## Squamous Cell Carcinoma

Squamous cell carcinoma is the second most common tumor arising on sun-exposed sites in older people, exceeded only by basal cell carcinoma. Except for lesions on the lower legs, these tumors have a higher incidence in men than in women. Invasive squamous cell carcinomas are usually discovered while they are small and resectable. Less than 5% of these tumors metastasize to regional nodes; these lesions are generally deeply invasive and involve the subcutis.

***Pathogenesis.*** **The most important cause of cutaneous squamous cell carcinoma is DNA damage induced by exposure to UV light.** Tumor incidence is proportional to the degree of lifetime sun exposure. A second common association is with immunosuppression, most notably chronic immunosuppression as a result of chemotherapy or organ transplantation. Immunosuppression may contribute to carcinogenesis by reducing host surveillance and increasing the susceptibility of keratinocytes to infection and transformation by oncogenic viruses, particularly human papilloma virus (HPV) subtypes 5 and 8. These same HPVs have been implicated in tumors arising in patients with a rare autosomal recessive condition, *epidermodysplasia verruciformis*, which is marked by a high susceptibility to cutaneous squamous cell carcinomas. In addition to its damaging effect on DNA, sunlight, through uncertain mechanisms, seems to cause a transient defect in cutaneous innate immunity that may diminish immune-mediated elimination of sun-damaged cells. Other risk factors for squamous cell carcinoma include industrial carcinogens (tars and oils), chronic ulcers and draining osteomyelitis, old burn scars, ingestion of arsenicals, ionizing radiation, and (in the oral cavity) tobacco and betel nut chewing.

Most studies on the genetics of squamous cell carcinoma have focused on acquired defects in sporadic tumors and their precursors (actinic keratoses), and the relationships between these defects and sun-exposure. The incidence of *TP53* mutations in actinic keratoses found in Caucasians is high, suggesting that p53 dysfunction is an early event in the development of tumors induced by sunlight. Normally, DNA damaged by UV light is sensed by checkpoint kinases such as ATM and ATR, which send out signals that up-regulate the expression and stability of p53. p53 in turn arrests cells in the $G_1$ phase of the cell cycle and promotes either "high-fidelity" DNA repair or the elimination by apoptosis of cells that are damaged beyond repair (Chapter 7). When these protective functions of p53 are lost, DNA damage induced by UV light is more likely to be "repaired" by error-prone mechanisms, creating mutations that are passed down to daughter cells. Of note, the mutations that are seen in *TP53* often occur at pyrimidine dimers, indicating that they, too, stem from damage caused by UV light. A similar story underlies the remarkable susceptibility of patients with *xeroderma pigmentosum* to squamous cell carcinoma. This disorder is caused by inherited mutations in genes in the nucleotide excision repair pathway, which is required for accurate repair of pyrimidine dimers; when this pathway is defective, error-prone repair pathways take over, leading to the rapid accumulation of mutations and eventual carcinogenesis.

As with all other forms of cancer, cutaneous squamous cell carcinoma stems from multiple driver mutations. In addition to defects in p53, mutations that increase RAS signaling and decrease Notch signaling are common and are also likely to contribute to the transformation process.

### MORPHOLOGY

Squamous cell carcinomas that have not invaded through the basement membrane of the dermoepidermal junction (termed in situ carcinoma) appear as sharply defined, red, scaling plaques. More advanced, invasive lesions are nodular, show variable keratin production (appreciated grossly as hyperkeratotic scale), and may ulcerate (Fig. 25-13*A*).

Unlike actinic keratoses, in squamous cell carcinoma in situ, cells with atypical (enlarged and hyperchromatic) nuclei involve all levels of the epidermis (Fig. 25-12*C*). Invasive squamous cell carcinoma (Fig. 25-13*B, C*) shows variable degrees of differentiation, ranging from tumors composed of polygonal cells arranged in orderly lobules and having numerous large areas of keratinization, to neoplasms consisting of highly anaplastic cells that exhibit only abortive, single-cell keratinization (dyskeratosis). The latter tumors may be so poorly differentiated that immunohistochemical stains for keratins are needed to confirm the diagnosis.

## Basal Cell Carcinoma

**Basal cell carcinoma is a distinctive locally aggressive cutaneous tumor that is associated with mutations that activate the Hedgehog pathway signaling.** Basal cell carcinoma is the most common invasive cancer in humans, numbering nearly 1 million cases per year in the United States. These are slow-growing tumors that rarely metastasize. The vast majority is recognized at an early stage and is cured by local excision. However, a small number of tumors (<0.5%) are locally aggressive and potentially disfiguring, or exceedingly rarely may metastasize to distant sites. They occur at sun-exposed sites in lightly pigmented elderly adults. As with squamous cell carcinoma, the incidence of basal cell carcinoma is increased in the setting of immunosuppression and in disorders of DNA repair, such as xeroderma pigmentosum (Chapter 7).

***Pathogenesis.*** **Most basal cell carcinomas have mutations that lead to unbridled Hedgehog signaling.** As is often the case in biology and medicine, study of a rare genetic syndrome associated with a high risk of a common disease (basal cell carcinoma) has led to the elucidation of pathogenic mechanisms of general importance. The syndrome in question, *nevoid basal cell carcinoma syndrome* (NBCCS; also known as *basal cell nevus* or *Gorlin syndrome*), is an autosomal dominant disorder characterized by the development of multiple basal cell carcinomas, often before age 20, accompanied by various other tumors (especially medulloblastomas and ovarian fibromas), odontogenic keratocysts, pits of the palms and soles, and certain developmental abnormalities. NBCCS is one of a number of cancer syndromes associated with skin manifestations (Table 25-3). The gene associated with NBCCS is *PTCH*, a tumor suppressor that is the human homologue of the *Drosophila* developmental gene *patched*. Individuals with