CHAPTER 13

MOLECULAR BIOLOGY OF BASAL AND SQUAMOUS CELL CARCINOMAS

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Abstract: The prevalent keratinocyte-derived neoplasms of the skin are basal cell carcinoma and squamous cell carcinoma. Both so called nonmelanoma skin cancers comprise the most common cancers in humans by far. Common risk factors for both tumor entities include sun-exposure, DNA repair deficiencies leading to chromosomal instability, or immunosuppression. Yet, fundamental differences in the development of the two different entities have been and are currently unveiled. The constitutive activation of the sonic hedgehog signaling pathway by acquired mutations in the PTCH and SMO genes appears to represent the early basal cell carcinoma developmental determinant. Although other signaling pathways are also affected, small hedgehog inhibitory molecules evolve as the most promising basal cell carcinoma treatment options systemically as well as topically in current clinical trials. For squamous cell carcinoma development mutations in the p53 gene, especially UV-induced mutations, have been identified as early events. Yet, other signaling pathways including epidermal growth factor receptor, RAS, Fyn, or p16INK4a signaling may play significant roles in squamous cell carcinoma development. The improved understanding of the molecular events leading to different tumor entities by de-differentiation of the same cell type have begun to pave the way for modulating new molecular targets therapeutically with small molecules.

INTRODUCTION

The skin is composed of three layers: The epidermis, the dermis or cutis, and the subcutis. The subcutis is composed of fat tissue. The dermis contains collagen


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and elastic fibers produced by fibroblasts, nerve cells, blood and lymph vessels, and several types of immune cells. Skin adnexal structures like sweat glands and hair follicles with sebaceous glands originate from the epidermis and extend into the deeper layers. The epidermis, separated from the dermis by the basal membrane, is devoid of vessels. The prevalent resident cell types within the epidermis are keratinocytes, but also melanocytes, Langerhans cells, and Merkel cells. The keratinocytes undergo a structured differentiation process from the basal layer of the epidermis toward the corneal layer which lasts about 30 days until they desquamate in the form of corneocytes. Malignant transformation of keratinocytes results in two major different and distinct tumor entities, basal and squamous cell carcinoma.1,2

**BASAL CELL CARCINOMA: EPIDEMIOLOGY AND CLINICAL FORMS**

Basal cell carcinoma, also termed basalioma, basal cell epithelioma, or, when ulcerated, ulcus rodens or ulcus terebrans, was first described by Arthur Jacob in 1827 as a malignant, locally invasive, and destructive cancer. This local growth behavior results in a rather benign course of the disease, with metastases being largely absent.4 Therefore, basal cell carcinomas are sometimes considered semi-malignant despite the true malignant cell transformation with invasive and destructive growth. The name basal cell carcinoma is retained by the WHO classification since 1974,5 reflecting the sometimes aggressive growth with extensive tissue destruction and metastasis to lymph nodes and inner organs.6-8 Basal cell carcinomas are the most common human invasively growing cancers by far and account for about 66% of all invasive cancers in Caucasians. In the USA about 1 million cases per year are reported.9,10 In Germany, the incidence of basal cell carcinoma is reported as 100 per 100,000 inhabitants.11 The mean age of patients affected with basal cell carcinomas is currently 60 years with a tendency toward a younger age for first tumor manifestation. On the good side, mortality rates are very low.12

Basal cell carcinomas are subdivided according to their clinical appearance.13,14 The nodular type (Fig. 1A) accounts for 60% of all basal cell carcinomas and is characterized by a pearly skin nodule and telangiectasias. Histologically, the basaloid cells are arranged in palisades at the tumor periphery surrounded by a strong stroma clearly separated from the tumor. The tumor cells show prominent chromatin-rich nuclei with frequent mitoses.15 The (multicentric) superficial growth form (Fig. 1B) accounts for 25% of all basal cell carcinomas and appears as an indurated, erythematous, eczematous plaque. Histologically, there are multiple tumor foci within the plaque that extend from the epidermis to the upper dermis. The most problematic basal carcinoma growth pattern is the sclerodermiform or morphea-like type (Fig. 1C) due to ill-defined tumor margins. This grown pattern is characterized by strings of tumor cells invading the surrounding tissue and accounts for approximately 2% of all basal cell carcinomas.16,17 In addition, several rare forms of basal cell carcinoma growth forms exist that can be discerned based on histological criteria and include basosquamous tumors, pigmented BCC, metatypic BCC, ulcus rodens or ulcus terebrans, fibroepithelioma of Pinkus, or collision tumors.