Cutaneous malignancies

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Buffalo, NY, April 12, 2016
Disclosure

• Unless otherwise noted the pictures and tables were borrowed from:

http://www.visualdx.com

http://www.dermnetnz.org/

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 skin
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
Keratinocyte differentiation

Stratum Basale
- keratin5/14
- plasmamebrane phospholipids

Stratum Spinosum
- keratin1/10

Stratum Granulosum
- K2e, involucrin, profilaggrin, loricin
- SPR1&2
- transgutaminase 1
- FFA, cholesterol, cholesterol-sulfate, sphingolipids (ceramides)

Stratum Corneum
- Cornified envelope
- (nucleus disappears)
- lipid lamellae

Corneocytes

Keratinocytes

Differentiation
Stratum basale

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

Fuchs E J Cell Biol 2008;180:273-284
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

<table>
<thead>
<tr>
<th>Properties</th>
<th>Stem cells</th>
<th>Transit amplifying cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-renewal*</td>
<td>Unlimited</td>
<td>Limited</td>
</tr>
<tr>
<td>Potential for differentiation*</td>
<td>Multipotent</td>
<td>Limited</td>
</tr>
<tr>
<td>Cycling in normal epidermis</td>
<td>Slow†</td>
<td>Rapid</td>
</tr>
<tr>
<td>Proliferative potential (e.g. during fetal development and wound healing)</td>
<td>High</td>
<td>Limited†</td>
</tr>
<tr>
<td>Growth in culture</td>
<td>Sustained clonal growth</td>
<td>Small abortive clones†</td>
</tr>
<tr>
<td>Maintenance of tissue homeostasis</td>
<td>Yes</td>
<td>Limited</td>
</tr>
</tbody>
</table>
Stem cells

- Epidermal proliferative unit
Stem cells

• Keratinocyte stem cells reside in:
  • dermal papilla
  • hair bulge

Stratum spinosum

- Spinous Layer
  - bundles of K1/K10-keratin filaments
  - intercellular junctions rich in desmosomes
  - AP2, C/EBP, Hes1, Notch 1/3

- Basal Layer
  - sparse K5/K14-keratin filaments
  - intercellular junctions rich in adherens junctions
  - p63, EGFR, IGFR, TβRII, Delta1
  - hemidesmosomes (α6β4), focal adhesions (α3β1)
  - laminin V, fibronectin, Col IV, TGFα, IGFs

Fuchs E J Cell Biol 2008;180:273-284
Stratum granulosum

Granular Layer:
- tight junctions,
- lamellar granules, keratoxylin granules,
- keratin filament bundles,
- profilaggrin, loricrin, lipids

Spinous Layer:
- bundles of K1/K10-keratin filaments,
- intercellular junctions
- rich in desmosomes
- AP2, C/EBP, Hes1, Notch 1/3

Basal Layer:
- sparse K5/K14-keratin filaments,
- intercellular junctions
- rich in adherens junctions
- p63, EGFR, IGFR, TβRII, Delta1
- hemidesmosomes (α6β4), focal adhesions (α3β1)

Basement Membrane/ECM:
- laminin V, fibronectin,
  Col IV, TGFα, IGFs

Fuchs E J Cell Biol 2008;180:273-284
Granular Layer

- **Keratohyalin granules (profilaggrin, loricrin)**
  - responsible for visible granularity under light microscopy

- **Lamellar granules**
  - AKA Lamellar bodies; membrane-coating granules, Odland bodies
  - Content: Mixture of lipids (phospholipids, sphingolipids and cholesterol) and mixture of hydrolytic enzymes (acid phosphatase, glycosidases, proteases and lipases)

Conrified envelope assembly begins in the granular cell layer (and upper stratum spinosum)
Lipid level changes during KC differentiation

Liebish G. et al University of Regensburg (unpublished data)
Major lipid classes in the barrier

- Cholesterol
- Free fatty acids
- Ceramides
Stratum corneum

- Basal Layer: sparse K5/K14-keratin filaments, intercellular junctions rich in adherens junctions, p63, EGFR, IGFR, TβRⅡ, Delta1, hemidesmosomes (α6β4), focal adhesions (α3β1)
- Spinous Layer: bundles of K1/K10-keratin filaments, intercellular junctions rich in desmosomes, AP2, C/EBP, Hes1, Notch 1/3
- Granular Layer: tight junctions, lamellar granules, keratohyalin granules, keratin filament bundles, profilaggrin, loricrin, lipids
- Stratum Corneum: lipid bilayers, cross-linked cornified envelope, keratin filament cables, filaggrin

Fuchs E J Cell Biol 2008;180:273-284

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**Lipid lamellae:**
A continuous tightly packed lipid matrix

*Composition:*
sphingolipids
very long chain highly saturated fatty acids
cholesterol, cholesterol sulfate

**Corneocytes:**
Protein scaffold of dead cells

*Composition:*
filaggrin, loricrin, involucrin ...

Chemical protective interface

Mechanical protective role
In many dermatological diseases: deregulation of normal KC differentiation.


http://www.medicinenet.com/image-collection/lichen_simplex_chronicus_picture/picture.htm

http://www.studyblue.com/notes/note/n/week-1-dermatological-pathology/deck/1830400

http://www.drgranny.com/2011/03/06/home-remedies-for-psoriasis/
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 percent 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

http://www.skincancer.org/skin-cancer-information/skin-cancer-facts
Cancer statistics

### Estimated New Cases

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>180,890</td>
<td>21%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>117,920</td>
<td>14%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,820</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>58,950</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>46,870</td>
<td>6%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,170</td>
<td>5%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,650</td>
<td>5%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>34,780</td>
<td>4%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34,090</td>
<td>4%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>28,410</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>841,390</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

### Estimated Deaths

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>85,920</td>
<td>27%</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,120</td>
<td>8%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,020</td>
<td>8%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,450</td>
<td>7%</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>18,280</td>
<td>6%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,130</td>
<td>4%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>4%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,820</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,520</td>
<td>4%</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,440</td>
<td>3%</td>
</tr>
<tr>
<td><strong>All Sites</strong></td>
<td><strong>314,290</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

**FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2016.**

Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

http://fortune.com/2016/01/08/cancer-deaths-hit-record-low/
Read the fine print

cases exclude basal cell and squamous cell skin cancers and in situ carcinoma...
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
- 3000-10,000 deaths per year

http://www.skincancer.org/skin-cancer-information/skin-cancer-facts
Risk factors for development of NMSC

<table>
<thead>
<tr>
<th>Environmental Exposures</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative/occupational sun exposure</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Intermittent/recreational sun exposure</td>
<td></td>
<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>
<td>+</td>
</tr>
</tbody>
</table>
Risk factors for development of NMSC

<table>
<thead>
<tr>
<th>Genetic syndromes</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma pigmentosum</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>Nevoid basal cell carcinoma syndrome</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Dystrophic epidermolysis bullosa</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Risk factors for development of NMSC

<table>
<thead>
<tr>
<th>Predisposing clinical settings</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>Immunosuppression</th>
<th>SCC</th>
<th>BCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ transplantation</td>
<td>+</td>
<td>+</td>
</tr>
<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

<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>

Image: [https://www.pinterest.com/pin/485262928569601188/](https://www.pinterest.com/pin/485262928569601188/)
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)

• **UVR induced skin changes**
  (sunburn, tanning, epidermal hyperplasia, vitamin D production, emotional effects, photoaging, photoimmunology, *photocarcinogenesis*)
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The visible light and the UV spectrum

- UV radiation

http://www.bestuv.com/about-uv/what-is-uv-light
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 (UVAI; 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

http://www.cleartechlamps.com/tanninglamps.shtml
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 absorbtion:
- DNA/RNA
- Elastin
- Collagen

http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_035.pdf
Erythema and DNA-damage action spectrum

Erythema and DNA-damage action spectra

UV-C  UV-B  UV-A

wavelength [nm]

http://www.temis.nl/uvradiation/info/uvaction.html
The action spectrum of photocarcinogenesis.

**Figure 2** An action spectrum for UV carcinogenesis. The curve shows the effectiveness of UV radiation for the induction of squamous cell carcinoma in hairless albino mice, as a function of wavelength. (From de Gruijl and van der Leun.⁶ With permission.)
Erythema and DNA-damage action spectrum

http://www.temis.nl/uvradiation/info/uvaction.html


Skin cancer and solar UV radiation

F.R. de Gruijl
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)

• **UVR induced skin changes**
  (sunburn, tanning, epidermal hypreplasia, vitamin D production, emotional effects, photoaging, photoimmunology, **photocarcinogenesis**
UV radiation targets in the skin

- Urocanic acid
- Tryptophan
- Tyrosine
- Melanin
- Elastin
- Collagen
- DNA / RNA
http://www.onepennysheet.com/2010/01/full-body-scanners-used-on-air-passengers-may-damage-human-dna/
UV effects on DNA

- Pyrimidine dimers
- Covalent link induced by UV radiation between adjacent pyrimidine bases
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-pyrimidones (6,4-photoproducts)
  • Occur less frequently (approx 1:3 of CPD frequency)
  • More efficiently removed from the genome
  • Much less mutagenic
UV induced oxidative stress

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

- These activate cellular oxygen

  → Indirect DNA damage

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

Chemixecitation of melanin derivatives induces DNA photoproducts long after UV exposure

Sanjay Premi¹, Silvia Wallisch¹, Camila M. Mano¹,², Adam B. Weiner¹,*, Antonella Bacchiocchi³, Kazumasa Wakamatsu⁴, Etelvino J. H. Bechara²,⁵,†, Ruth Halaban³,⁶, Thierry Douki⁷,†, Douglas E. Brash¹,⁶,‡

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DOI: 10.1126/science.1256022
Chemieexcitation of melanin derivatives induces DNA photoproduts long after UV exposure

Sanjay Premi¹, Silvia Wallisch¹, Camila M. Mano¹,², Adam B. Weiner¹,*, Antonella Bacchiocchi³, Kazumasa Wakamatsu⁴, Etelvino J. H. Bechara²,⁵,†, Ruth Halaban³,⁶, Thierry Douki⁷,†, Douglas E. Brash¹,⁶,†
Nucleotide excision repair

DNA is damaged

Transcription-coupled repair

Global excision repair

RNA polymerase stalls

XPC/hHR23B (+/- DDB) binds

damage is recognized

XPA, RPA, XPG, and TFIIH bind

TFIIH unwinds DNA helix

XPG and XPF/ERCC1 cut, lesion excised

DNA polymerase fills gap, ligase seals nick

normal nucleotide sequence restored

clean template for transcription

clean template for replication
Xeroderma pigmentosum

• Symptoms: Development of numerous lentigines at an early age

(DiGiovanna et al. 2012)
Xeroderma pigmentosum

Photosensitivity goes along with increased skin cancer incidence:

<table>
<thead>
<tr>
<th></th>
<th>XP</th>
<th>general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>median age of first NMSC:</td>
<td>9 yrs</td>
<td>67 yrs</td>
</tr>
<tr>
<td>median age of first melanoma:</td>
<td>22 yrs</td>
<td>55 yrs</td>
</tr>
</tbody>
</table>

(Kraemer et al. 1994; Bradford et al. 2011; DiGiovanna et al. 2012)
Repair is error prone

- Most common UV induced mutations
  - C → T
  - CC → TT

- UVB and daylight UV induce CPDs preferentially at 5-methylcytosine(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

Cellular UV damage responses—Functions of tumor suppressor p53

Leena Latonen, Marikki Laiho
Outline

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

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  (biomolecules effected by UV, DNA damage)

• **UVR induced skin changes**
  (sunburn, tanning, epidermal hypreplasia, vitamin D production, emotional effects, photoaging, photoimmunology, **photocarcinogenesis**)

UVR induced skin changes

sunburn
tanning
epidermal hypreplasia
vitamin D production
emotional effects
photoaging
photoimmunology
photocarcinogenesis
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
Decision about cell fate
Importance of sunburn cell formation

- p53-deficient mice:
  - decreased sunburn cell 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 correlate

• Suberythemogenic doses of UV radiation may still lead to small amount of sunburn cell formation

Sunburn cells

- Short term survival = homeostatic balance

- Cell proliferation (mutations)
- Terminal differentiation apoptosis
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

Cancer Res. 2007;67:4648-4656.
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 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

Cancer Res. 2001 Feb 1;61(3):977-83.
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 expasion?

Cancer Res. 2001 Feb 1;61(3):977-83.
Cancer Res.2007;67:4648-4656.
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

Cancer Res. 2001 Feb 1;61(3):977-83.
Cancer Res. 2007;67:4648-4656.
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

RESEARCH ARTICLE

High burden and pervasive positive selection of somatic mutations in normal human skin

Iñigo Martincorenñ1, Amit Roshan2, Moritz Gerstung1, Peter Ellis1, Peter Van Loo1,3,4, Stuart McLaren1, David C. Wedge1, Anthony Fullam1, Ludmil B. Alexandrov1, Jose M. Tubio1, Lucy Stebbings1, Andrew Menzies1, Sara Widaa1, Michael R. Stratton1, Philip H. Jones2,* , Peter J. Campbell1,5,*

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Science 22 May 2015:
Vol. 348, Issue 6237, pp. 880-886
DOI: 10.1126/science.aaa6806
Genes significantly mutated in normal human skin

- NOTCH1 (Notch homolog 1)
- FAT1 (Ubiquitin-like protein FAT10)
- NOTCH2 (Notch homolog 2)
- TP53 (tumor protein p53)
- RBM10 (RNA binding protein 10)
- NOTCH3 (Notch homolog 3)

https://www.sciencenews.org/node/191212?mode=pick&context=166
Non-melanoma Skin Cancers

https://www.sciencenews.org/node/191212?mode=pick&context=166
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
Field Treatment effects shortly after treatment

Before

Shortly after treatment
Field treatment long term effects

Before

After
Cutaneous Squamous Cell Carcinoma (SCC)

• 400,000-1,000,000 per year in US

• Risk Factors:
  • Cumulative long term exposure to UV light
  • Radiation tx
  • Immunosuppression
    • Renal transplant pts have 65-253 fold increased risk
    • Lesions appear 2-4 yrs post transplantation
  • Chronic ulceration, scar, HPV, chemical carcinogens
Squamous Cell Carcinoma

- 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
Squamous cell carcinoma variants

- Keratoacanthoma
- Squamous cell carcinoma in situ
- 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
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%)
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

Squamous Cell Carcinoma

**Low risk**
- Mask areas—face <6 mm
  - Cheeks, forehead, neck, scalp <10 mm
  - Trunk, extremities <20 mm
- Well differentiated <4 mm depth
- Slow growing
- Well-defined borders
- Negative perineural or vascular invasion

**High risk**
- Central face, periorbital and periauricular areas >6 mm
  - Cheeks, forehead, neck, scalp >10 mm
  - Trunk, extremities >20 mm
- Poorly differentiated >4 mm depth
- Rapid growth
- Ill-defined borders
  - Lip, Ears
- Perineural invasion
- Recurrence
- Immunosuppression
- Site of chronic inflammation
- Recurrent tumor
- Previous radiotherapy

**Mohs micrographic surgery**
- Highest cure rate
- Conservation of tissue
- Expensive

**Radiation therapy**
- Recurrent BCE
- Good cosmetic results
- Tolerated by elderly
- Not for young patients
- Expensive

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>Tumor Type</th>
<th>Incidence Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma</td>
<td>65 to 250 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

• Photoprotection
• Skin checks

• 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

http://pulpbits.net/7-skin-structure-anatomy-diagrams/epidermis-structure-systems/
BCC histological patterns
Nodular BCCs

- Most common variant
- 60% of all BCCs
- Face
- Raised, glassy/pearly papule or nodule
- Overlying telangiectases
- Large, extend deeply
- Ulceration
- Pigmented
Superficial BCC

• Second most common
• 15% of BCC
• Favors the trunk and extremities
• Pink, erythematosus 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

**Low risk**
- Central face, periorbital and periauricular areas <6 mm
  - Cheeks, forehead, neck, scalp <10 mm
  - Trunk, extremities <20 mm
- Well-defined borders
- Slow growing
- Histologic subtype
  - Nodular
  - Superficial

**High risk**
- Central face, periorbital and periauricular areas >6 mm
  - Cheeks, forehead, neck, scalp >10 mm
  - Trunk, extremities >20 mm
- Ill-defined borders
- Fast growing
- Recurrent BCC
- Incomplete excision
- Histologic subtype
  - Morpheaform
  - Basosquamous
  - Micronodular

**Moh's micrographic surgery**
- Highest cure rate
- Conservation of tissue
- Expensive

**Excision**
- Rapid healing
- Histologic margin control

**ED & C**
- Tissue conservation
- No histologic margin control
- Slow healing by secondary intention
- Scarring

**Radiation therapy**
- Recurrent BCE
- Good cosmetic results
- Tolerated by elderly
- Not for young patients
- Expensive

Extent of tumor after excision – clinical appearance may be misleading as far as extent of tumor beneath the skin surface
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

Radiation therapy

Systemic therapies: 
alpha-interferon, capecitabine, retinoids

Small molecular inhibitors
Basal cell carcinoma: beyond surgery and irradiation
Hedgehog signaling pathway in BCC

https://commons.wikimedia.org/wiki/File:Sonic_hedgehog_pathway.svg
Therapeutic options for advanced BCC

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

Vismodegib

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

Response rate: 43%
Complete response: 21%
Vismodegib

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

Adverse events in 55%:
  moderate to mild: 30%
  serious adverse events: 25%
Commonly reported adverse events

- Alopecia
- Fatigue
- Muscle spasms
- Dysgeusia / 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

John A. D’Orazio, Stuart Jarrett, Amanda Marsch, James Lagrew and Laura Cleary (2013). Melanoma — Epidemiology, Genetics and Risk Factors, Recent Advances in the Biology, Therapy and Management of Melanoma
Melanocyte function in the epidermis

- Melanocytes load keratinocytes with melanosomes for protection against ultraviolet radiation
<table>
<thead>
<tr>
<th>Skin type</th>
<th>Typical Features</th>
<th>Tanning ability</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Pale white skin, blue/hazel 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 darkly easily</td>
</tr>
<tr>
<td>VI</td>
<td>Dark brown or black skin</td>
<td>Never burns, always tans darkly</td>
</tr>
</tbody>
</table>

http://www.mirabellabeauty.com/fitzpatrick-landing
# Abnormalities of pigmentation

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentigo simplex</td>
<td>May be due to sunburn</td>
<td>Pigmented elongated rete ridges, Increased melanocytes along basal layer, Ink-spot variety (deeply pigmented)</td>
</tr>
<tr>
<td>Solar lentigo (1)</td>
<td>Scattered small brown lesions on sun-damaged areas</td>
<td>Pigmented elongated &amp; clubb rete ridges, Increased melanocytes along basal layer, Solar elastosis</td>
</tr>
<tr>
<td>Solar lentigo (2)</td>
<td>Large well-defined oval patch on face in mature individuals</td>
<td></td>
</tr>
</tbody>
</table>
# Abnormalities of pigmentation

<table>
<thead>
<tr>
<th>Naevus</th>
<th>Site of melanocytes (naevus cell nests)</th>
<th>Clinical image</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional naevus</td>
<td>Dermal-epidermal junction</td>
<td><img src="image" alt="Clinical image" /></td>
</tr>
<tr>
<td>Compound naevus</td>
<td>Dermal-epidermal junction and dermis</td>
<td><img src="image" alt="Clinical image" /></td>
</tr>
<tr>
<td>Dermal/intradermal naevus</td>
<td>Dermis</td>
<td><img src="image" alt="Clinical image" /></td>
</tr>
<tr>
<td>Blue naevus</td>
<td>Intradermal (heavily melanised)</td>
<td><img src="image" alt="Clinical image" /></td>
</tr>
<tr>
<td>Mongolian spot</td>
<td>Intradermal (melanised)</td>
<td><img src="image" alt="Clinical image" /></td>
</tr>
</tbody>
</table>

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

Genetic susceptibility:
CDKN2A (p16/ARF), CDK4, MC1R, BRAF

Melanoma pathogenesis

- **Benign Nevus**
  - **Epidemis**
    - **Basement membrane**
    - **BRAF mutation**
  - **Dermis**
- **Dysplastic Nevus**
  - **Radial Growth Phase**
    - **CDKN2A & PTEN loss**
  - **Vertical Growth Phase**
    - **E-cadherin loss**
    - **CD1 increase**
- **Metastatic Melanoma**
  - **Distant metastases**

Melanoma in numbers

From: Surveillance, Epidemiology, and End Results Program
Melanoma incidence
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
Nodular Melanoma

• Second most common
  • 15-30% of melanomas
• Commonly in 6\textsuperscript{th} decade of life
• No radial growth phase $\rightarrow$ 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
- 7\textsuperscript{th} 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

Tumor pictured—reported by pathologist as:
1. Depth of invasion 3.3 mm
2. Clark level 4
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**: < 0.8 mm no ulceration  
  - **T1b**: ≤ 1.0 mm with ulceration  
  - **T1c**: 0.8 - 1.0 mm no ulceration

- **T2**: >1.0 - 2.0 mm  
  - **T2a**: no ulceration  
  - **T2b**: with ulceration

- **T3**: >2.0 - 4.0 mm  
  - **T3a**: no ulceration  
  - **T3b**: with ulceration

- **T4**: > 4.0mm  
  - **T4a**: no ulceration  
  - **T4b**: with ulceration

Localized primary melanoma prognosis

Localized primary melanoma prognosis

Tumor status predicts node positivity

• Early disease features define risk of distant disease

• **Risk of SLN positivity based on tumor thickness**
  - <1 mm: 5%
    - <0.76 mm: 2.5%
    - ≥0.76 mm: 6.3%
    - 0.76-1.0 mm with ≥1/mm² mitotic rate: 10%
  - 1.01-2.0 mm: 12%
  - 2.01-4.0 mm: 28%
  - >4 mm: 44%

Locoregional melanoma categories (N1-3a&b)

• Nx: Lymph nodes cannot be evaluated
• N0: No evidence of cancer in the lymph nodes
• N1: 1 lymph node
  • N1a: clinically occult
  • N1b: clinically detected
• N2: 2 or 3 lymph nodes
  • N2a: clinically occult
  • N2b: clinically detected
• N3: Any of the following:
  • N3a: 4 or more clinically occult
  • N3b: 4 or more positive lymph nodes with at least one clinically detected, or any matted nodes
In-transit satellite and or microsatellite metastasis
Locoregional melanoma categories (N1-3c)

c: any number of in-transit satellite and or microsatellite metastasis

+ below number of nodes involved

- N1c: no regional lymph nodes
- N2c: one regional lymph node (CO/CD)
- N3c: two or more regional lymph nodes (CO/CD) and or the presence of matted nodes
Kaplan-Meier Melanoma-Specific Survival Curves According to N Subcategories

Melanoma survival in stage IIIA - IIID disease

In locoregional disease besides locoregional spread the primary tumor features still maintain prognostic significance

Melanoma survival in stage IIIA - IIID disease

Pathologic staging of metastatic melanoma

Stage IV  Any T  Any N  M1
Melanoma survival rates stage I – IV

Prognosis in melanoma with distant metastasis

• Site of metastasis
• Number of metastases
• Serum lactate dehydrogenase (LDH)

• Surgical resectability
• Duration of remission
• Response to therapy

Site of distant metastasis

- Mx: metastases cannot be evaluated
- M0: No evidence of metastases
- M1a: sites skin, subcutaneous or distant nodes
- M1b: metastases to lung
- M1c: metastases to other non-CNS visceral sites
- M1d: metastases to CNS

1-year survival rates:
- M1a: 62%*
- M1b: 53%*
- M1c: 33%*
- M1d: 19%**

LDH if elevated: M1a(1), M1b(1), M1c(1), M1d(1)
LDH if not elevated: M1a(0), M1b(0), M1c(0), M1d(0)

M categories

- Mx: metastases cannot be evaluated
- M0: No evidence of metastases
- M1a: sites skin, subcutaneous or distant nodes
- M1b: metastases to lung
- M1c: metastases to other non-CNS visceral sites
- M1d: metastases to CNS

LDH if elevated: M1a(1), M1b(1), M1c(1), M1d(1)
LDH if not elevated: M1a(0), M1b(0), M1c(0), M1d(0)

1-year survival rates:
- M1a: 62%*
- M1b: 53%*
- M1c: 33%*
- M1d: 19%**

Stage IV melanoma prognosis

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

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

- **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%)

Melanoma pathogenesis

This is not this simple

Exome sequencing identifies recurrent mutations in *NF1* and RASopathy genes in sun-exposed melanomas

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Exome sequencing identifies recurrent mutations in NF1 and RASopathy genes in sun-exposed melanomas

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

• Small molecular inhibitors
• Immunotherapy
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

Figure 2: Schematic diagram representing aberrant signaling pathways responsible for resistance to BRAF or MEK inhibitors in metastatic melanoma and pharmacological strategies to overcome this resistance.

Notes: Briefly, the molecular mechanisms of resistance to BRAF or MEK inhibitors in metastatic melanomas are highlighted. Pharmacological agents targeting key factors of these pathways undergoing clinical trials are listed.

Abbreviations: PDGFR, platelet-derived growth factor receptor; IGF, insulin-like growth factor; ERK, extracellular-signal-regulated kinase.
Immune checkpoint blockade for melanoma therapy
Hope for the future in melanoma therapy
Prevention of skin cancer

• Tanning of the skin is started by DNA damage

\[ \text{TAN} = \text{damage} \]
Sun-protection

Do not burn
Avoid tanning
Seek the shade
Avoid peek UV index hours
Use a broad spectrum sunscreen
Cover up
with sun-protective clothing:
  broad-brimmed hat
  UV-blocking sunglasses
SPF30-50 long sleeve clothes
Sun protection

Other effects of sunlight:
  • Wrinkles
  • Skin discoloration and blemishes

helioslaserstudio.com.au
By Dr. Vikram Singh Yadav
Self skin check

- Examine head and face, using one or both mirrors. Use blow-dryer to inspect scalp.
- Check hands, including nails. In full-length mirror, examine elbows, arms and underarms.
- Focus on neck, chest and torso. Women: check under breasts.
- Use mirror to inspect back of neck, shoulders, upper arms, back, buttocks and legs.
- Check legs and feet, including soles, heels, and nails. Use hand mirror to examine genitals.

• Best with someone's help
The ABCDEs for melanoma detection are:

A  •  A is for **Asymmetry** where one-half of the mole is unlike the other.

B  •  B is for **Border** where the mole is irregular, scalloped or poorly defined.

C  •  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  •  D is for **Diameter** of a mole when it is bigger than the size of a pencil eraser.

E  •  E is for **Evolving or changing in size, shape or color.**
Concerning features: Non-melanoma skin cancers

- Growing pink papules
- Sores that do not heal (>4 weeks)
- Skin areas that bleed frequently after limited trauma
- Spontaneously appearing growing scars
• Early diagnosis is key to cure

• Report concerning skin lesions to dermatology
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

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