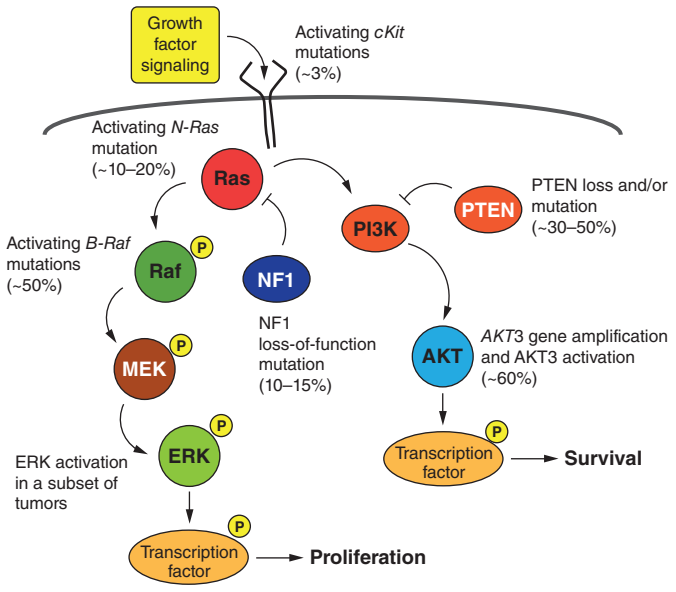

FIGURE 105-2 Major pathways involved in melanoma. The MAP kinase and PI3K/AKT pathways, which promote proliferation and inhibit apoptosis, respectively, are subject to mutations in melanoma. ERK, extracellular signal-regulated kinase; MEK, mitogen-activated protein kinase kinase; NF-1; neurofibromatosis type 1 gene; PTEN, phosphatase and tensin homolog.

RAS and *BRAF*, members of the MAP kinase pathway, which classically mediates the transcription of genes involved in cell proliferation and survival, undergo somatic mutation in melanoma and thereby generate potential therapeutic targets. *N-RAS* is mutated in approximately 20% of melanomas, and somatic activating *BRAF* mutations are found in most benign nevi and 40–60% of melanomas. Neither mutation by itself appears to be sufficient to cause melanoma; thus, they often are accompanied by other mutations. The *BRAF* mutation is most commonly a point mutation (T→A nucleotide change) that results in a valine-to-glutamate amino acid substitution (V600E). V600E *BRAF* mutations do not have the standard UV signature mutation (pyrimidine dimer); they are more common in younger patients and are present in most melanomas that arise on sites with intermittent sun exposure and are less common in melanomas from chronically sun-damaged skin.

Melanomas also harbor mutations in *AKT* (primarily in *AKT3*) and *PTEN* (phosphatase and tensin homolog). *AKT* can be amplified, and *PTEN* may be deleted or undergo epigenetic silencing that leads to constitutive activation of the PI3K/AKT pathway and enhanced cell survival by antagonizing the intrinsic pathway of apoptosis. Loss of *PTEN*, which dysregulates AKT activity, and mutation of *AKT3* both prolong cell survival through inactivation of BAD, Bc12-antagonist of cell death, and activation of the forkhead transcription factor FOXO1, which leads to synthesis of prosurvival genes. A loss-of-function mutation in *NF1*, which can affect both MAP kinase and PI3K/AKT pathways, has been described in 10–15% of melanomas. In melanoma, these two signaling pathways (MAP kinase and PI3K/AKT) enhance tumorigenesis, chemoresistance, migration, and cell cycle dysregulation. Targeted agents that inhibit these pathways have been developed, and some are available for clinical use (see below). Optimal treatment of patients with melanoma may require simultaneous inhibition of both MAPK and PI3K pathways as well as promotion of immune eradication of malignancy.

PROGNOSTIC FACTORS

The prognostic factors of greatest importance to a newly diagnosed patient are included in the staging classification (Table 105-3). The best predictor of metastatic risk is the lesion's Breslow thickness. The Clark level, which defines melanomas on the basis of the layer of skin to which a melanoma has invaded, does not add significant prognostic information and has minimal influence on treatment decisions. The anatomic site of the primary is also prognostic; favorable sites are the forearm and leg (excluding the feet), and unfavorable sites include the scalp, hands, feet, and mucous membranes. In general, women with stage I or II disease have better survival than men, perhaps in part because of earlier diagnosis; women frequently have melanomas on the lower leg, where self-recognition is more likely and the prognosis is better. The effect of age is not straightforward. Older individuals, especially men over 60, have worse prognoses, a finding that has been explained in part by a tendency toward later diagnosis (and thus thicker tumors) and in part by a higher proportion of acral melanomas in men. However, there is a greater risk of lymph node metastasis in young patients. Other important adverse factors recognized via the staging classification include high mitotic rate, presence of ulceration, microsatellite lesions and/or in-transit metastases, evidence of nodal involvement, elevated serum lactate dehydrogenase (LDH), and presence and site of distant metastases.

STAGING

Once the diagnosis of melanoma has been made, the tumor must be staged to determine the prognosis and treatment. Staging helps determine prognosis and aids in treatment selection. The current melanoma staging criteria and estimated 15-year survival by stage are depicted in Table 105-3. The clinical stage of the patient is determined after the pathologic evaluation of the melanoma skin lesion and clinical/radiologic assessment for metastatic disease. Pathologic staging also includes the microscopic evaluation of the regional lymph nodes obtained at sentinel lymph node biopsy or completion lymphadenectomy as indicated. All patients should have a complete history, with attention to symptoms that may represent metastatic disease such as malaise, weight loss, headaches, visual changes, and pain, and physical examination directed to the site of the primary melanoma, looking for persistent disease or for dermal or subcutaneous nodules that could represent satellite or in-transit metastases, and to the regional draining lymph nodes, CNS, liver, and lungs. A complete blood count (CBC), complete metabolic panel, and LDH should be performed. Although these are low-yield tests for uncovering occult metastatic disease, a microcytic anemia would raise the possibility of bowel metastases, particularly in the small bowel, and an unexplained elevated LDH should prompt a more extensive evaluation, including computed tomography (CT) scan or possibly a positron emission tomography (PET) (or CT/PET combined) scan. If signs or symptoms of metastatic disease are present, appropriate diagnostic imaging should be performed. At initial presentation, more than 80% of patients will have disease confined to the skin and a negative history and physical exam, in which case imaging is not indicated.

TREATMENT MELANOMA

MANAGEMENT OF CLINICALLY LOCALIZED MELANOMA (STAGE I, II)

For a newly diagnosed cutaneous melanoma, wide surgical excision of the lesion with a margin of normal skin is necessary to remove all malignant cells and minimize possible local recurrence. The following margins are recommended for a primary melanoma: in situ, 0.5–1.0 cm; invasive up to 1 mm thick, 1 cm; >1.01–2 mm, 1–2 cm; and >2 mm, 2 cm. For lesions on the face, hands, and feet, strict adherence to these margins must give way to individual considerations about the constraints of surgery and minimization of morbidity. In all instances, however, inclusion of subcutaneous fat in the surgical specimen facilitates adequate thickness measurement and assessment of surgical margins by the pathologist. Topical imiquimod also has been used, particularly for lentigo maligna, in cosmetically sensitive locations.

Sentinel lymph node biopsy (SLNB) is a valuable staging tool that has replaced elective regional nodal dissection for the evaluation of regional nodal status. SLNB provides prognostic information and