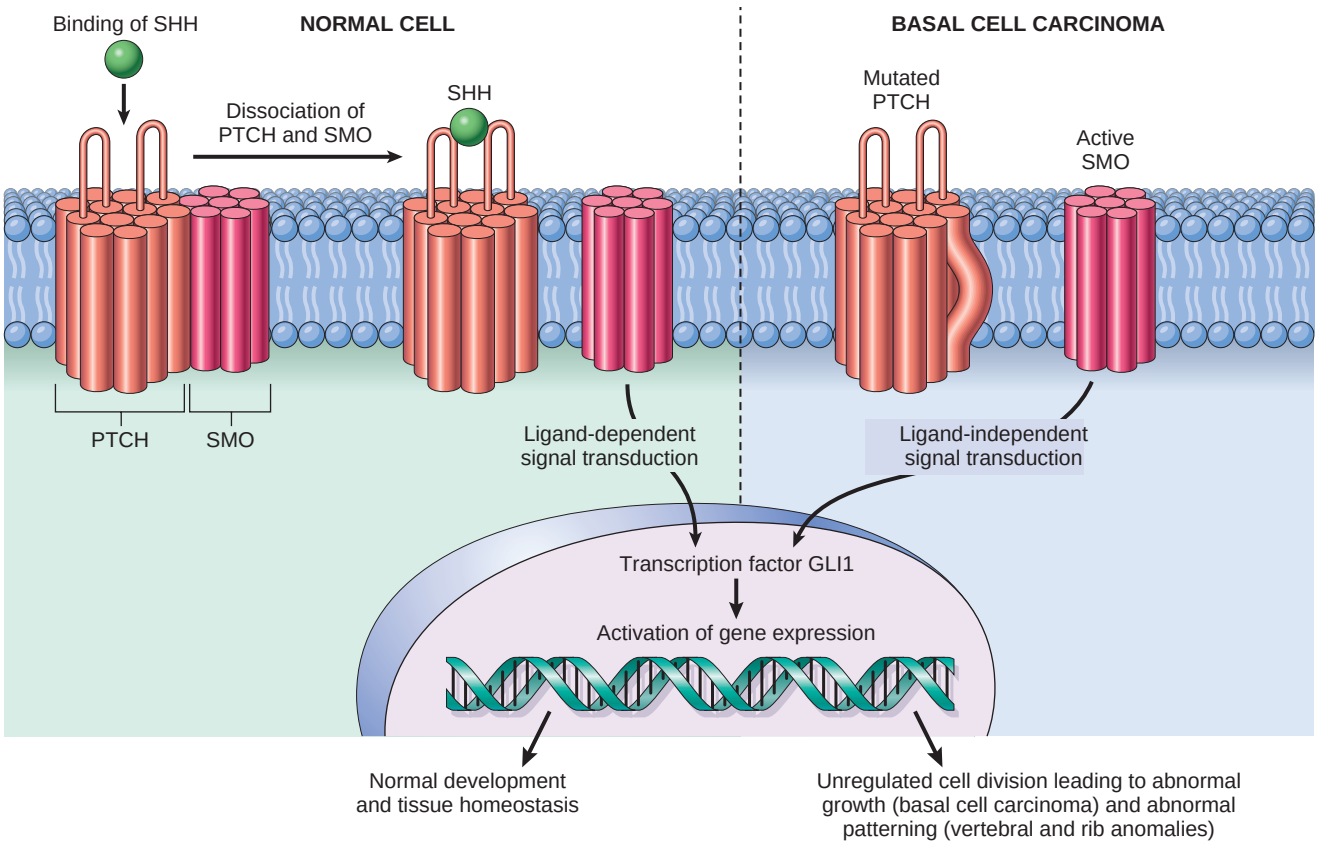

Figure 25-14 Normal and oncogenic hedgehog signaling. *Left,* Normally, PTCH and SMO form a receptor complex that can bind sonic hedgehog (SHH). In the absence of SHH, PTCH blocks SMO activity. When SHH binds PTCH, SMO is released to trigger a signal transduction cascade that leads to activation of GLI1 and other transcription factors. *Right,* Mutations in *PTCH*, and less often in *SMO*, allow SMO to signal without SHH binding and produce constitutive activation of GLI1. GLI signaling is a characteristic feature of sporadic basal cell carcinomas and tumors associated with the nevoid basal cell carcinoma (Gorlin) syndrome.

of these mutations consist of C→T transitions that are considered hallmarks of UV damage. Other tumors have activating mutations in *SMO*. This insight has paved the way for the development of small molecule inhibitors of the Hedgehog pathway, which produce excellent clinical responses in patients with locally aggressive or metastatic basal cell carcinoma.

MORPHOLOGY

Basal cell carcinomas usually present as **pearly papules** containing prominent dilated subepidermal blood vessels (**telangiectasias**) (Fig. 25-15*A*). Some tumors contain melanin and superficially resemble melanocytic nevi or melanomas. Advanced lesions may ulcerate, and extensive local invasion of bone or facial sinuses may occur after many years of neglect or in unusually aggressive tumors, explaining the archaic designation **rodent ulcers**. One common and important variant, the superficial basal cell carcinoma, presents as an erythematous, occasionally pigmented plaque that may resemble early forms of melanoma.

Histologically, the tumor cells resemble those in the normal basal cell layer of the epidermis. They arise from the epidermis or follicular epithelium and do not occur on mucosal surfaces. Two patterns are seen: **multifocal growths** originating from the epidermis and sometimes extending over several square centimeters or more of skin surface (multifocal superficial type) and **nodular lesions** growing downward deeply into the dermis as cords and islands of variably basophilic cells with hyperchromatic nuclei, embedded in a mucinous matrix, and often surrounded by many fibroblasts and lymphocytes (Fig. 25-15*B*). The cells at the periphery of the tumor cell islands tend to be arranged radially with their long axes in parallel alignment **(palisading)**. In sections, the stroma retracts away from the carcinoma (Fig. 25-15*C*), creating clefts or separation artifacts that assist in differentiating basal cell carcinomas from certain appendage tumors that are also characterized by proliferation of basaloid cells, such as trichoepithelioma.

KEY CONCEPTS

Malignant Epidermal Tumors

- The incidence of both basal cell and squamous cell carcinoma is strongly correlated with increasing lifetime sun exposure.
- Cutaneous squamous cell carcinoma can progress from actinic keratoses but also arises from chemical exposure, at thermal burn sites, or in association with HPV infection in the setting of immunosuppression.
- Cutaneous squamous cell carcinoma has potential for metastasis but is much less aggressive than squamous cell carcinoma at mucosal sites.