Molecular Events in Skin Cancer

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Skin cancer represents the most frequent cancer in humans and includes different entities, based on the cell types and tissues affected. Next to epithelial tumors, such as keratinocyte-derived basal cell carcinomas (BCC) and squamous cell carcinomas (SCC), and neuroendocrine Merkel cell carcinoma (MCC), skin malignancies also include neuroectodermal malignant melanoma (MM), as well as tumors of skin-associated tissues, lipomas, angiosarcomas, tumors of connective tissue, and cutaneous lymphomas. Ultraviolet (UV) radiation is an important risk factor for epithelial tumors and MM, because most of the tumor lesions occur in sun-exposed skin areas and contain UV signature mutations [1, 2]. However, some tumors are located in sun-protected body areas, indicating other factors involved in carcinogenesis. These factors include immunosuppression, chemical carcinogens, ionizing radiation, and physical factors such as fair complexion [3]. At least for SCC, human papillomavirus (HPV) may also be involved in pathogenesis [4]. In addition, predisposition to skin cancer is mediated by genetic factors including both germinal and somatic mutations.

The role of germinal (inherited) mutations is well known for patients with xeroderma pigmentosum (XP), an autosomal recessive disorder affecting DNA repair [5]. Several polymorphisms of genes involved in DNA repair were described to be associated with the development of skin cancer. An increased risk of skin cancer at younger ages, including MM, SCC, and BCC, is seen in patients with mutations in XPD [6].

In patients with the nevoid basal cell carcinoma syndrome (NBCCS, Gorlin syndrome), as well as in many cases of sporadic BCC, tumorigenesis is associated with abrogation of the sonic hedgehog pathway (SHH) [7]. Germinal mutations detected in NBCCS include both loss-of-function mutations of the PTCH gene encoding a suppressor of the hedgehog pathway and activating mutations of the gene SMOH encoding a signal transducer of the SHH pathway [8, 9].

Susceptibility genes for the development of MM were identified in genetic studies of families with a high incidence of melanoma. These genes were represented

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by CDKN2A encoding the cyclin-dependent kinase inhibitor $p16^{INK4a}$ and tumor suppressor $p14^{ARF}$, as well as CDK4 and CDK6 encoding cyclin-dependent kinases 4 and 6 [10]. Variants of melanocortin-1 receptor (MC1R) are also associated with increased risk of both MM and BCC [11,12]. MC1R is involved in regulation of skin pigmentation. The MC1R gene is highly polymorphic, and variant alleles, mainly those associated with red hair colour, were described to be associated with fair pigmentation, more frequent development of nevi, and increased melanoma risk [11].

The development of MM and SCC is generally considered a multistep process that requires additional genetic changes (somatic mutations) affecting cell proliferation, induction of apoptosis, angiogenesis, and invasion of the basal membrane [13]. For MM, mutations in N-*ras* and BRAF were reported to lead from benign precursors to dysplastic nevi and superficial melanoma [14]. The progression to nodular melanomas, which invade into the dermis and are capable of metastasis, is associated with additional mutations, reflected by cytogenetic changes such as gains of chromosomes 7q and 8q and losses of chromosomes 1p, 3, 6q, and 10q. Loss of chromosomes 3 and 10q results in abrogation of growth suppression. Loss of heterozygosity (LOH) of 10q affects expression of phosphatase PTEN, a negative regulator of PI3K pathway, promoting proliferation and cell survival [15]. c-*myc* overexpression, as a result of gain of chromosome 8, also induces cell proliferation [16]. Gain of 7q corresponds to increased expression of c-MET, a tyrosine-kinase receptor for HGF, which after stimulation induces cell growth and disruption of cell adhesion by downregulation of E-cadherin and desmoglein 1 [17].

Early molecular events in the development of SCC include mutations of p53. Most of these represent UV signature mutations underlining the importance of cumulative UV exposure as a risk factor. p53 mutations have been detected in patches of both normal skin and in precancerous lesions (actinic keratosis, AK). The progression towards invasive SCC is associated with additional cytogenetic changes. In AKs, gains of chromosomes 7, 9, and 18 have been detected [18]; in SCC, cytogenetic changes were reported for several other chromosomes. Losses of chromosomal regions mainly relate to 3p, 4q, and 18, whereas gains were most frequently observed for 3q, 17q, 4p, Xq, 14q, 8q, and 9q [19].

Cell culture studies using the HaCaT in vitro skin cancer progression model provided some clues of the genes that might be affected by these changes. HaCaT cells are spontaneously immortalized keratinocytes with UV-specific p53 mutations and some chromosomal aberrations, such as loss of 3p and 9p and gain of 3q [20]. These cells are not tumorigenic in immunocompetent mice but require additional mutations for tumorigenic conversion, such as Ha-ras expression [21]. Gain of 11q, which correlates with amplification of the cyclin D1 locus and overexpression of the protein, was shown recently to be an essential early step in skin carcinogenesis [22]. The shift from benign to malignant phenotype was found to be associated with the expression of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF), as well as loss of chromosome 15 [23–25]. The latter results in a loss of thrombospodin (TSP-1), a matrix protein with antiangiogenetic properties, and thus would promote vascularization of tumor tissue. Furthermore, the metastatic potential of HaCaT cells, as determined by in

vivo passages of the cells, is associated with increased Ha-*ras* oncogene expression, gains of parts of 11q, and loss of chromosome 2p [26]. The relevant genes of 2p and 11q are still not identified, but gain of 11q may correspond to upregulation of matrix metalloproteinase 1 (MMP1), located on 11q22.3, as recently identified by microarray expression profiling [27].

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