Etiological Factors in Cutaneous Carcinogenesis – An Introduction

Hermina C. Wisgerhof and Jan N. Bouwes Bavinck

Risk factors for skin cancer in organ transplant recipients largely overlap with risk factors that are known in the nonimmunosuppressed population and consist of a complex interplay between environmental and host-related factors.

Well-known environmental risk factors are exposure to sunlight [1–3], ionizing radiation [4–6], and various chemical carcinogens. Infections with certain viruses are also likely to be involved in skin cancer carcinogenesis. Human herpes virus type 8 is almost always present in Kaposi’s sarcomas [7–9]; mucosal human papillomaviruses play an important role in the development of cervical carcinoma and anogenital carcinomas [10–12]; and beta papillomaviruses are thought to play a role in the development of cutaneous squamous cell carcinoma and possibly basal cell carcinoma [13–16].

Increasing age is an important nongenetic, host-related factor for the development of skin cancer [17–19]. Other host-related risk factors for skin cancer include genetic factors such as male sex, fair complexion, inability to tan, and nongenetic factors such as chronic scars and ulcers of the skin [20, 21]. Well-known genes that influence skin cancer susceptibility are, among others, melanocortin 1 receptor variants (MCR1); nucleotide excision repair (NER) genes, involved in xeroderma pigmentosum; the p53 tumor suppressor gene; stat 3 regulated genes (c-myc, cdc25A, COX 2); the IKB kinase gene; human leukocyte antigens (HLA); and many other possible genes [22–30].

In organ transplant recipients, long-term immunosuppressive therapy forms one of the most important risk factors [31,32]. Specifically, cumulative doses of immunosuppressive agents play a role, but there may also be differences in the carcinogenic potential of the different immunosuppressive agents. Prospective randomized studies with skin cancer as the final outcome are still lacking, and therefore one has to rely on retrospective follow-up studies with differences in the immunosuppressive regimens. Conclusions based on these types of studies are not always reliable.

Donor-related factors, such as HLA and other antigens that are present in the transplanted organ but not present in the recipient, are additional potential risk
factors for skin cancer in transplant recipients. HLA mismatching is the best known example that donor-related antigens directly or indirectly may play a role in skin cancer carcinogenesis [33–38]. The HLA in the mismatched organ may exert a direct effect, but may also be associated with higher rates of rejection and, therefore, with more intense immunosuppression, which may increase the risk of skin cancer. The association between HLA mismatching and risk of skin cancer could not be confirmed in all studies. The exact role of HLA mismatching in the risk of skin cancer, therefore, remains still unclear.

In organ transplant recipients, both the nonspecific immunosurveillance against skin cancer and the specific immunosurveillance may be hampered because of a depressed natural killer cell function and a decreased function of CD8-positive cytotoxic T lymphocytes after antigenic stimulation in the context of HLA class I antigens. There are a number of theoretical mechanisms by which HLA antigens may be associated with an increased risk of skin cancer in transplant recipients. HLA plays a pivotal role in the cellular immune response to viral and tumor antigens. The HLA class II antigens are involved in recognizing foreign peptides by CD4-positive regulatory T lymphocytes, whereas the HLA class I antigens mainly serve as restriction elements for the reactivity of CD8-positive cytotoxic T lymphocytes.

Both HLA class II and class I antigens have been found to be associated with skin cancer. HLA-DR7 has been found to be associated with an increased risk of skin cancer [37], suggesting that an impaired response of CD4-positive regulatory T cells in the context of class II antigens may play a role in the etiology of skin cancer. HLA-B27 has been reported to be associated with skin cancer in both the Netherlands and Australia [34, 36, 37]. HLA-A11 has been found to be associated with a decreased risk of skin cancer [34], suggesting that reactivity of CD8-positive cytotoxic T lymphocytes in the context of class I is hampered in these patients. However, in Australia and the northern part of the United States of America, HLA-A11 was associated with an increased risk of skin cancer [33, 36], and other studies did not show any association between HLA-A11 and the risk of skin cancer [35, 37–39]. It is not clear whether differences among these studies reflect differences in patient population, differences in environmental antigens (such as viruses), or differences in immunosuppression protocols, in geography and climate, or in methodology, or whether other, still unknown, factors may play a role. Alternatively, individual HLA types may be linked to nonimmune risk factors, such as skin pigmentation [33].

References