FUNDAMENTALS: Pathophysiology
Basal cell cancer (BCC)

• Cell of origin is debated: most arise from epidermal cells differentiated in the direction of the primitive hair bulb.
• UVB is the main trigger, but not exclusively
  – Sunlight exposure causes thymine dimers to form in the basal cell; cumulative DNA damage leads to mutations
  – Also see genetic mutations in the hedgehog signaling pathway (ex. PTCH gene)
• Basal cell skin cancer almost never spreads
  – But, if untreated, it may grow into surrounding areas
• Resection of basal cell cancers is usually curative
Actinic keratosis

- UVB-induced carcinoma in situ; “solar keratosis”
- Caused by mutations in several genes, including telomerase, TP53
- 1% of cases yearly are expected to change into invasive squamous cell carcinoma

(courtesy of Dermatology Clinic: Bellevue Hospital Center)
Molecular model of actinic keratosis

An evolving phase precedes clinically recognizable stages. The potential precursor cells have minimal but critical genetic alterations (ex. p53 mutation). Stimulation by sustained UV irradiation drives the progression of p53-mutated clones. LOH, loss of heterozygosity.

1. Takata M, Saida T
Squamous cell cancer (SCC)

• Malignant epidermal tumor arising from keratinocytes

• Squamous cell cancer typically remains localized but certain risk factors predispose to spread to regional lymph nodes and distant sites.

• Clinical features that increase the risk of metastasis for squamous cell cancer include:
  – Size greater than 2 cm
  – Poorly differentiated lesions with vascular or perineural invasion
  – Local recurrence of the lesions
  – Lesions in immunosuppressed patients
Metastatic Disease

- The most common site of metastasis is the regional lymphatics although distant metastasis can occur to the visceral organs.

- Survival decreases significantly with metastatic disease.

<table>
<thead>
<tr>
<th>Risk of metastasis for squamous cell carcinoma</th>
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<td><strong>Form</strong></td>
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<td>Cutaneous, from actinic keratosis</td>
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<tr>
<td>Cutaneous, from Bowen disease</td>
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<td>Mucous, from erythroplasia</td>
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2. Sterry W, Paus R, Burgdorf W
Melanoma skin cancer

- Melanoma has a wide a biologic variability in terms of local growth, spread and distant metastases.

- Typically, primary melanoma growth is characterized by a biphasic growth pattern that is initially characterized by radial growth confined to the epidermis without metastatic potential.

- Later, the lesion takes on a vertical growth pattern into the dermis, and this is associated with dermal lymphatic and vascular invasion and the potential for metastatic spread.
Melanoma skin cancer

• Early diagnosis can significantly impact melanoma survival.

• The 5 year survival for localized, regionally advanced, and metastatic lesions are 99%, 65% and 15%, respectively.

• About 80% of melanomas are diagnosed at a localized stage. Melanoma can spread through lymphatics, and distant metastasis occur to any organ including the skin (dermal metastases).

• Melanoma metastases that develop within the regional dermal and subdermal lymphatics between the primary tumor and the draining lymphatic basin are called in-transit metastasis.

• Melanoma can also remain dormant for 20 years or more and then present as a distant metastasis.
In this model, stem cell lineage cells (1) implant into the dermis (2). When necessary to replenish melanocytes in the epidermal compartment, these cells (2) migrate and implant in the basal layer of the epidermis (3). The cells in the epidermis proliferate and differentiate giving rise to mature melanocytes (4). Eventually, the mature melanocytes are shed through the stratum corneum (5). Mutations can occur at any level, in the epidermal cells (3) dermal cells (2, 7), and mutated cells attempt to follow normal differentiation pathways.

Loose non-adherent cells (from benign or malignant process) could “wash” into the lymph system (8). Non-adherent stem-like cells may pass through the lymph node and circulate systemically (9) as a mutated stem-like cell (1).
Footnote References:
