Chapter 1

Introductory Chapter: A Short Primer on Human Skin Cancers

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Additional information is available at the end of the chapter

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Skin cancers constitute arguably the most common and increasingly prevalent human neoplasms. In United States alone, it is estimated that 76,400 patients will develop melanoma and 10,100 will die from the disease [1]. Several risk factors, ultraviolet light the most important of these, but also environmental carcinogens, contribute to the increasing incidence of skin cancers, especially among light-skinned individuals [2]. The most common human skin cancers are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), but the most serious and most often fatal are malignant melanoma (MM) and Merkel cell carcinoma (MCC) [3].

Basal cell carcinoma is the most common type of skin cancer, caused by ultraviolet (UV) light, specifically UV-B, and its incidence increases with age. Most commonly, it occurs on sun-exposed areas, such as the face, neck, scalp, forearms, hands, legs and feet. Usually, it is a slowly growing, very rarely metastasizing, locally destructive tumor, which, if ignored, may invade the underlying tissues, bone or cartilage [4].

Basal cell carcinomas arise in keratinocyte stem cells [5]. Usually, in BCCs, the hedgehog signaling pathway is activated causing neoplastic transformation of keratinocytes. Signaling by smoothened, via the cognate receptors, activates the hedgehog signaling pathway and has been implicated in BCC pathogenesis [6].

The most common treatment for BCC is surgical excision, nowadays using Mohs micrographic surgery to ensure complete excision while sparing the surrounding tissue [4]. Curettage, cryotherapy or laser ablation is sometimes used for lesions considered less risky.

Squamous cell carcinoma is the second most common skin cancer worldwide. It usually occurs in sun-exposed areas, frequently on lips, forehead and scalp, ears and pre-auricular regions, but can occur anywhere on skin [7]. It can both invade locally and can metastasize. Chronic sun exposure is the main risk factor for SCC occurrence. Human papillomaviruses and

exposure to carcinogens, such as arsenic or polycyclic aromatic hydrocarbons, are contributing risk factors. Transplant recipients and other immunosuppressed patients are at significantly increased risk for SCC [8].

The appearance of SSCs is variable, and it may present as an ulcer, lump or red patch on the skin, often with scaling or crusting. It is common in elderly. Actinic or solar keratosis, caused by exposure to UV light, is a premalignant lesion, a risk factor potentially leading to progression to invasive SCC. SCCs starting within actinic keratosis are generally low risk, with a more favorable prognosis [7].

Squamous cell carcinoma is usually surgically excised, using Mohs micrographic surgery, with chemotherapy including cisplatin or 5-fluorouracil less common [4]. Actinic keratoses may be treated as a prevention modality for SCC.

Merkel cell carcinoma is a rare but very aggressive primary skin cancer with high mortality rate [9]. While ultraviolet light and immunosuppression seem to have a role in causing MCC, association has been established with Merkel cell polyomavirus [10]. MCC appears as a rapidly growing lesion, usually on the head and neck skin. It quickly proceeds to metastasize, locally and distantly. It is treated with aggressive surgery, but the survival rates are poor.

Malignant melanoma is by far the deadliest of skin cancers! MM is highly invasive locally and, unfortunately, has a high propensity to metastasize [11, 12]. It is usually recognized as a new or newly changed lesion on the skin. Flat superficial spreading form of MM can appear in a variety of colors, from black or blue to brown, gray, pink or white. The nodular form of MMs is usually darkly pigmented and asymmetrical, and sometimes poorly differentiated, unpigmented to appear amelanotic, pink or red. Lentigo maligna melanoma develops on sun-exposed skin in the elderly, slowly enlarging over several years.

Melanoma is a malignant neoplasm of melanocytes, not keratinocytes. The main risk factor is UV light, especially UV-B, and both occasional severe sunburn and chronic sun exposure have been associated with MM formation [13]. People who burn easily, with light skin, blue eyes, red hair and freckles are at increased risk of MM. Giant congenital melanocytic nevi present a high risk, although MM can arise within pre-existing benign melanotic nevi or in normal appearing skin. MM can appear at any site, on skin as well as on oral, genital, urinary or ocular epithelial surfaces.

Population is urged to use the ABCDE rule when ascertaining the presence of MM [14]. These stand for A—asymmetry of the lesion, B—border (irregular), C—color (non-uniform), D—diameter (>6 mm, size of a pencil eraser) and E—evolving (changing in size, shape, color etc.). These features should raise apprehension of MM.

Wide local excision of the area of diagnosis is required. A sentinel lymph node biopsy is performed often, and whole body CT and PET scan are used occasionally in search for metastases. Conventional chemotherapy generally does not work. Recent research into mutations associated with MM identified BRAF gene as frequently mutated [15]; this led to development of specific inhibitors of the corresponding signal transduction pathways such as

Vemurafenib, specifically targeting a recurrent mutation in BRAF, or Imatinib, a more general tyrosine kinase inhibitor [16]. Ipilimumab, a monoclonal antibody blocking CTLA-4, enhances immunotherapy against MM. Prognosis depends very much on the stage at which the tumor is detected.

In this volume, most chapters, understandably, deal with melanoma, the deadliest of skin cancers, and in particular with the cell surface proteins, potential melanoma markers [17].

In conclusion, this volume presents various aspects of human skin cancers, their mechanisms of formation, potential biomarkers and therapeutic targets, a component of the large world-wide effort to combat and eradicate this growing health concern.

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