Cutaneous malignancies

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Disclosure

• Unless otherwise noted the pictures and tables were borrowed from:
  - VisualDx
  - DermNet NZ

Learning objectives

• Introduction to the skin
• Introduction to epidermal carcinogenesis
• Epidemiology of common cutaneous malignancies
• Classification of common cutaneous malignancies
• Treatment of common cutaneous malignancies

The skin is our largest organ

• Largest
• Most visible

Functions of the skin

• Maintaining internal homeostasis in light of variable external stimuli
  • Mechanical protection
  • Regulates temperature
  • Photoprotection
  • Barrier against micro-organisms
• Metabolic function (vitamin D)
• Detects sensory stimuli
• Excretion
• Esthetic, psychosocial role

Acute barrier deficiency
SJS & TEN skin symptoms

The structure of the epidermis and epidermal cells

- Keratinocytes (85-90%)
- Melanocytes
- Langerhans cells
- Merkel cells
- Leukocytes

Keratinocyte differentiation

 Tight regulation of function

barrier formation (lipid lamellae and corneocytes)
quick transformation
preparation for generation of the barrier
interaction with transiently present cells
cell division, uptake of precursors, mechanical attachment to the dermis

Stratum basale

- AKA stratum germinativum
- Single layer of cuboidal/columnar cells
- Divided into stem cells and transit amplifying cells

Stem cells

- Self renewing
- Slow rate of division
- Relative greater protection from accumulating mutations
- Division asymmetric: gives rise to transit amplifying cells and new stem cells

Stem cells
- Epidermal proliferative units

Stem cells
- Keratinocyte stem cells reside in:
  - dermal papilla
  - hair bulge

Stratum spinosum
- Spinous Layer
- Basal Layer
- Bundles of K1K10-keratin filaments, intercellular junctions, desmosomes
- Sparse K5K14-keratin filaments, intercellular junctions, desmosomes
- lamina V, fibronectin, Coll IV, TGFα, IGFs

Stratum granulosum
- Granular Layer
- Spinous Layer
- Basal Layer
- lamina V, fibronectin, Coll IV, TGFα, IGFs

Granular Layer
- Keratohyalin granules (profilaggrin, loricrin)
  - responsible for visible granularity under light microscopy
- Lamellar granules
  - AKA Lamellar bodies; membrane-coating granules, Oiland bodies
  - Content: Mixture of lipids (phospholipids, sphingolipids and cholesterol) and mixture of hydrolytic enzymes (acid phosphatase, glycosidases, proteases and lipases)

Lipid level changes during KC differentiation
- Basal Cells
- Granular Cells
- Stratum Corneum Cells
- Phospholipids
- Glycosylceramide
- Carbohydrate
- Cholesterol
- Sulfate
- Triacylglycerol
- Cholesterol Ester
- Fatty Acids

Conflated envelope assembly begins in the granular cell layer (and upper stratum spinosum)
Major lipid classes in the barrier

- Cholesterol
- Free fatty acids
- Ceramides

Outline

- Non-melanoma skin cancer
  - Epidemiology
  - Risk factors
  - UV radiation
  - Photocarcinogenesis
- Non-melanoma skin cancer
  - Basal cell carcinoma
  - Squamous cell carcinoma
- Melanoma
  - Melanocyte biology
  - Epidemiology
  - Melanoma subtypes
  - Therapy

Non-melanoma Skin Cancers

- Includes basal cell carcinomas (BCC) & squamous cell carcinomas (SCC)
- Most common malignancies in humans
- 5.4 million cases annually in the US, in 3.3 million patients
  - 20-25% of the US population is projected to develop NMSC during their life
  - 40-50% of Americans who live to age 65 will have either basal cell carcinoma or squamous cell carcinoma at least once
  - Worldwide in all races
  - BCCs: 2,800,000 in US per year (~80%)
  - SCCs: 700,000 in US per year (~20%)
  - ~80% rise in incidence in the last 2 decades

Cancer statistics
Non-melanoma Skin Cancers

- Total cost of NMSC approximately $4.8 billion for the US healthcare system
- Melanoma: $3.3 billion
- Within 5 years, second NMSC diagnosed in 70% of men, 50% of women
- 2000-2500 deaths per year

Read the fine print


Non-melanoma Skin Cancers

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Read the fine print


Risk factors for development of NMSC

Environmental Exposures

<table>
<thead>
<tr>
<th>Factor</th>
<th>SCC</th>
<th>BCC</th>
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</thead>
<tbody>
<tr>
<td>Cumulative/occupational sun exposure</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Intermittent/recreational sun exposure</td>
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<td></td>
</tr>
<tr>
<td>Other exposures to UV light (PUVA, tanning beds)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Chemicals (Arsenic)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Human papillomavirus (HPV)</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>+</td>
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</tbody>
</table>

Genetic syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>SCC</th>
<th>BCC</th>
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<tbody>
<tr>
<td>Xeroderma pigmentosa</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oculocutaneous albinism</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Epidermodysplasia verruciformis</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Muir-Torre syndrome</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neviod basal cell carcinoma syndrome</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>+</td>
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</tbody>
</table>

Immunosuppression

<table>
<thead>
<tr>
<th>Condition</th>
<th>SCC</th>
<th>BCC</th>
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<tbody>
<tr>
<td>Organ transplantation</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Other (e.g. chronic lymphocytic leukemia treated with fludarabine, AIDS pts with HPV infection)</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Risk factors for development of NMSC

Predisposing clinical settings

<table>
<thead>
<tr>
<th>Condition</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic non-healing wounds</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Long standing discoid lupus erythematosus</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lichen planus (erosive) or lichen sclerosus</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Linear porokeratosis</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Risk factors for development of NMSC

<table>
<thead>
<tr>
<th>Pigmentary phenotype</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fair skin</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Always burns, never tans</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Freckling</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Red hair</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

The effects of UV radiation on the skin

Outline

- **Introduction**
  (definition, physical properties, UV sources, depth of penetration into the skin, action spectrums)
- **Cellular effects of UVR**
  (biomolecules effected by UV, DNA damage)
- **UV induced skin changes**
  (sunburn, tanning, epidermal hyperplasia, vitamin D production, emotional effects, photoaging, photoimmunology, photocarcinogenesis)

The visible light and the UV spectrum

- **UV radiation**

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Relevant UV spectrum

- Dermatologically important UV categories:
  - UVA 315-400nm
  - UVA1 340-400nm
  - UVA2 315-340nm
  - UVB 290-315nm
  - UVC 200-290
What happens to the UV radiation reaching physical matter

- Reflection
- Scattering
- Transmission
- Absorption

Solar radiation spectrum

Atmospheric effects on solar UV radiation

Sunlight at the top of the atmosphere:
- 1366 watts/m²
  - 50% infrared light (IR)
  - 40% visible light (VL)
  - 10% ultraviolet light (UVR) (137 watts/m²)

Sunlight at ground level:
- 1000–1100 watts/m²
  - 53% IR
  - 44% VL
  - 3% UVR (Sun at zenith)

With Sun at zenith at ground level:
- IR: 527 W/m², VL: 445 W/m², UVR: 32 W/m²

Artificial UV sources

- UV radiation
  - Artificial light sources
    - Germicidal light (UVC)
    - Welding arc (UVC-visible)
    - Short distance not sufficient for oxygen to absorb the light
    - Counterfeit money detectors (UVA; 380-395nm)
    - Nail salon UV light
    - Other artificial sources:
      - Tanning booths
      - Black lights
      - Curing lamps
      - Mercury vapor lamps
      - Halogen lights
      - High-intensity discharge lamps
      - Fluorescent and incandescent sources
      - Some types of lasers (excimer lasers, nitrogen lasers, and third harmonic Nd:YAG lasers).

UV spectrum of tanning beds

- Typically 99-97% UVA
- 1-3% UVB

Nail lamp UV spectrum

UV carcinogenic potential similar to 1 session of NBUVB*:
- 13000 sessions of Nail UV with devices A & B were needed
- 40000 sessions of Nail UV with device C

*15-30 treatments
UV radiation penetration into the skin

5% of UVR is reflected

UVB
Epidermal absorption:
- urocanic acid
- DNA / RNA
- Tryptophan
- Tyrosine
- Melanin
Dermal absorption:
- DNA / RNA
- Elastin
- Collagen

Erythema and DNA-damage action spectrum

The action spectrum of photocarcinogenesis.

Outline

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UV radiation targets in the skin

• Urocanic acid
• Tryptophan
• Tyrosine
• Melanin
• Elastin
• Collagen
• DNA / RNA
UV effects on DNA

- Pyrimidine dimers
- Covalent link induced by UV radiation between adjacent pyrimidine bases

UV induced oxidative stress

- UV activates covalent double bond containing small molecules (riboflavin, tryptophan and porphyrin)
- These activate cellular oxygen

8-hydroxyguanine (8OH-G)
thymine glycol
strand breaks

UV effects on DNA

- Cyclobutane pyrimidine dimers (CPD)
  - CPDs are the most common UV mutation
  - TT dimer is the most common CPD
  - The most common mutation is C-T
  - Base pairing cannot take place during DNA replication
  - 6,4 pyrimidine-pyrimidines (6,4 photoproducts)
    - Occur less frequently (approx. 1:3 of CPD frequency)
    - More efficiently removed from the genome
    - Much less mutagenic
    - Mutagenic conversions are not known
Nucleotide excision repair

Xeroderma pigmentosum

- Symptoms: Development of numerous lentigines at an early age

Repair is error prone

- Most common UV induced mutations
  - C \rightarrow T
  - CC \rightarrow TT

UVB and daylight UV induce CPDs preferentially at 5-methyl-cytosine(mC)-containing dipyrimidine sites

UV signature mutations occur frequently at the dipyrimidine sites associated with methylated CpG

Difference between UVA and UVB mutagenesis

- UVB: mostly direct DNA damage with limited secondary ROS effect
- UVA: 8-hydroxyguanine, CPDs (high amount compared to previously expected) no 6,4PPs or Dewar isomers

DNA damage signaling
Outline

• Introduction
  (definition, physical properties, UV sources, depth of penetration into the skin, action spectrums)

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UVR induced skin changes
  sunburn
  tanning
  epidermal hyperplasia
  vitamin D production
  emotional effects
  photoaging
  photoimmunology
  photocarcinogenesis

UV signature mutations

• The majority of the mutations are at dipyrimidine sites (T-T, C-C, C-T or T-C) and correspond to a C to T transition.
• More than 20% correspond to tandem mutations involving the two adjacent nucleotides of the dipyrimidine sites (C-C to T-T).

Photocarcinogenesis

unrepaired damage
mutation of tumor suppressor genes or oncogenes
carcinogenesis
Sunburn cells

- Pyknotic nucleus
- Eosinophilic cytoplasm
- Keratin 5 +
- Lack of late differentiation markers
- Appear 6-24 hrs after UV exposure

Apoptotic keratinocytes

Sunburn cells

- Sunburn cells (SBC) are keratinocytes undergoing apoptosis
- Protective mechanism against the carcinogenic effects of ultraviolet-B irradiation
- Sunburn cell formation is critically regulated by signaling cascades arising from DNA damage, membrane receptor clustering and generation of reactive oxygen species
- The mitochondria act as major checkpoint, integrating upstream survival and pro-apoptotic pathways
- The final post-mitochondrial apoptotic phase is executed by caspases
- Deregulation of signaling cascades controlling SBC formation can ultimately lead to the development of skin cancer

Importance of sunburn cell formation

- p53-deficient mice:
  - decreased sunburn cells production after UVB, develop more skin cancers
- GADD45 deficient mice
  - decreased sunburn cell production after UVB, develop more skin cancers

Sunburn cell formation and erythema

- Multiple studies show that erythema and inflammatory response and sunburn cell production correlates
- Sub erythemogenic doses of UV radiation may still lead to small amount of sunburn cell formation

Sunburn cells

- Short term survival = homeostatic balance
Early mutant cell clones

p53 mutations in UV carcinogenesis

- UV induced skin cancers show up to 100% p53 mutation rate (54-100%)
- p53 defective cells are less prone to apoptosis induction by UV light
- p53 mutations are present in sun-damaged skin and AKs
- Most loss of function p53 mutations result in increased p53 immunopositivity given accumulation of mutated / dysfunctional p53 protein

p53 positive cell clones

- p53 positive cells are otherwise normal appearing and on H&E they are indistinguishable from normal KC
- The cell groups are clonal expansion of a single mutated cell
- These clones, 10–3000 cells in size, are present at frequencies exceeding 40 cells per cm² and together involve as much as 4% of the epidermis

p53 positive cell clones are likely earliest detectable precursors of SCC

- The mutation spectra found in epidermal p53 clones resemble that of non-melanoma skin cancer.
- Coexisting AK, CIS and SCC have been found to share similar mutations, further supporting the notion that p53 mutations appear early in the development of skin cancer.
- The exact same mutations were not identified in the same geographic lactations.
- The p53 clones in normal skin surrounding SCC were significantly more frequent and larger in size than those in skin surrounding BCC or melanocytic nevus, indicating an association between p53 clones and SCC.

p53 cell clones expand with continued UVB exposure

p53 clone growth is promoted by UVB

- p53 clones contain p53 UV signature mutations
- In mouse models after p53 clone formation is stopped clones regress.
- Regression also takes place in mice defective in adaptive immunity.

What is the driving force behind UV induced p53 clone expansion?
Apoptosis of surrounding normal keratinocytes drives p53 clone expansion

- Survivin is an apoptosis inhibitor
- Keratinocyte overexpression of survivin (decreased apoptosis) increases number of p53 clones but decreases their size and rate of growth.
- UV induced apoptosis of KCs surrounding p53 clones is one of the driving forces of clone expansion
- p53 clones regress with good sun protection

Effect of marked genotoxic trauma on p53 clones

- UV-induced ablation of the epidermal basal layer including p53-mutant clones reduces UV induced keratinocyte carcinogenesis

Genes significantly mutated in normal human skin

- NOTCH1 (Notch homolog 1)
- FAT1 (Ubiquitin-like protein FAT10)
- NOTCH2 (Notch homolog 2)

Non-melanoma Skin Cancers

- TPH2 (tumor protein p53)
- RBM10 (RNA binding protein 10)
- NOTCH3 (Notch homolog 3)
Actinic Keratoses

• AKA solar keratoses or “precancers”
• Precancerous
• If untreated, 0.1% per year turn into SCC
• the average patient at time of diagnosis has 7.7 AKs
• 60% of SCCs develop from AKs
• Risk factors are the same as SCC
• May be prevented with sunscreen and low fat diet

Actinic Keratosis

• Occur on sun-damaged skin of head, neck, upper trunk, extremities
• Often clusters on ears, upper forehead, nasal bridge, malar eminences, dorsal hands, extensor forearms, and scalp in bald individuals

• Classic appearance:
  • rough or gritty pink to red macule or papule
  • angular borders
  • angular yellow scale

Destructive treatment

• Cryotherapy

Field treatment

• 5-fluorouracil cream
• photodynamic therapy (PDT with ALA or MAL)
• imiquimod
• ingenol mebutate gel 0.05%
• diclofenac 3% gel
• chemical peels
Squamous Cell Carcinoma

- 300,000 per year in US
- Most common skin cancer in AA
- Risk Factors:
  - Cumulative long term exposure to UV light
  - Radiation tx
  - Immunosuppression
    - Renal transplant pts have 253-fold increased risk
    - Lesions appear 2-4 yrs post transplantation
  - Chronic ulceration, scar, HPV, chemical carcinogens

SCC variants

- Keratoacanthoma
- SCC in situ: Bowen's disease, Erythroplasia of Queyrat
- Invasive SCC
- Marjolin's Ulcer

Keratoacanthoma

- Rapid growth, plateau phase, regression
- Clinically "benign" and spontaneously involutes
  - Currently we are unable to differentiate from well differentiated SCC with potential aggressive phenotype
- Head and neck or sun-exposed extremities
- Solitary

- Risk of metastasis
  - 5-year rate of metastasis - 5%
- Risk of recurrence
  - 5-year rate of recurrence - 8%
- Factors affecting risk:
  - Size >2 cm (15% recur, 30% metastasize)
  - High risk locations: lip & ear (10 – 25%)
  - Injured/chronically diseased skin (38%)
  - Perineural invasion (35%)
  - Immunosuppression

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Syndromes with multiple keratoacanthomas

- The Grzybowski type:
  - typically diagnosed in adulthood
  - sudden appearance of hundreds of lesions in a disseminated fashion
  - the lesions are generally 2-3 mm in diameter
  - found anywhere on the body:
    - even palms, soles, larynx, and oral mucosa

- The Ferguson-Smith variant:
  - typically first lesions in 2nd or 3rd decade of life
  - multiple self-healing squamous epitheliomas of Ferguson-Smith
  - sun-exposed areas and sites of trauma
  - often multiple lesions at a time
  - red macule – papule grows rapidly for 2-4 weeks
  - 2-3 cm in diameter, stable for up to 2 months
  - involutes and leaves scar
  - can be locally aggressive, metastasis is rare
  - Loss-of-function TGFBR1 mutations

SCC variants

- Keratoacanthoma
- SCC in situ: Bowen’s disease, Erythroplasia of Queyrat
- Invasive SCC
- Marjolin’s Ulcer

SCC in situ

- Bowen’s disease
- Elderly
- Sun-exposed skin
- De novo or from Aks
- Head & neck >> extremities and trunk
- DDx: AK, SBCC, psoriasis, nummular eczema
- On the penis: Erythroplasia of Queyrat
- If SCC rises from Bowen’s increased risk of metastasis (30%)
SCC variants
- Keratoacanthoma
- SCC in situ: Bowen’s disease, Erythroplasia of Queyrat
  - Invasive SCC
  - Marjolin’s Ulcer

Invasive SCC
- Invasive squamous cell carcinoma
- Elderly
- Sun-exposed skin
- De novo or from AKs
- Head & neck >> extremities and trunk
- DDx: AK, sBCC, warts

SCC variants
- Keratoacanthoma
- SCC in situ: Bowen’s disease, Erythroplasia of Queyrat
  - Invasive SCC
  - Marjolin’s Ulcer
Treatment

• Depends on risk, location, subtype

Skin Cancer in Transplant Patients

- Clinical Characteristics

• Skin cancer is most common post-transplant malignancy
• Ranges from minor inconvenience to major morbidity to lethal
• Increased risk of metastasis and death

Population-Based Standard Incidence Ratios of Skin Cancer in Transplant Patients

<table>
<thead>
<tr>
<th>Skin Cancer Type</th>
<th>Incidence Ratio</th>
</tr>
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<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>65-fold increase</td>
</tr>
<tr>
<td>SCC of the lip</td>
<td>20–38 fold increase</td>
</tr>
<tr>
<td>BCC</td>
<td>10-fold increase</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1.2–3.4 fold increase</td>
</tr>
<tr>
<td>Kaposi sarcoma</td>
<td>84-fold increase</td>
</tr>
</tbody>
</table>

Skin Cancer in Different Types of Transplants

• Cardiac transplants have a 2.9-fold higher risk of SCC compared to renal transplants
  • Cardiac transplant pts older
  • Immunosuppression more intense
  • Skin cancer is less common in liver transplants than renal or cardiac

Management of Skin Cancer in Transplant Patients – Basic Principles

- Sun protection
  • Avoid natural or artificial tanning
  • Limit outdoor activities 10 am – 3 pm
  • Broad spectrum (UVA/UVB) sunscreen and lip balm
  • Protective clothing and broad-brimmed hats

Management of Skin Cancer in Transplant Patients – Basic Principles

- Education pre- and post-transplant
- Regular surveillance by dermatologist
- Monthly self skin exam
- Monthly self nodal exam with h/o SCC or melanoma
- Annual complete physical and history focused on metastatic potential
Management of Skin Cancer in Transplant Patients

- Aggressive treatment of AKs
- Cryotherapy
- 5-fluorouracil cream
- Topical retinoids
- Photodynamic therapy (PDT)
- Chemoprophylaxis
  - Systemic retinoids
  - Capecitabine (Xeloda)
- Reduce and alter immunosuppression

- Because of higher risk of metastasis aggressive management is needed

Basal Cell Carcinoma

- Most common malignant cutaneous neoplasm
- Incidence: 2.8 million in the US (M:F = 2:1)
- Risk Factors:
  - Intermittent, intense sun exposure (20% in pts under 50)
  - Distribution: head and neck, sometimes sun-protected

Basal Cell Carcinoma

- No universal classification
- Variants
  - Nodular*
  - Superficial*
  - Morpheaform / Sclerosing *
- Very rarely metastasize (~1/10,000)

* all may be pigmented (morpheaform least likely)

Basal Cell Carcinoma

- Epidermal basal layer epithelial cell differentiation
- Nodular BCCs
  - Most common variant
  - 60% of all BCCs
  - Face
  - Raised, glassy/pearly papule or nodule
  - Overlying telangiectases
  - Large, extend deeply
  - Ulceration
  - Pigmented

http://pulpbits.net/7-skin-structure-anatomy-diagrams/epidermis-structure-systems/
Superficial BCC
• Second most common
• 15% of BCC
• Favors the trunk and extremities
• Pink, erythematous macule/thin plaque
• Difficult to differentiate from benign inflammatory lesion/SCC/AK

Morpheaform BCC
• AKA sclerosing or infiltrating
• Locally aggressive subtype
• Flat, slightly atrophic or ill-defined plaque
• May appear scar-like
• Actual size often greater than clinically apparent
• Often a histologic determination
Metastatic basal cell carcinoma

- Rate 1:3000 – 1: 30,000
- Mostly in cases of longstanding deep disease (>8-9 yrs)
- Male to female ratio 2:1
- Median age of first sign of primary tumor: 45yrs
- Route of metastasis: lymphogenic and hematogenic
- Sites: lymph nodes, lungs, bones

Treatment: Depends on risk, location and subtype

Mohs Surgery

- Developed in the 1938 by Dr Frederick Mohs, a Wisconsin General Surgeon
- Provides superior margin control, maximal tissue sparing and the highest cure rates
- Drawbacks: time and labor intensive, relatively few Mohs surgeons
Other therapeutic options for advanced BCC

Systemic therapies:
alpha-interferon, capecitabine, retinoids

Small molecular inhibitors

Basal cell carcinoma: beyond surgery and irradiation

Hedgehog signaling pathway in BCC
Therapeutic options for advanced BCC

Small molecular inhibitors of PTCH signaling:
- LDE-225/Erismodigib
- GDC-0449/Vismodegib

Vismodegib

Multicenter, international, two-cohort, non-randomized study:
63 locally advanced BCC patients

Response rate: 43%
Complete response: 21%

Commonly reported adverse events

- Alopecia
- Fatigue
- Muscle spasms
- Dygeusia/ageusia
- Weight loss
- Nausea
- Decreased appetite
- Diarrhea
- Amenorrhea
- Keratitis
- Electrolyte imbalance and azotemia.

Potential drawbacks

- Unknown long term efficacy and side effects
- Potential development of resistance
- Only free for qualifying patients through Genentech Access Solutions, potential significant expenses
Melanocytes

• Melanocyte origin

Melanin Biosynthesis

Tyrosine → DOPA → DOPAquinone
Both steps are catalyzed by tyrosinase

Melanosome Formation

Melanocortin 1 Receptor

• G-protein-coupled receptor on surface of melanocytes
• Seven transmembrane domain
• αMSH binds MC1R
• Dysfunctional MC1R favors synthesis of pheomelanin

Melanocyte function in the epidermis

• Melanocytes load keratinocytes with melanosomes for protection against ultraviolet radiation

Tanning

Fitzpatrick skin types

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Typical Features</th>
<th>Tanning ability</th>
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<tbody>
<tr>
<td>I</td>
<td>Pale white skin, blue/azel eyes, blond/red hair</td>
<td>Always burns, does not tan</td>
</tr>
<tr>
<td>II</td>
<td>Fair skin, blue eyes</td>
<td>Burns easily, tans poorly</td>
</tr>
<tr>
<td>III</td>
<td>Darker white skin</td>
<td>Tans after initial burn</td>
</tr>
<tr>
<td>IV</td>
<td>Light brown skin</td>
<td>Burns minimally, tans easily</td>
</tr>
<tr>
<td>V</td>
<td>Brown skin</td>
<td>Rarely burns, tans rarely</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black skin</td>
<td>Never burns, always tans darkly</td>
</tr>
</tbody>
</table>
Abnormalities of pigmentation

- Lentigo simplex
  - May fade or disappear in winter and with age
  - Pigmented elongated reticulate ridges
  - Increased melanocytes along basal layer
  - 1-3 mm spots variety (deeper pigmentation)

- Solar lentigo
  - Scattered small brown lesions on sun-damaged areas
  - Pigmented elongated & flat reticulate ridges
  - Increased melanocytes along basal layer
  - Solar elastosis

http://www.dermnetnz.org/doctors/lesions/melanocytic.html
DermNet New Zealand Trust

### Melanoma pathogenesis

- UV
- Melanoma excision (e.g. MSLT)
- Blister melanoma (e.g. MCLT)
- Carcinoma
- Genetic susceptibility

Genetic susceptibility:
- CDKN2A
- CDK4
- MC1R
- BRAF
- p16/ARF genes


### Melanoma incidence

- White
- Black
- Asian-Pacific Islander
- American Indian/Alaska Native
- Hispanic

Incidence per 100,000

<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>50</td>
<td>60</td>
<td>70</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

### Surveillance, Epidemiology, and End Results Program

- SEER Stat Fact Sheets: Melanoma of the Skin
- SEER Stat Fact Sheets: Melanoma of the Skin

At a Glance

- Incidence
- Mortality
- Survival

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence</th>
<th>Mortality</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>10,000</td>
<td>5,000</td>
<td>60%</td>
</tr>
<tr>
<td>2000</td>
<td>15,000</td>
<td>7,500</td>
<td>70%</td>
</tr>
<tr>
<td>2010</td>
<td>20,000</td>
<td>10,000</td>
<td>80%</td>
</tr>
</tbody>
</table>

Number of New Cases and Deaths per 100,000: The number of new cases of melanoma of the skin was 73,870 per 100,000 men and women per year. The number of deaths was 4,530 per 100,000 men and women per year. These rates are age-standardized and based on 2000-2002 years and deaths.

Lifelong Risk of Developing Cancer: About 2.5 percent of men and women will be diagnosed with melanoma of the skin at some point during their lifetime, based on 2001-2007 data.

Prevalence of This Cancer: In 2012, there were an estimated 99,587 people living with melanoma of the skin in the United States.

Melanoma

- Incidence in Caucasians has tripled in the last 30 years
- Lifetime risk 1:35-75
- Median age of diagnosis is 53
- Most common cancer in women aged 25-29

Melanoma Types

- Superficial Spreading Melanoma
- Nodular Melanoma
- Acral Lentiginous Melanoma
- Lentigo Maligna Melanoma

Superficial spreading melanoma

- Most common type of melanoma
- 70% of all melanomas
- Between ages of 30 and 50 years
- Can arise de novo or in a pre-existing nevus

Superficial Spreading Melanoma

- Initial phase (months to years)
  - Size, not palpable
  - Not palpable from other early melanomas
- Initial growth phase (months to 5 years)
  - Began irregular
  - Area of regression appear with angular notching
  - Thick area appear at about 2.5 cm—naked normal skin
- Vertical growth phase (months to years)
  - Normal skin, depending on degree
  - Growth and increasing pain
  - Darker color
  - Regression elevation at border
  - Nodule or crater
  - Areas of atrophy and scaling

Superficial spreading melanoma

- Brown, brown-black
  - Light blue
  - Hair set small and white
- Dark area become more prominent
- Angular notching
- Slightly depressed area
- Shiny central or darker
- Blue-gray, blue-black, red and white

The ABCDEs for melanoma detection are:

- **A** is for Asymmetry where one-half of the mole is unlike the other.
- **B** is for Border where the mole is irregular, scalloped or poorly defined.
- **C** is for Color which varies from one area to another or has different shades of tan, brown, black and sometimes white, red or blue.
- **D** is for Diameter of a mole when it is bigger than the size of a pencil eraser.
- **E** is for Evolving or changing in size, shape or color.

**Nodular Melanoma**

- Second most common
- 15-30% of melanomas
- Commonly in 60th decade of life
- No radial growth phase → Rapid growth
- Trunk, head and neck most common
- Male predominance
- Usually thicker and more advanced stage at diagnosis
- Poorer prognosis

**Acral Lentiginous Melanoma**

- Uncommon
- 5 – 10% of all melanomas
- Incidence similar across all racial groups
- 7th decade of life
- Represents disproportionate percentage of melanomas in African Americans (70%) and Asians (40%)
- Palms and soles or in and around the nail apparatus

**Lentigo Maligna Melanoma**

- Lentigo maligna analogous to the radial growth phase (5-20yrs)
- Lentigo maligna melanoma means invasive growth
- 4-15% of Melanomas
- Sun-damaged skin: face - nose and cheek
- Usually slow growth of large precursor lesion
Melanoma management

• Generous biopsy

Treatment

• Wide excision
• Mohs Surgery
• Sentinel lymph node biopsy
• Staging workup—imaging not recommended under 4mm thickness
• Adjuvant therapy
  • Small molecule pathway inhibitors
  • Immunotherapy
• Close follow up

! Breslow depth is key

Melanoma thickness and Survival

<table>
<thead>
<tr>
<th>Breslow Depth</th>
<th>5-Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mm</td>
<td>95%</td>
</tr>
<tr>
<td>&lt; 2 mm</td>
<td>89% (77% if ulcerated)</td>
</tr>
<tr>
<td>&gt; 4 mm</td>
<td>67% (45% if ulcerated)</td>
</tr>
</tbody>
</table>

Metastasis = 6-18% depending on site

Tumor status

• Tx: Primary tumor cannot be assessed
• T0: No evidence of primary tumor
• Tis: Melanoma in situ
• T1: < 1.0mm
  • T1a: no ulceration and mitotic rate < 1/mm²
  • T1b: with ulceration or mitotic rate > 1/mm²
• T2: 1.01 - 2.0mm
  • T2a: no ulceration
  • T2b: with ulceration
• T3: 2.01 - 4.0mm
  • T3a: no ulceration
  • T3b: with ulceration
• T4: > 4.0mm
  • T4a: no ulceration
  • T4b: with ulceration

Staging of localized primary melanoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>Tis</td>
<td>N0</td>
</tr>
<tr>
<td>IA</td>
<td>T1a</td>
<td>N0</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>N0</td>
</tr>
<tr>
<td>II A</td>
<td>T2a</td>
<td>N0</td>
</tr>
<tr>
<td>II B</td>
<td>T2b</td>
<td>N0</td>
</tr>
<tr>
<td>IIIA</td>
<td>T3a</td>
<td>N0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>N0</td>
</tr>
<tr>
<td>III C</td>
<td>T4a</td>
<td>N0</td>
</tr>
<tr>
<td>IIIIC</td>
<td>T4b</td>
<td>N0</td>
</tr>
</tbody>
</table>

Tumor status predicts node positivity

- Early disease features define risk of distant disease
- Risk of SLN positivity based on tumor thickness
  - <1 mm: 5%
    - <0.75 mm: 2.5%
    - 0.75 mm: 3%
    - 0.75-1.0 mm with >1/mm mitotic rate: 15%
  - 1.01-2.0 mm: 12%
  - 2.01-4.0 mm: 28%
  - >4 mm: 44%

Node status

- N0: Lymph nodes cannot be evaluated
- N1: No evidence of cancer in the lymph nodes
  - N1a: micrometastasis
  - N1b: macrometastasis
- N2: 2 or 3 lymph nodes
  - N2a: micrometastasis
  - N2b: macrometastasis
  - N2c: in transit or satellite lesions but no positive lymph nodes
- N3: Any of the following:
  - Lymph nodes
  - 2 or more lymph nodes that are not part of a chain
  - In transit or satellite lesions with any number of positive lymph nodes

Pathologic staging of locally advanced melanoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>TI-4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>TI-4a</td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>TI-4b</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>TI-4b</td>
<td>N1b</td>
<td>M0</td>
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<tr>
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<td>TI-4a</td>
<td>N2a</td>
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<td>TI-4a</td>
<td>N2b</td>
<td>M0</td>
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<td></td>
<td>TI-4a</td>
<td>N2c</td>
<td>M0</td>
</tr>
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<td>IIIC</td>
<td>TI-4b</td>
<td>N1b</td>
<td>M0</td>
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<td></td>
<td>TI-4b</td>
<td>N2b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>TI-4b</td>
<td>N2c</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
</tbody>
</table>

Melanoma survival based on node status and in stage IIIA - IIIC disease
Pathologic staging of metastatic melanoma

Stage IV  Any T  Any N  M1

Metastasis site

- Mx: metastases cannot be evaluated
- M0: no evidence of metastases
- M1a: sites skin, subcutaneous or distant lymph nodes
- M1b: metastases to lung
- M1c: metastases to all other visceral sites

1-year survival rates:
- M1a: 62%
- M1b: 53%
- M1c: 33%

Prognosis in melanoma with distant metastasis

- Site of first metastasis
- Serum lactate dehydrogenase (LDH)
- Number of metastases
- Surgical resectability
- Response to therapy
- Duration of remission

Prognostic importance of LDH level

Lactate dehydrogenase (LDH)
- Released after cell damage or death
- Higher tumor burden and progression
- Included in current staging system
  - Not specific:
    - Other malignancies, hemolysis, infection, inflammation and ischemic tissue damage
    - Negative predictive value for metastatic relapse

Stage IV melanoma prognosis

1 year

normal LDH  elevated LDH

65%  40%  32%  18%
Other prognostic factors

- Anatomic site
- Age
- Gender
- Marital status
- Tumor infiltrating lymphocytes and other immunologic markers
- Molecular markers of prognosis
  - Serum markers
  - Circulating tumor cells and other tumor cell derived factors
- Clark’s level
- Vertical growth phase
- Regression
- Increased tumor vascularity
- Angiotropism
- Lymphovascular invasion
- Neurotropism

Molecular markers of melanoma progression: mRNA signatures

- mRNA based studies:

  - Very few overlapping genes were identified by the studies
  - Many of even the overlapping signals were likely form not melanocytes

Molecular markers of melanoma progression: mRNA signature based clinical prognostic test

- 28 target genes and 3 control genes, proprietary gene expression profile evaluation
  - FFPE tissue, q-RT-PCR based gene expression analysis
  - Development dataset (n=107)
  - Training dataset (n=164)
  - Validation dataset (n=104)
  - Predicts risk of nodal metastasis
    - 5-year disease free survival rate in the validation set:
      - 97% class 1
      - 31% class 2
    - NPV and PPV were 93% and 72%, respectively

  - 28 target genes and 3 control genes, proprietary gene expression profile evaluation
    - prognostic accuracy compared with sentinel lymph node biopsy (SLNB) in a multicenter cohort of 217 patients
    - disease-free, distant metastasis-free, and overall survivals:
      - more significant and better predictor of each end point compared to SLNB
      - in combination with SLNB improved prognostication
      - class 2 (high-risk outcome) and a negative SLNB result
        - 5-year disease-free (35%), distant metastasis-free (49%), overall survivals (54%)

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  - in combination with SLNB improved prognostication
  - class 2 (high-risk outcome) and a negative SLNB result
    - 5-year disease-free (35%), distant metastasis-free (49%), overall survivals (54%)

Melanoma pathogenesis

This is not this simple

Exome sequencing identifies recurrent mutations in NFI and RASopathy genes in sun-exposed melanomas

Michael Krawinthemann1, 2, Ying Kang1, Antonia Bachschmidt3, Perry Evans1, Nupur Pantapatapong1, Cen Xu1, James E. Eubanks1,2, Moungsup Suw Angular1,2, Marika Chang1,2, Robert Strong1,2, Michael Jarrett1,2, Marcus Rosenberg1,2, Stephan Arianz1,2, Deepak Nambiar1,2, Maria Sitoh1,2, Barrie Huggett1,2, Mervin Elsby1,2, Joseph Drummenger1,2, Richard P. May1, 2 & Ruth kald SIZE

4/12/2016
Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas

Michael Kastanaki1,2, Yung King1,2, Antonella Donadio2, Perry Fried1, Nathanael Pasut1,2, Can Wei1, James P. McConkey3,5, Zorumski MC4,6, Elian Cheng1, Robert Straus1, Marko Nacarevic7,8, Marian Blumenthal4,5, Marisa Benevides8,9, Stephen Aitken1,2, Daniel St. Hugues7,9, Mehla Mainil9,6, Joseph Schmiegel10,6, Richard P. Gilbert11,12 & Rathi Halahar13

- Very high mutation burden in melanoma
- Mutation profile groups (BRAF, RAS, NF1)
- Most of the mutations are present also in melanocytic nevi

BRAF inhibitor treatment in melanoma

- Typical response for patients on BRAF inhibitors. BRAF inhibitor (vemurafenib) can induce PET-CT responses in as little as two weeks.

Small molecular inhibitors in melanoma therapy

Immune checkpoint blockade for melanoma therapy

Summary: Cutaneous malignancies

- Skin: barrier
- UV radiation: most important epidermal carcinogen
- Precancerous lesions: Actinic keratosis
- Most common skin cancers
  - Non melanoma skin cancers:
    - Basal cell carcinoma
    - Squamous cell carcinoma
  - Melanoma
Questions

• Email: Gyorgy.Paragh@roswellpark.org