three features of the HLA system: (1) germline HLA allele polymorphisms in immunocompetent and immunosuppressed patients; (2) HLA mismatching and homozygosity in organ transplant patients undergoing immunosuppression; and (3) cell-surface expression levels of HLA proteins in cSCC tumor lesions versus in healthy skin of both immunocompetent and immunosuppressed cSCC patients. Evaluating such associations provides an understanding of the immunogenetic risk factors and immune mechanisms involved in cSCC pathogenesis, which could illuminate novel approaches to the prevention and treatment of these cutaneous neoplasms [2,3].

2. Material and methods

2.1. Selection criteria

Study selection criteria are illustrated in Fig. 1. We included observational association studies between the HLA system and cSCC risk in immunocompetent and immunosuppressed patients. Inclusion criteria were: (1) publications between January 1, 1980

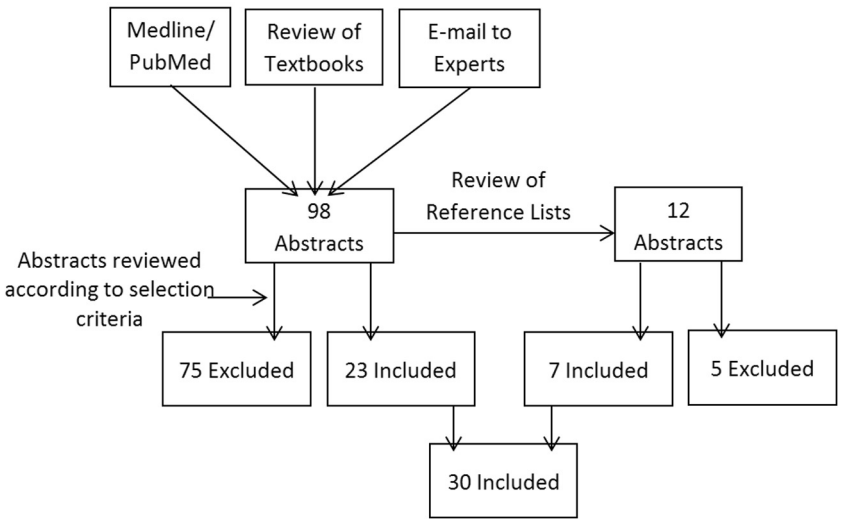

Fig. 1. Diagram of study selection.