Experimental Models for BCC

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Non-melanoma skin tumors

Skin cancers are the most frequent human malignancies among Caucasians and the incidence is rising alarmingly due likely at least in part to increased exposure to ultraviolet-light (UV) as a consequence of decreasing ozone levels and increase in outdoor recreational activities. Skin tumors include malignant melanomas and non-melanoma skin cancers (NMSC) that are neoplasms of epithelial origin such as Basal Cell carcinoma (BCC) and Squamous Cell Carcinoma (SCC). Organ transplant recipients (OTR) have a 60- to 100-fold higher risk for developing these tumors, and they behave significantly more aggressively than in immunocompetent patients [1]. BCCs infiltrate and destroy normal tissue but metastasize only rarely. Ultraviolet-light exposure, white skin, blue eyes, red hair, Celtic ancestry, and inability to tan have been identified as risk factors for BCC [2]. Sunlight, especially UVB (290–315 nm) radiation, is most effective in inducing BCCs. Current approved treatments include standard excisional surgery, Mohs micrographic surgery, radiation, cryosurgery, photodynamic therapy (PDT), local chemotherapy and application of immunomodulators such as imiquimod [3,4]. Following treatment, tumors have a 5-year recurrence rate of 1-40% [3]. The highest overall cure rate for primary skin cancers is achieved by Mohs micrographic surgery but it may result in esthetic damage, especially in patients with aggressive histological BCC subtypes (e.g., morpheaform BCC) [3]. Although significant progress has been made in understanding the pathogenesis of NMSC, the host immune defense mechanisms that predict patient outcome are still largely unknown. Currently, most research on tumor immunosurveillance in NMSC has focused mainly on T-cell mediated, adaptive immune mechanisms. However, there is evidence that innate immune mechanisms are also importantly in NMSC [1]. Today it is well known that keratinocytes and other immune cells through various genes of the innate immune system such as toll-like receptors (TLRs) can also play a role in NMSC [1]. Since most of the tumors occur on the face, head and neck, patients will benefit from a more specific targeting of tumor cells with minimal damage to the healthy parts of the skin. A reliable experimental model is necessary to develop and evaluate new treatments.

The lake of BCC xenografts in animal models

Tumor xenograft models are the standard for the evaluation of new treatments for clinical use. However, to the best of our knowledge, there is no record of successful, repeatable xenograft implantation of human BCCs in animal models. Attempts to grow human BCCs as mouse xenografts met with little success [5]. Lack of predictive in-vivo models for BCC delays the assessment of new treatments against these prevalent skin tumors.

Numerous attempts to transplant NMSC, especially BCC, resulted in failure to grow in the host and to develop lesions with histology similar to the original human BCC in the hosts [6-15]. More recently, Carlson et al [16]. transplanted 14 individual BCC tumors into 18 SCID-beige mice. Only 3 of them yielded anaplastic tumors. However these anaplastic tumors did not resemble the transplanted human BCC from which they originated. For example, they did not express keratins but expressed vimentin and smooth muscle specific actin, and most closely resembled BCC stroma. In their paper Carlson et al discuss the reasons for the inability to implant BCC in nude or skid mice and have suggested several biological explanations: A) The host response blocks BCC tumor transplantation [16;17]. B) The presence of normal appearing keratinocytes that may produce an inhibitory factor [18]. C) Increased NK cells and macrophage activity are responsible for the lack of BCC tumor growth in athymic mice [16].

Murine BCC model in genetically-engineered mice with dysregulated hedgehog (HH) pathway

All BCCs have activation of hedgehog signaling pathway as their pivotal molecular abnormality. Approximately 90% of sporadic BCCs have loss-of-function mutations in PATCHED 1 (PTCH1), and others have activating mutations in the downstream SMOOTHEENED (SMO) gene [19]. Based on this knowledge, several murine models have been developed in which the transgenic overexpression of activators or the deletion of repressors drives skin HH signaling. Epstein et al have focused on the Ptch1 heterozygous Ptch1+/- mice in which p53 had been deleted specifically from keratin 14 (K14)-expressing keratinocytes (Ptch1+/-K14-Cre-ER p53 fl/fl). Ionizing (IR) or UV radiation produces multiple BCCs in these mice [20], thus mimicking basal cell nevus (Gorlin) syndrome patients. Next, they have establish murine BCC allografts by transplantation of these BCC cells to NOD/SCID mice [21]. They have demonstrated that allografts respond to tazarotene treatment, a retinoid with retinoic acid receptor (RAR) β/γ specificity, in a manner similar to that of autochthonous tumors, indicating that the allografts may indeed be a useful anti-BCC agent evaluation system [22]. Recently, they used the same model system to evaluate non-thermal, low energy, nanosecond pulsed electric fields (nsPEF) nanoelectroablation of murine BCCs [23].
Ex-vivo organ culture system

Recently, we have developed a new organ culture system of human BCC and SCC skin tumors. Skin samples were removed surgically from patients according to the standard regimen used in the Department of Dermatology at Hadassah in Jerusalem, cut at 500µm thickness slices and were kept in growth medium. We have demonstrated viability of the tissues ex vivo for 3-7 days. Solid tissue maintenance in organ culture provides an ex-vivo experimental system to overcome some of the shortcomings of both tissue culture and animal in-vivo model systems. Markers of keratinocyte early progenitor (stem) cells such as p63, keratin 15 and keratin 14 have been localized in the basal layer of the ex-vivo cultured skin, indicating the presence of a differentiation spectrum of keratinocyte population from early progenitor to fully mature cells.

We use of this system in an evaluation of HSV1 and AD oncolytic viruses activities on these tumors [24]. Following infection, HSV-1 induced apoptosis in the BCC and SCC cells. Histological analysis revealed that HSV-1 targeted a specific sub-population of early lineage keratinocyte in the BCC and SCC tissues, cells that express p63 but not keratin15 or keratin 14 antigens. The same system was used to evaluate UV damage to human skin and the protective properties of a natural antioxidant [25]. The ex-vivo model has advantages since the tumor tissues restore their three dimensional structure that includes several cell types and a variety of extracellular matrix components that may affect efficiency of the anti-tumor treatment.

Discussion: advantages and disadvantages of the currently evaluable experimental models

Non-melanoma skin cancers are the most common malignancies in Caucasians worldwide. However, no human BCC and SCC xenograft animal models have been developed thus far. Lack of predictive models delays the assessment of BCC and SCC xenograft animal models have been developed may affect efficiency of the anti-tumor treatment. Restoration of their three dimensional structure that includes several cell types and a variety of extracellular matrix components that may affect efficiency of the anti-tumor treatment.

REFERENCES


