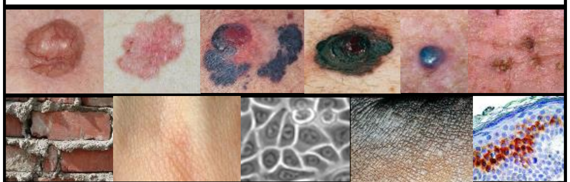
Cutaneous malignancies



Gyorgy Paragh, MD, PhD, FAAD
Assistant professor
Department of Dermatology
Roswell Park Cancer Institute
Buffalo, NY, April 12, 2016

Disclosure

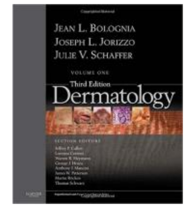
- Unless otherwise noted the pictures and tables were borrowed from:

VisualDx

http://www.visualdx.com

DermNet NZ

http://www.dermnetnz.org/



Bolognia: Dermatology, Third Edition 2012, Elsevier

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

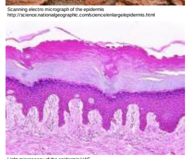
- Largest
- Most visible

Image: The Skin Man. Copyright: Gunther von Hagens' BODY WORLDS, Institute for Plastination, Heidelberg, Germany, www.bodyworlds.com

Functions of the skin

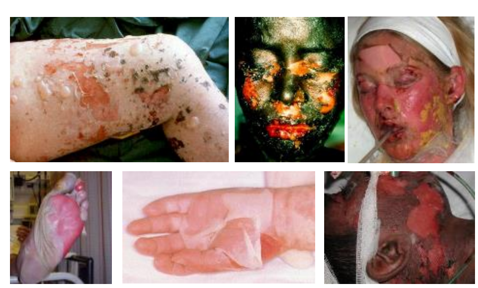
- Maintaining internal homeostasis in light of variable external stimuli
  - Mechanical protection
  - Regulates temperature
  - Photoprotection
  - Barrier against micro-organisms
- Metabolic function (vitamin D)
- Detects sensory stimuli
- Excretion
- Esthetic, psychosocial role

Scanning electro micrograph of the epidermis
http://science.nationalgeographic.com/science/enlarge/epidermis.html



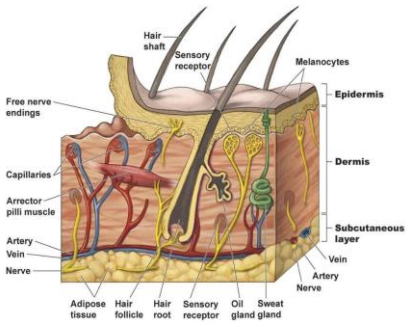
Light microscopy of the epidermis H&E
http://microanatomy.net/skin/skin_and_mammary_glands.htm

Acute barrier deficiency
SJS & TEN skin symptoms



Dermatol Ther. 2009 Sep-Oct;22(5):441-51.; Thieme clinical companions: Dermatology; http://www.medscape.com/; & http://www.uptodate.com

The structure of the skin



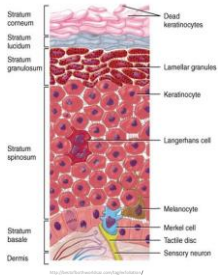
http://pulpbits.net/7-skin-structure-anatomy-diagrams/epidermis-structure-systems/

The structure of the epidermis and epidermal cells

!

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

- Leukocytes



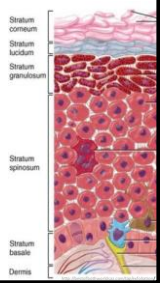
Keratinocyte differentiation tight regulation of function

barrier formation (lipid lamellae and corneocytes)

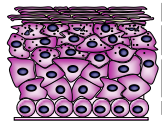
quick transformation

preparation for generation of the barrier interaction with transiently present cells

cell division, uptake of precursors, mechanical attachment to the dermis



Keratinocyte differentiation



Stratum Corneum
Stratum Granulosum
Stratum Spinosum
Stratum Basale

Corneocytes

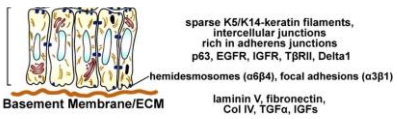
Keratinocytes

St. Basale	St. Spinosum	St. Granulosum	St. Corneum
keratin5/14	keratin1/10	K2e, involucrin, profilaggrin, loricrin SPR1&2 transgutamainase 1	Cornified envelope (nucleus disappears)
plasmamebrane phospholipids		FFA, cholesterol, cholesterol-sulfate, sphingolipids (ceramides)	lipid lamellae

Differentiation

Stratum basale

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

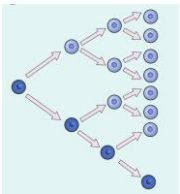


Fuchs E J Cell Biol 2008;180:273-284

JCB

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



Bolognia: Dermatology, Third Edition, 2012, Elsevier

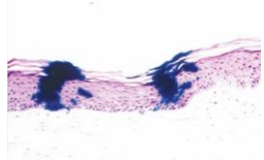
PROPERTIES OF STEM CELLS, TRANSIT AMPLIFYING CELLS AND TERMINALLY DIFFERENTIATED CELLS

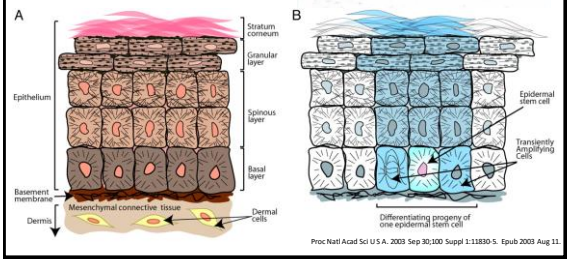
	Stem cells	Transit amplifying cells
Self-renewal*	Unlimited	Limited
Potential for differentiation*	Multipotent	Limited
Cycling in normal epidermis	Slow[†]	Rapid
Proliferative potential (e.g. during fetal development and wound healing)	High	Limited[‡]
Growth in culture	Sustained clonal growth	Small abortive clones[‡]
Maintenance of tissue homeostasis	Yes	Limited

Bolognia: Dermatology, Third Edition, 2012, Elsevier

Stem cells

- Epidermal proliferative units



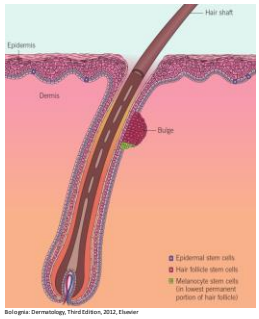


Proc Natl Acad Sci U S A. 2003 Sep 30;100 Suppl 1:11830-5. Epub 2003 Aug 11.

Stem cells

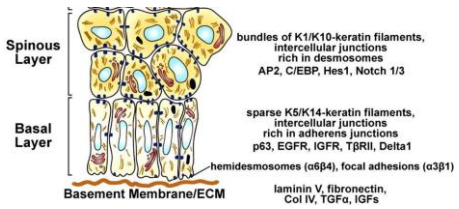
!

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



Bolognia: Dermatology, Third Edition, 2012, Elsevier

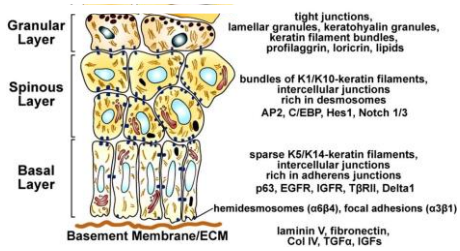
Stratum spinosum



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

JCB

Stratum granulosum



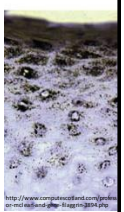
Fuchs E J Cell Biol 2008;180:273-284

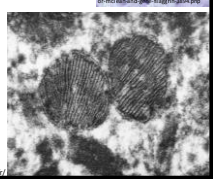
JCB

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)

Filaggrin staining in normal skin

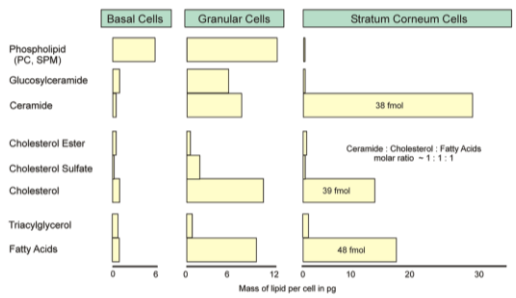




Conrified envelope assembly begins in the granular cell layer (and upper stratum spinosum)

http://biologiedelapeau.fr/

Lipid level changes during KC differentiation

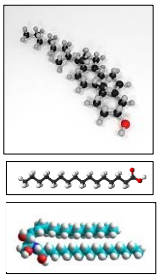


Liebish G. et al University of Regensburg (unpublished data)

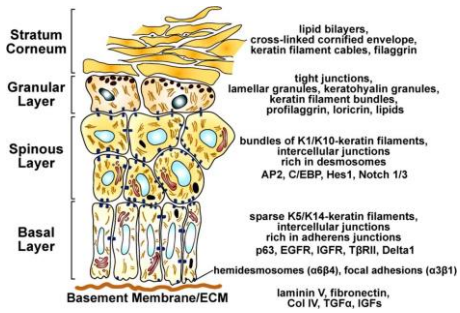
Major lipid classes in the barrier

!

- Cholesterol
- Free fatty acids
- Ceramides



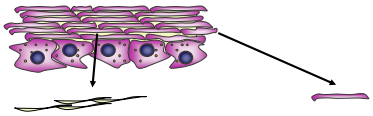
Stratum corneum



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

JCB

Basic structure and function of the stratum corneum



Lipid lamellae:
A continuous tightly packed lipid matrix

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

Chemical protective interface

Corneocytes:
Protein scaffold of dead cells

Composition:
filaggrin, loricrin, involucrin ...

Mechanical protective role

Outline

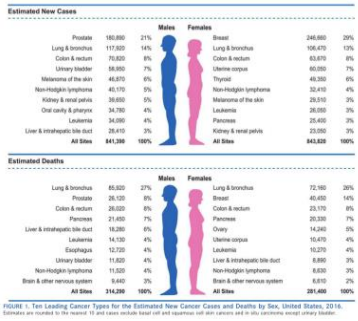
- Non-melanoma skin cancer
  - Epidemiology
  - Risk factors
  - UV radiation
  - Photocarcinogenesis
  - Non-melanoma skin cancer
    - Basal cell carcinoma
    - Squamous cell carcinoma
- Melanoma
  - Melanocyte biology
  - Epidemiology
  - Melanoma subtypes
  - Therapy

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

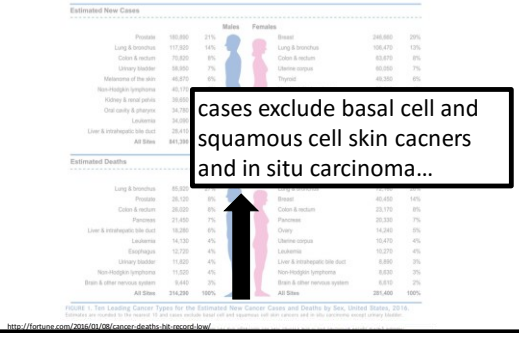
http://www.skincancer.org/skin-cancer-information/skin-cancer-facts

Cancer statistics



http://fortune.com/2016/01/08/cancer-deaths-hit-record-low/

Read the fine print



http://fortune.com/2016/01/08/cancer-deaths-hit-record-low/

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

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

Risk factors for development of NMSC

Environmental Exposures	SCC	BCC
Cumulative/occupational sun exposure	+	
Intermittent/recreational sun exposure		+
Other exposures to UV light (PUVA, tanning beds)	+	+
Ionizing radiation	+	+
Chemicals (Arsenic)	+	+
Human papillomavirus (HPV)	+	
Cigarette smoking	+	

Risk factors for development of NMSC

Genetic syndromes	SCC	BCC
Xeroderma pigmentosum	+	+
Oculocutaneous albinism	+	+
Epidermodysplasia verruciformis	+	
Muir-Torre syndrome	+	+
Nevoid basal cell carcinoma syndrome		+
Dystrophic epidermolysis bullosa	+	

Risk factors for development of NMSC

Predisposing clinical settings	SCC	BCC
Chronic non-healing wounds	+	
Long standing discoid lupus erythematosus	+	
Lichen planus (erosive) or lichen sclerosus	+	
Linear porokeratosis	+	

Risk factors for development of NMSC

Immunosuppression	SCC	BCC
Organ transplantation	+	+
Other (e.g. chronic lymphocytic leukemia treated with fludarabine, AIDS pts with HPV infection)	+	

Risk factors for development of NMSC

Pigmentary phenotype		SCC	BCC
Fair skin		+	+
Always burns, never tans		+	+
Freckling		+	+
Red hair		+	+

Image: 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 hypreplasia, vitamin D production, emotional effects, photoaging, photoimmunology, **photocarcinogenesis**)

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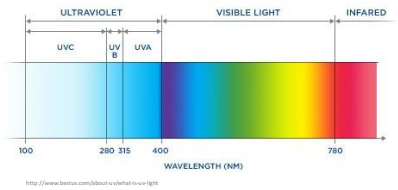
The visible light and the UV spectrum

- UV radiation



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

Relevant UV spectrum

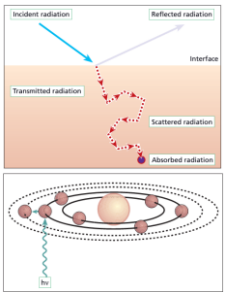
!

- Dermatologically important UV categories:

UVA	**315-400nm**
UVA1	**340-400nm**
UVA2	**315-340nm**
UVB	**290-315nm**
UVC	**200-290**

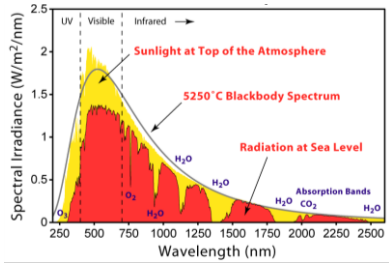
What happens to the UV radiation reaching physical matter

- Reflection
- Scattering
- Transmission
- Absorption



Rook's Textbook of Dermatology

Solar radiation spectrum

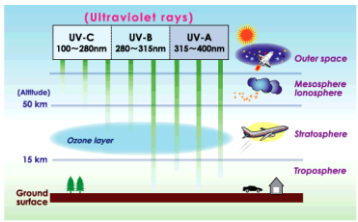


https://en.wikipedia.org/wiki/File:Solar_Spectrum.png

Atmospheric effects on solar UV radiation

Sunlight at the top of the athmosphere:
1366 watts/m^2
- 50% infrared light (IR)
- 40% visible light (VL)
- 10% ultraviolet light (UVR) (137 watts/m^2)

Sunlight at ground level:
1000–1100 watts/m^2
- 53% IR
- 44% VL
- 3% UVR (Sun at zenith)



With Sun at zenith at ground level:
IR: 527 W/m^2, VL: 445 W/m^2, UVR 32 W/m^2

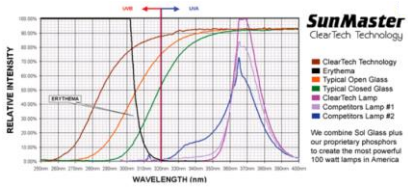
http://curry.eas.gatech.edu/Courses/6140/ency/Chapter3/Ency_Atmos/Radiation_Solar.pdf

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

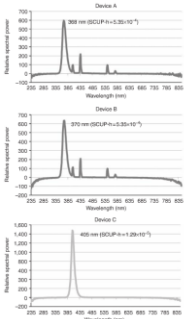


http://www.cleartechlamps.com/tanninglamps.shtml

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



Journal of Investigative Dermatology (2013) 133, 1097–1099; doi:10.1038/jid.2012.440

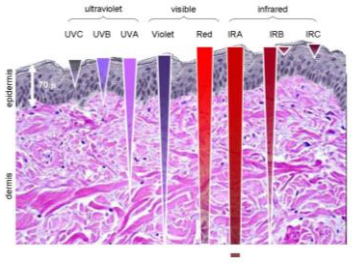
UV radiation penetration into the skin

!

5% of UVR is reflected

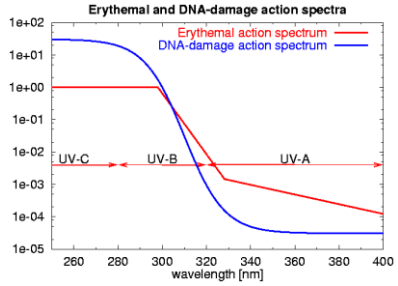
UVB
Epidermal absorption:
- urocanic acid
- DNA / RNA
- Tryptophan
- Tyrosine
- Melanin

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



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

The action spectrum of photocarcinogenesis.

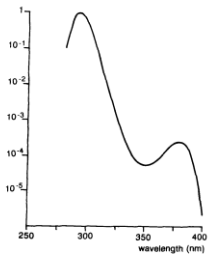
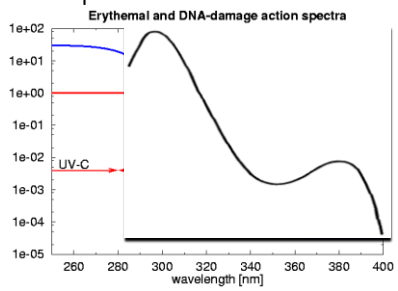


Figure 2 An action spectrum for UV carcinogenesis. The curve shows the effectiveness of UV radiation for the induction of squamous cell carcinoma in hairless albino mice, as a function of wavelength. (From de Gruijl and van der Leun.* With permission.)

Volume 35, Issue 14, December 1999, Pages 2003–2009
Skin cancer and solar UV radiation
F.R. de Gruijl

Erythema and DNA-damage action spectrum



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

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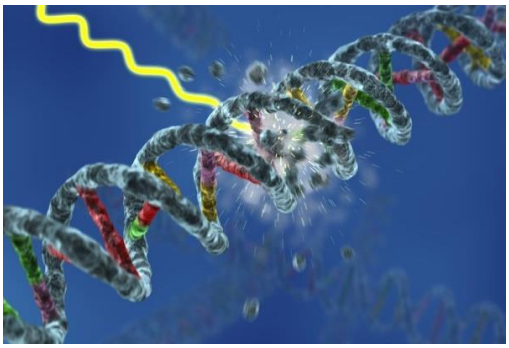
UV radiation targets in the skin

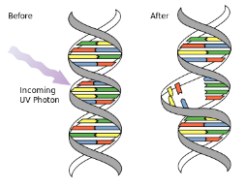
- Urocanic acid
- Tryptophan
- Tyrosine
- Melanin
- Elastin
- Collagen
- DNA / RNA



http://www.onepennynsheet.com/2010/01/full-body-scanners-used-on-eit-passengers-may-damage-human-dna/

UV effects on DNA

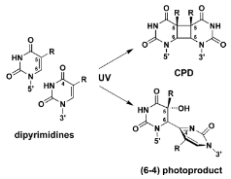
- Pyrimidine dimers
- Covalent link induced by UV radiation between adjacent pyrimidine bases



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
  - Mutgenic conversions are not know

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

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RESEARCH ARTICLE

Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure

Sanjay Premi[1], Silvia Wallisch[1], Camila M. Mano[1,2], Adam B. Weiner[1,*], Antonella Bacchiocchi[3], Kazumasa Wakamatsu[4], Etelvino J. H. Bechara[2,5,†], Ruth Halaban[3,6], Thierry Douki[7,†], Douglas E. Brash[1,6,‡]

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Chemiexcitation of melanin derivatives induces DNA photoproducts long after UV exposure

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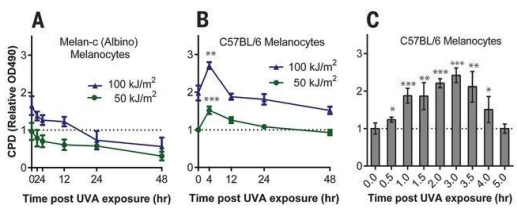
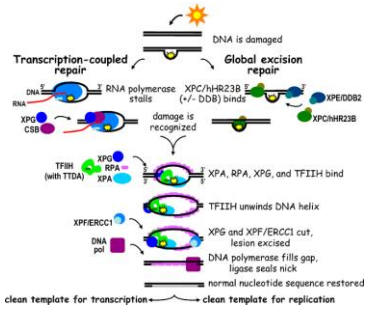


Science. 2015 Feb 20;347(6224):842-7.

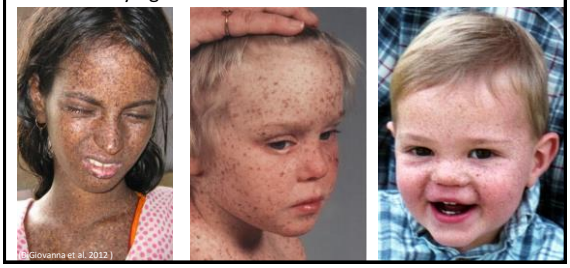
Nucleotide excision repair

!



Xeroderma pigmentosum

- Symptoms: Development of numerous lentigines at an early age

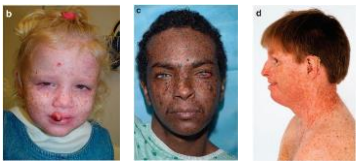


(DiGiovanna et al. 2012)

Xeroderma pigmentosum

Photosensitivity goes along with increased skin cancer incidence:

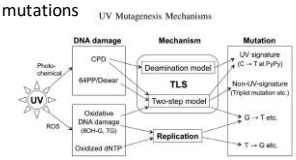
	XP	general population
median age of first NMSC:	9 yrs	67 yrs
median age of first melanoma:	22 yrs	55 yrs



(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



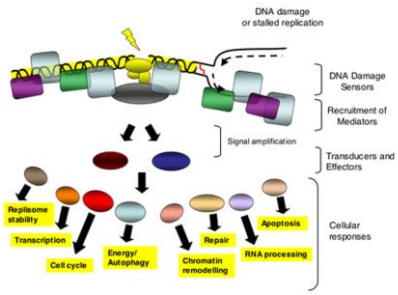
- UVB and daylight UV induce CPDs preferentially at 5-methyl-cytosine(mC)-containing dipyrimidine sites
- UV signature mutations occur frequently at the dipyrimidine sites associated with methylated CpG

Difference between UVA and UVB mutagenesis

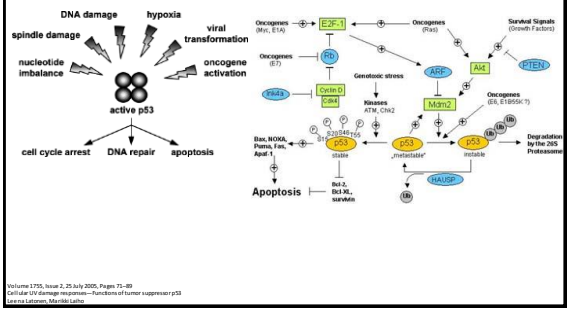
- UVB: mostly direct DNA damage with limited secondary ROS effect
- UVA: 8-hydroxyguanine, CPDs (high amount compared to previously expected) no 6,4PPs or Dewar isomers

J Radiat. Res., 52, 115–125 (2011) Hironobu IKEHATA and Tetsuya ONO The Mechanism of UV Mutagenesis

DNA damage signaling



Jackson SP and Bartek J. (2009) The DNA-damage response in human biology and disease. Nature 461, 1071–1078



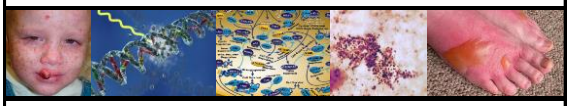
Outline

- **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**)

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

↓

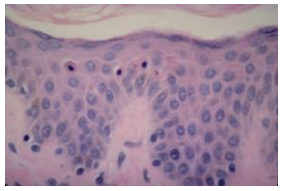
mutation of tumor suppressor genes or oncogenes

↓

carcinogenesis

Sunburn cells

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



medscape.com

apoptotic keratinocytes

Photodermatol Photoimmunol Photomed. 1995 Aug;11(4):149-54

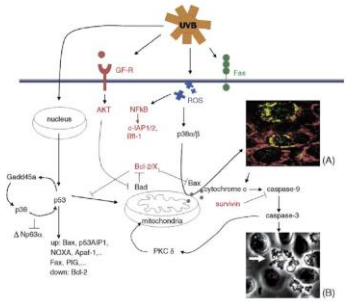
Sunburn cells

!

- 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

The International Journal of Biochemistry & Cell Biology 37 (2005) 1547–1553

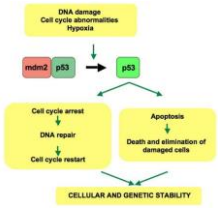
Decision about cell fate



Z. Assefa et al. / Biochimica et Biophysica Acta 1755 (2005) 90 – 106

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



Attardi, L. D., & Jacks, T. (1999). The role of p53 in tumour suppression: Lessons from mouse models.Cell Mol. Life Sci., 55, 48–63
Brurin, W., Zwart, E., Attardi, L. D., Iwakuma, T., Hoogervorst,
E. M., Beems, R. B., et al. (2004). Increased sensitivity to UV radiation in mice with a p53 point mutation at Ser389.Mol. Cell Biol., 24, 8884–8894.

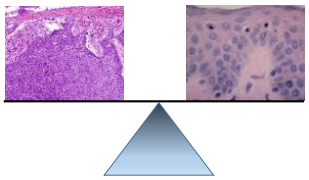
Sunburn cell formation and erythema

- 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

J Dermatol Sci. 2009 Jul;55(1):10-7. doi: 10.1016/j.jdermsci.2009.03.011. Epub 2009 May 2.
J Drugs Dermatol. 2013 Apr;12(4):464-8.
Journal of Investigative Dermatology (2004) 123, 781–787
Kaidbey KH: The photoprotective potential of the new superpotent sunscreens. J Amer Acad Dermatol 22(3):449-452, 1990.
Ziegler A, Jonason AS, Leffell DJ, et al.: Sunburn and p53 in the onset of skin cancer. Nature 372(6508):773-776, 1994

Sunburn cells

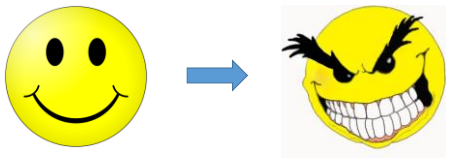
cell proliferation (mutations)



terminal differentiation apoptosis

- Short term survival = homeostatic balance

Early mutant cell clones



p53 mutations in UV carcinogenesis

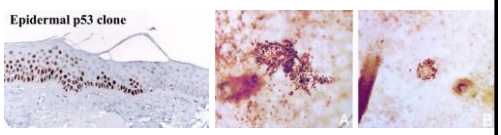
!

- 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

Cancer Res. 1993 Jul 1;53(13):2961-4.
Neoplasia. 1999 Nov;1(5):468-75.
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 cm^2 and together involve as much as 4% of the epidermis



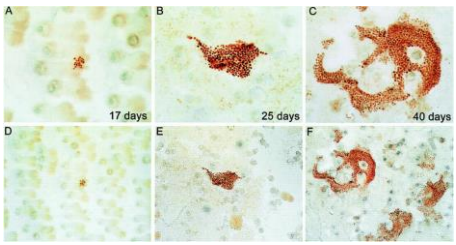
Proc Natl Acad Sci U S A. 1996 Nov 26;93(24):14025-9.

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.

Exp Dermatol. 2004 Oct;13(10):643-50.
Oncogene. 1996 Feb 15;12(4):765-73.

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.
Semin Cancer Biol. 2005 Apr;15(2):97-102.
Cancer Res.2007;67:4648-4656.

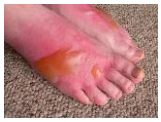
Apoptosis of surrounding normal keratinocytes drives p53 clone expansion

- 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

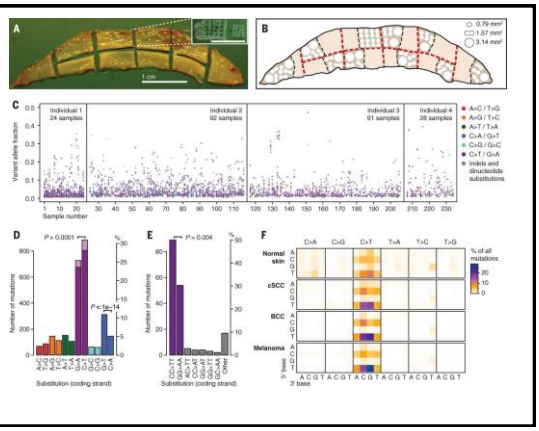
Cancer Res. 2001 Feb 1;61(3):977-83.
Semin Cancer Biol. 2005 Apr;15(2):97-102.
Cancer Res. 2007;67:4648-4656.

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

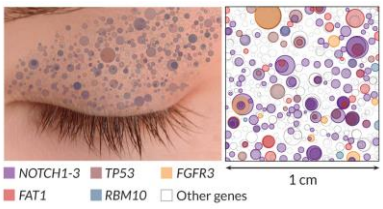


Carcinogenesis (2012) 33 (3):714-720.



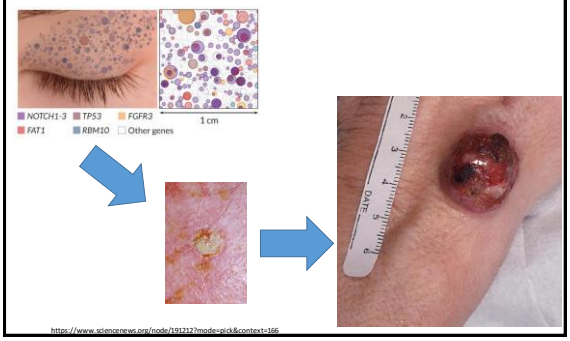
Genes significantly mutated in normal human skin !

- 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

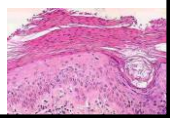
Non-melanoma Skin Cancers



https://www.sciencenews.org/node/191212?mode=pick&context=166

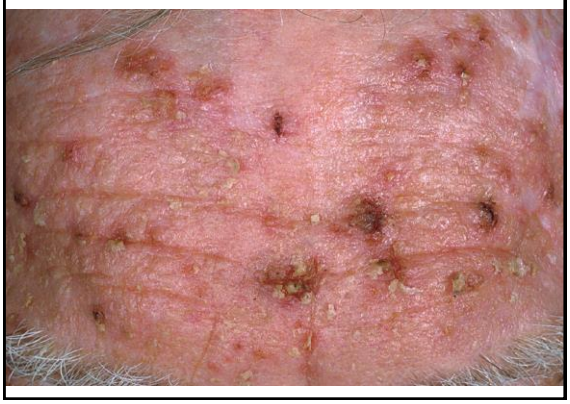
Actinic Keratoses

- 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



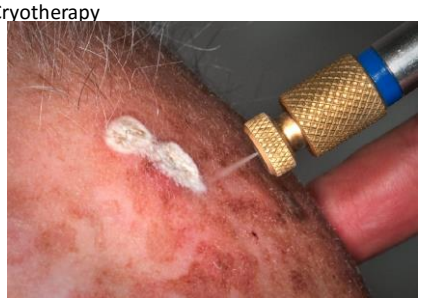
Actinic Keratosis

- 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

5-fluorouracil treatment effects (2x/day for 30 days)

http://www.sunnerud.com/people/efudex/

5-fluorouracil healing after treatment

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

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

SCC variants

!

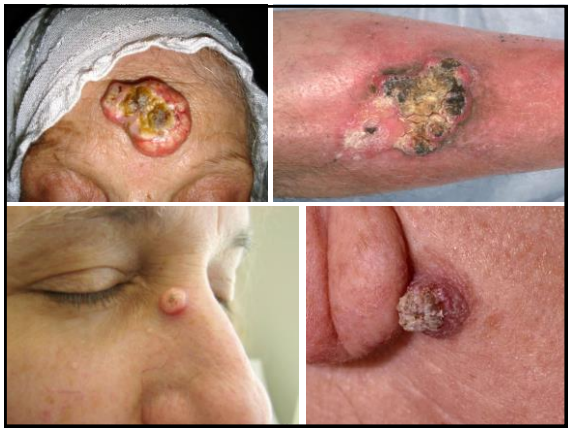
- Keratoacanthoma
- SCC in situ: Bowen's disease, Erythroplasia of Queyrat
- Invasive SCC
- Marjolin's Ulcer

SCC variants

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

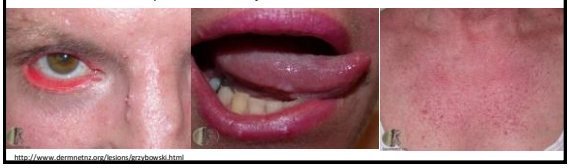
Keratoacanthoma

- 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



Syndromes with multiple keratoacanthomas

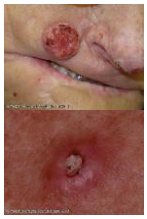
- The Grzybowski type:
  - typically diagnosed in adulthood
  - sudden appearance of hundreds of lesions in a disseminated fashion
  - the lesions are generally 2-3mm in diameter
  - found anywhere on the body:
    - even palms, soles, larynx, and oral mucosa



http://www.dermnetnz.org/lesions/grzybowski.html

Syndromes with multiple keratoacanthomas

- 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 wks
  - 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
    Nat Genet. 2011 Feb 27;43(4):365-9.



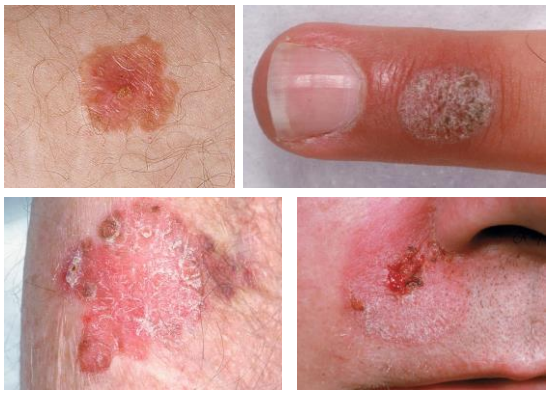
http://www.dermnetnz.org/lesions/grzybowski.html

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%)

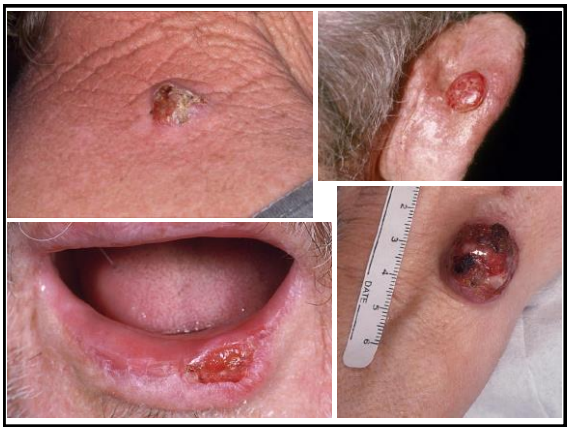


SCC variants

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

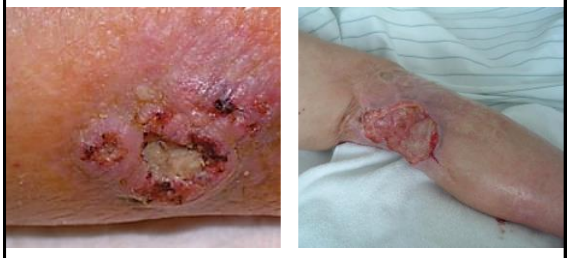
Invasive SCC

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



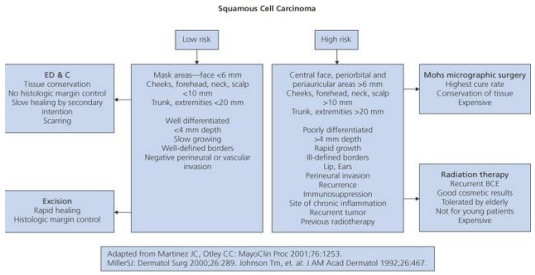
SCC variants

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



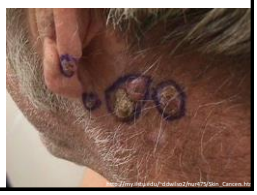
Treatment

- 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

Squamous cell carcinoma	65 –fold increase
SCC of the lip	20 – 38-fold increase
BCC	10-fold-increase
Melanoma	1.2 – 3.4-fold increase
Kaposi sarcoma	84-fold increase

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

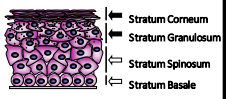
Basal Cell Carcinoma

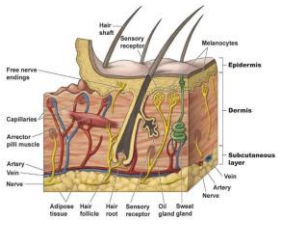
- No universal classification
- Variants
  - Nodular*
  - Superficial*
  - Morpheaform / Sclerosing *
- Very rarely metastasize (~1/10,000)

* all may be pigmented (morpheaform least likely)

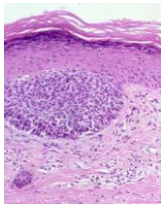
Basal Cell Carcinoma

- Epidermal basal layer epithelial cell differentiation

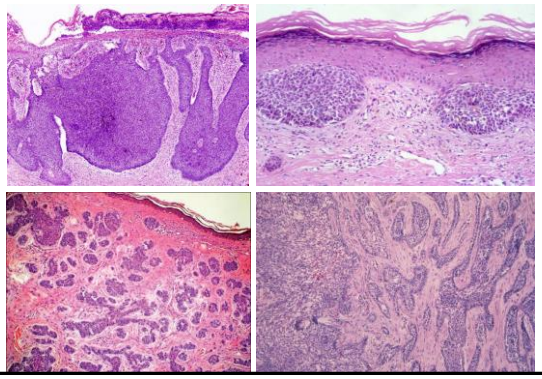




http://pulpbits.net/7-skin-structure-anatomy-diagrams/epidermis-structure-systems/



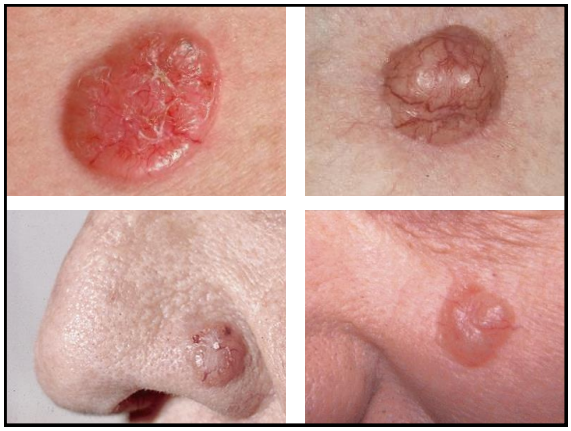
BCC histological patterns



Nodular BCCs

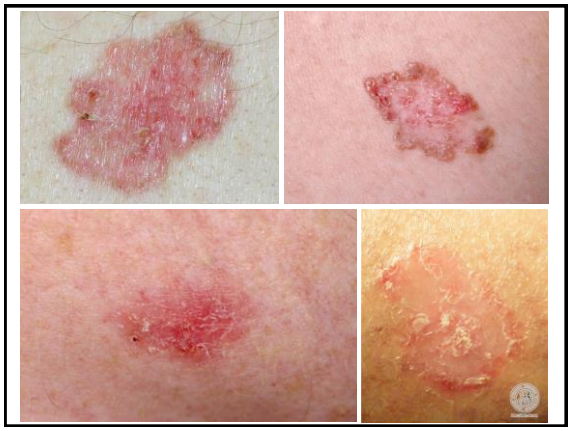
!

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



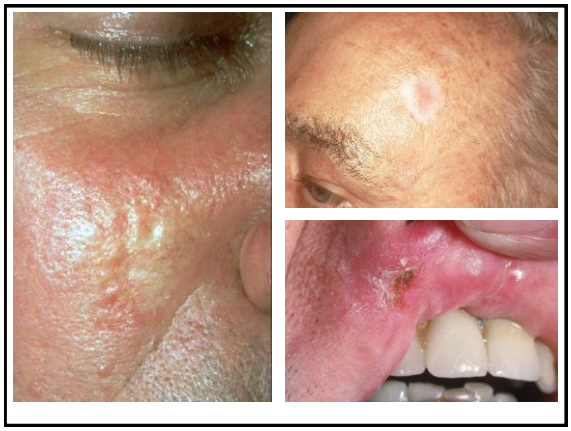
Superficial BCC

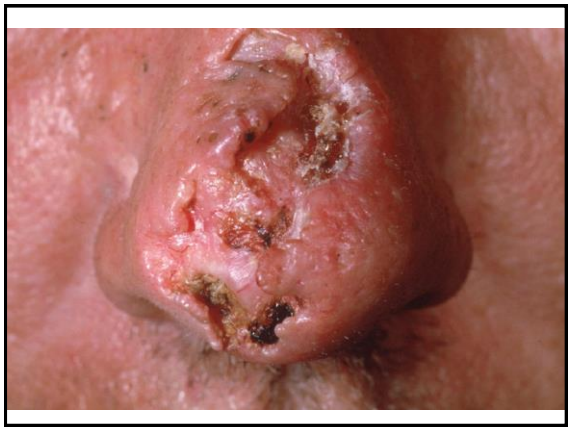
- Second most common
- 15% of BCC
- Favors the trunk and extremities
- Pink, erythematous macule/thin plaque
- Difficult to differentiate from benign inflammatory lesion/SCC/AK

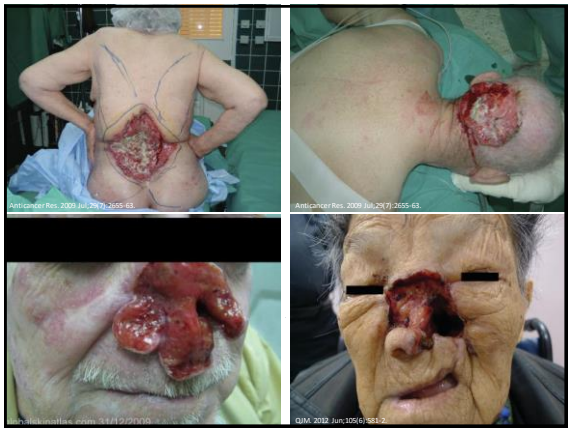


Morpheaform BCC

- 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



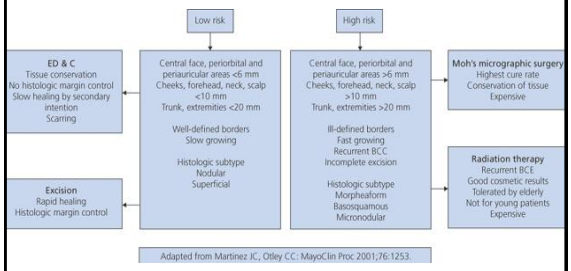


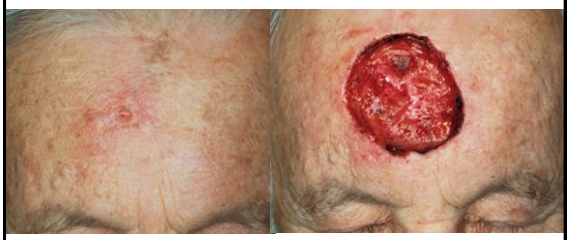


Metastatic basal cell carcinoma !

- 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

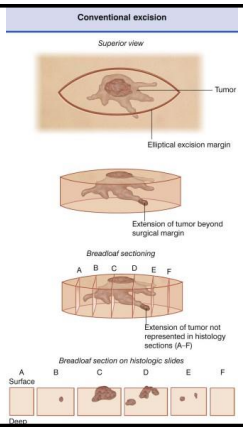


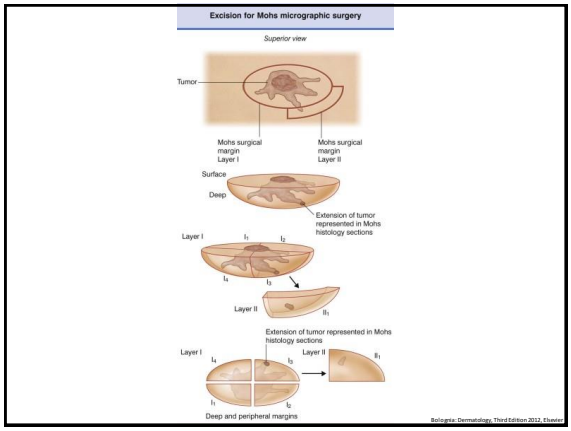


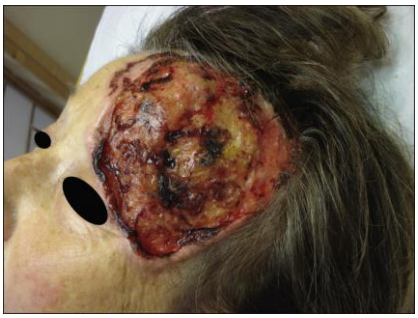
Extent of tumor after excision – clinical appearance may be misleading as far as extent of tumor beneath the skin surface

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





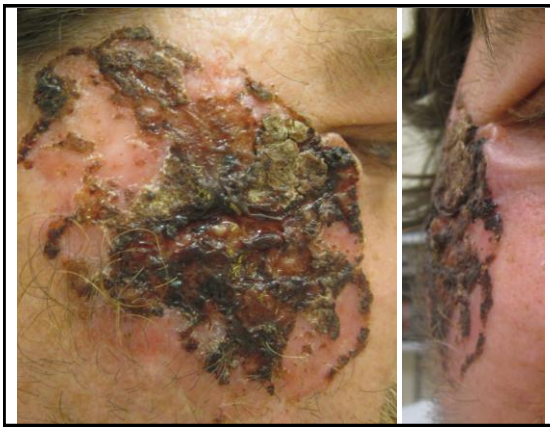


Other therapeutic options for advanced BCC

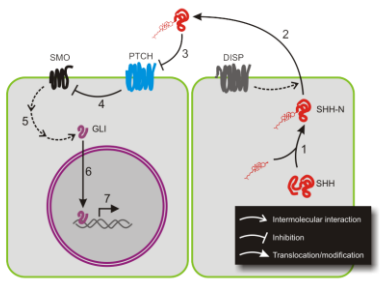
Systemic therapies:
alpha-interferon, capecitabine, retinoids

Small molecular inhibitors

Basal cell carcinoma: beyond surgery and irradiation



Hedgehog signaling pathway in BCC



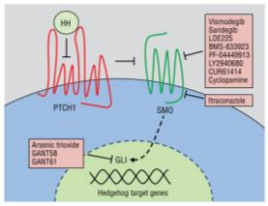
Therapeutic options for advanced BCC

!

Small molecular inhibitors of PTCH signaling:

LDE-225/Erismodegib

GDC-0449/Vismodegib



JAMA Dermatol. 2013;149(5):607-608. doi:10.1001/jamadermatol.2013.448

Vismodegib

Multicenter, international, two-cohort, non-randomized study:

63 locally advanced BCC patients

Response rate: 43%

Complete response: 21%

N Engl J Med 2012; 366:2171-2179June 7, 2012DOI: 10.1056/NEJMoa1113713

Vismodegib

Multicenter, international, two-cohort, non-randomized study:

63 locally advanced BCC patients

Adverse events in 55%:

moderate to mild: 30%

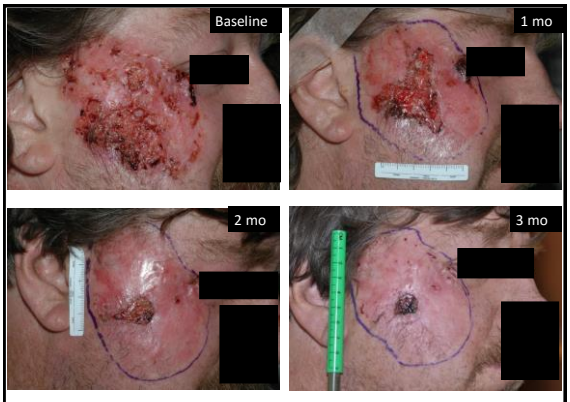
serious adverse events: 25%

N Engl J Med 2012; 366:2171-2179June 7, 2012DOI: 10.1056/NEJMoa1113713

Commonly reported adverse events

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

N Engl J Med 2012; 366:2171-2179June 7, 2012DOI: 10.1056/NEJMoa1113713

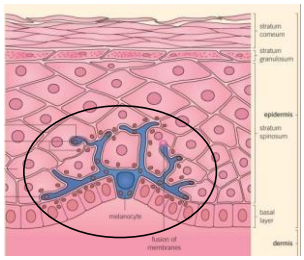


Potential drawbacks

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

Melanocytes

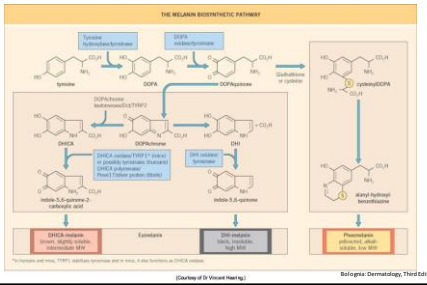
- Melanocyte origin



Bolognia: Dermatology, Third Edition, 2012, Elsevier

Melanin Biosynthesis

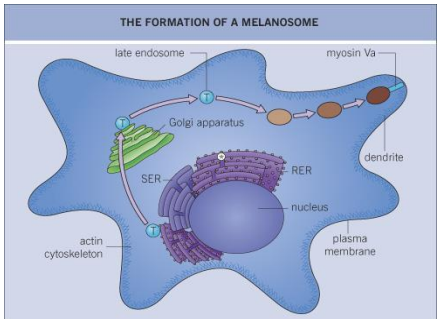
Tyrosine → DOPA →DOPAquinone
Both steps are catalyzed by tyrosinase



(Courtesy of Dr Vincent Hearing.)

Bolognia: Dermatology, Third Edition, 2012, Elsevier

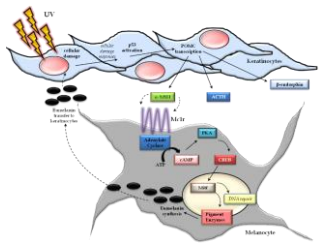
Melanosome Formation



Bolognia: Dermatology, Third Edition, 2012, Elsevier

Melanocortin 1 Receptor

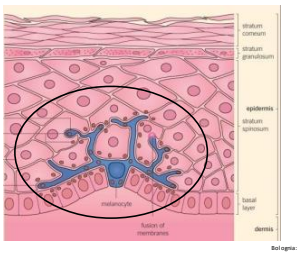
- G-protein-coupled receptor on surface of melanocytes
- Seven transmembrane domain
- αMSH binds MC1R
- Dysfunctional MC1R favors synthesis of pheomelanin



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 agains ultraviolet radiation



Bolognia: Dermatology, Third Edition, 2012, Elsevier

Tanning

Fitzpatrick skin types

Skin type	Typical Features	Tanning ability
I	Pale white skin, blue/hazel eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

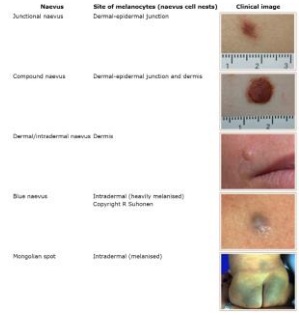
http://www.mirabellabeauty.com/fitzpatrick-landing

Abnormalities of pigmentation

	▪ May fade or disappear in winter and with age	
Lentigo simplex	▪ May be due to sunburn	▪ Pigmented elongated rete ridges ▪ Increased melanocytes along basal layer ▪ Ink-spot variety (deeply pigmented)
Solar lentigo (1)	▪ Scattered small brown lesions on sun-damaged areas	▪ Pigmented elongated & clubb rete ridges ▪ Increased melanocytes along basal layer ▪ Solar elastosis
Solar lentigo (2)	▪ Large well-defined oval patch on face in mature individuals	

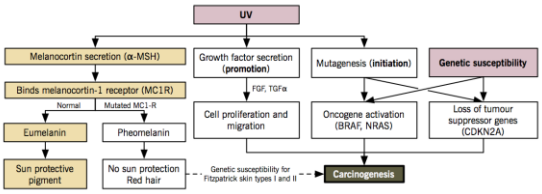
http://www.dermnetnz.org/doctors/lesions/melanocytic.html
DermNet New Zealand Trust

Abnormalities of pigmentation



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

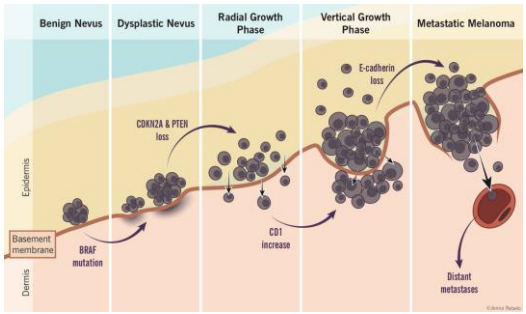
Melanoma pathogenesis



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

Lancet. 2005 Feb 19-25;365(9460):687-701.

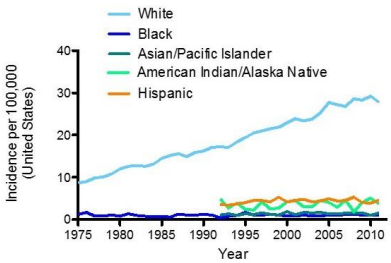
Melanoma pathogenesis



Lancet. 2005 Feb 19-25;365(9460):687-701.

Melanoma incidence

!



Surveillance, Epidemiology, and End Results Program

!

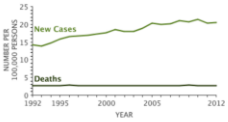
SEER Stat Fact Sheets: Melanoma of the Skin

Expand All | Collapse All

Statistics at a Glance — Show Less

At a Glance

Estimated New Cases in 2015	73,870
% of All New Cancer Cases	4.5%
Estimated Deaths in 2015	9,940
% of All Cancer Deaths	1.7%



Percent Surviving 5 Years
91.5%
2005-2011

Number of New Cases and Deaths per 100,000: The number of new cases of melanoma of the skin was 21.6 per 100,000 men and women per year. The number of deaths was 2.7 per 100,000 men and women per year. These rates are age-adjusted and based on 2008-2012 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 2.1 percent of men and women will be diagnosed with melanoma of the skin at some point during their lifetime, based on 2010-2012 data.

Prevalence of This Cancer: In 2012, there were an estimated 996,587 people living with melanoma of the skin in the United States.

http://seer.cancer.gov/statfacts/html/melan.html

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

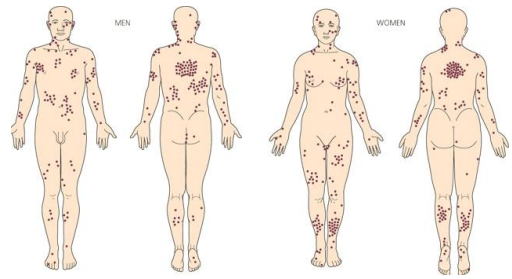
Melanoma Types

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

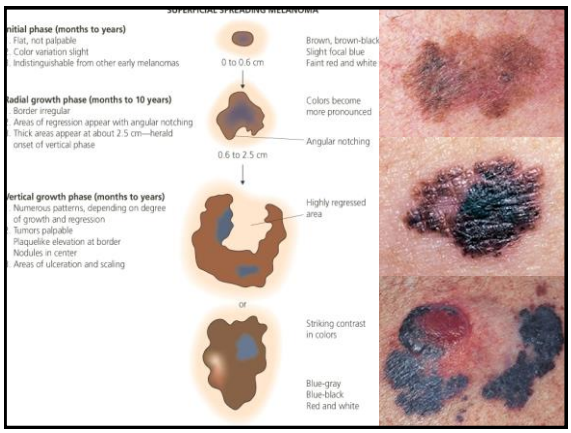
Superficial spreading melanoma

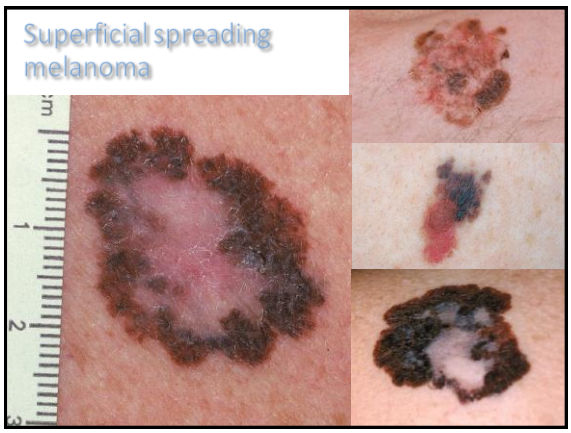
- Most common type of melanoma
  - 70% of all melanomas
- Between ages of 30 and 50 years
- Can arise *de novo* or in a pre-existing nevus

Superficial Spreading Melanoma



Bolognia: Dermatology, Third Edition, 2012, Elsevier





ABCDEs of pigmented lesions

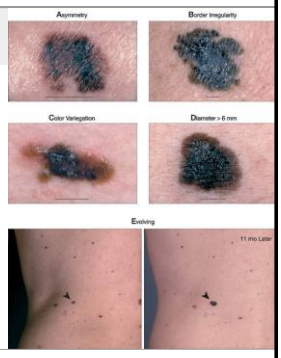
The JAMA Network

From: **Early Diagnosis of Cutaneous Melanoma: Revisiting the ABCD Criteria**

JAMA. 2004;292(22):2771-2776. doi:10.1001/jama.292.22.2771

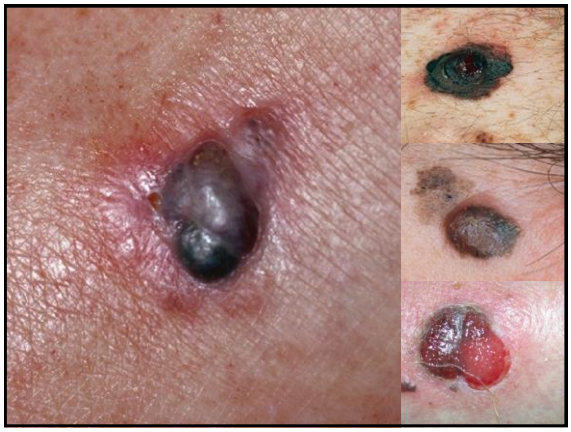
The ABCDEs for melanoma detection are:

- 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.



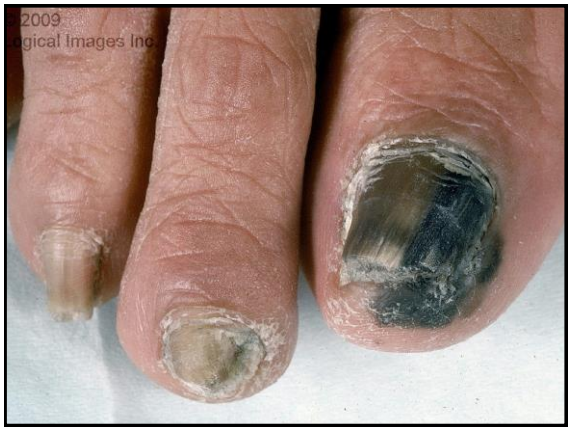
Nodular Melanoma

- 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



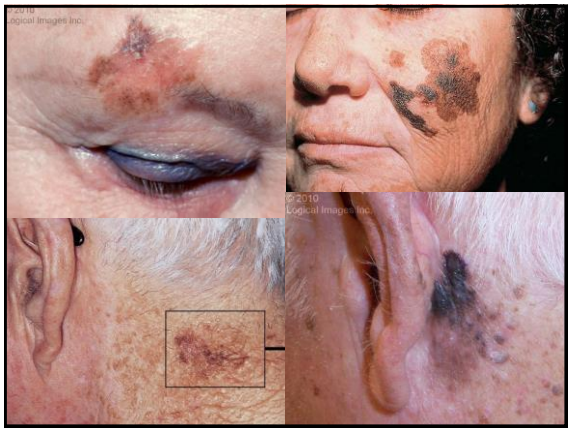
Acral Lentiginous Melanoma

- 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



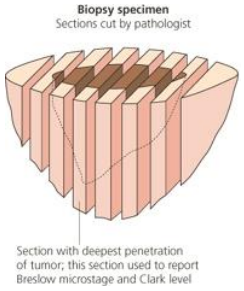
Lentigo Maligna Melanoma

- 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



Bolognia: Dermatology, Third Edition, 2012, Elsevier

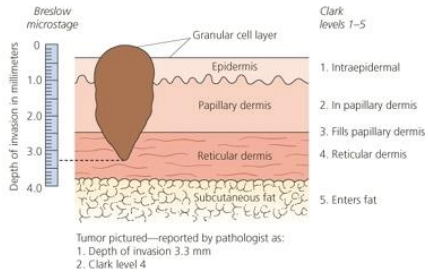
Treatment

!

- **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

Breslow Depth	5-Year Survival
< 1mm	95%
< 2 mm	89% (77% if ulcerated)
> 4 mm	67% (45% if ulcerated)

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

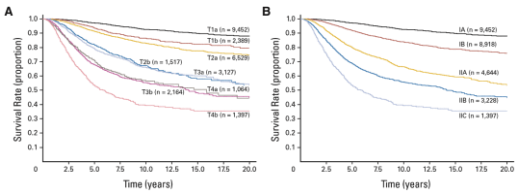
Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

Staging of localized primary melanoma

	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0

Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

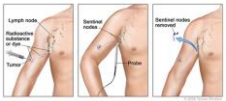
Localized primary melanoma prognosis



Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

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%
    - 0.76-1.0mm with ≥1/mm² mitotic rate: 10%
  - 1.01-2.0 mm: 12%
  - 2.01-4.0 mm: 28%
  - >4 mm: 44%



http://www.cancer.gov/

Roussseau DL Jr et al. Ann Surg Oncol 2003; 10:569.
Han D et al. Sentinel Lymph Node Metastasis in Thin Melanoma. J Clin Oncol 2013.
Andtbacka RH et al. J Natl Compr Canc Netw 2009; 7:308

Node status

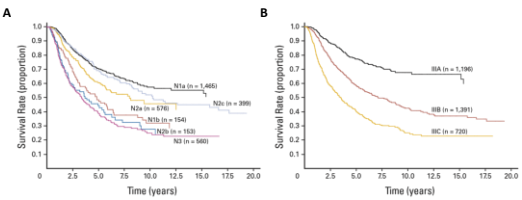
- Nx: Lymph nodes cannot be evaluated
- N0: No evidence of cancer in the lymph nodes
- N1: 1 lymph node
  - N1a: micrometastasis
  - N1b: macrometastasis
- N2: 2 or 3 lymph nodes
  - N2a: micrometastases
  - N2b: macrometastases
  - N2c: in transit or satellite lesions but NO positive lymph nodes
- N3: Any of the following:
  - 4 lymph nodes
  - 2-3 positive lymph nodes that are matted
  - In transit or satellite lesions with any number of positive lymph nodes

Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

Pathologic staging of locally advanced melanoma

Stage IIIA	Tl-4a	N1a	M0
	Tl-4a	N2a	M0
Stage IIIB	Tl-4b	N1a	M0
	Tl-4b	N2a	M0
	Tl-4a	N1b	M0
	Tl-4a	N2b	M0
	Tl-4a	N2c	M0
Stage IIIC	Tl-4b	N1b	M0
	Tl-4b	N2b	M0
	Tl-4b	N2c	M0
	Any T	N3	M0

Melanoma survival based on node status and in stage IIIA - IIIC disease

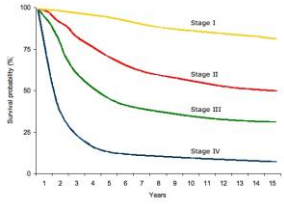


Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

Pathologic staging of metastatic melanoma

Stage IV Any T Any N M1

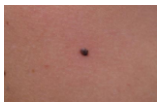
Melanoma survival rates stage I – IV



Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009

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

Weide B et al Br J Cancer 107: 422-428, 2012.
Tarhini AA et al J Clin Oncol 27: 38-44, 2009.

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
  Distant metastases to any site + elevated serum LDH

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

Balch CM, Gershenwald JE, Soong S, et al, J Clin Oncol 27(36): 6199-206, 2009

Prognostic importance of LDH level

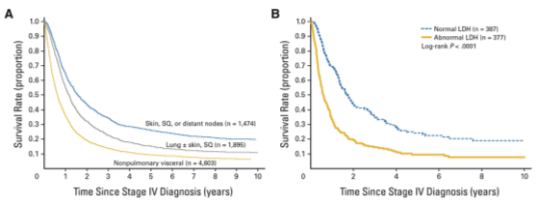
Lactate dehydrogenase (LDH)

- 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

	survival	
	1 year	2 year
normal LDH	65%	40%
elevated LDH	32%	18%

Kluger HM et al. Clin Cancer Res (2011) 17(8):2417–25.
Blach CM et al. J Clin Oncol 27(36): 6199-206, 2009
Solassol J et al. Int J Biol Markers (2011) 26(2):82–7.
Vereecken P et al. Dermatol Res Pract (2012) 2012:260643.
Ho J et al. Mol Cancer (2012) Oct 9, 11:76.

Stage IV melanoma prognosis



Balch CM, Gershenwald JE, Soong S, et al, J Clin Oncol 27(36): 6199-206, 2009

Other prognostic factors

- Anatomic site
- Age
- Gender
- Marrital 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:**
  Winnepenninckx V et al. J Natl Cancer Inst. 2006;98:472-482. 57.
  Brunner G et al. Cancer Biother Radiopharm. 2008;23:451-459.
  Gschaider M et al. PLoS One. 2012;7:e49865.
  Brunner G et al. J Cancer Res. Clin Oncol. 2013;139:249-258.
  Wardwell-Ozgo J et al. Oncogene. 2014;33:1017-1026.
  Sivendran S et al. J Invest Dermatol. 2014;134:2202-2211.
  Gerami P et al. J Am Acad Dermatol. 2015;72:780.e3-785.e3.
  Gerami P et al. Clin Cancer Res. 2015;21:175-183.
  - **Very few overlapping genes were identified by the studies**
  - **Many of even the overlapping signals were likely form not melanocytes**

Weiss SA et al. Cancer. 2015 Dec 1;121(23):4108-23.

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

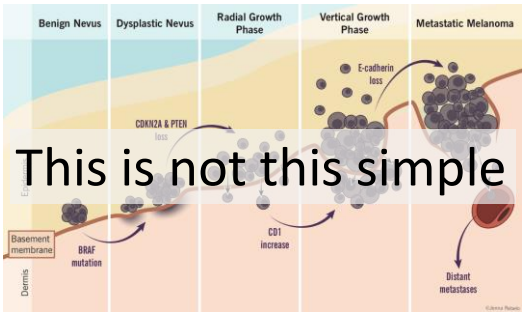
Gerami P et al. Clin Cancer Res. 2015;21:175-183.

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%)

Gerami P et al. J Am Acad Dermatol. 2015;72:780.e3-785.e3.

Melanoma pathogenesis



This is not this simple

Lancet. 2005 Feb 19-25;365(9460):687-701.


ARTICLES

nature genetics

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

Michael Krauthammer[1,2], Yong Kong[3], Antonella Bacchiocchi[4], Perry Evans[1], Natapol Pornputtapong[2], Cen Wu[5], James P McCusker[2], Shuangge Ma[5], Elaine Cheng[4], Robert Straub[4], Merdan Serin[4], Marcus Bosenberg[2,4], Stephan Ariyan[6], Deepak Narayan[6], Mario Sznol[7], Harriet M Kluger[7], Shrikant Mane[8,9], Joseph Schlessinger[10], Richard P Lifton[9,11] & Ruth Halaban[4]

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

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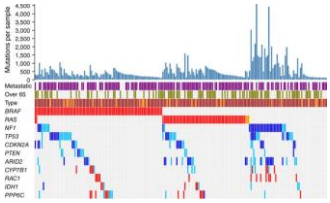
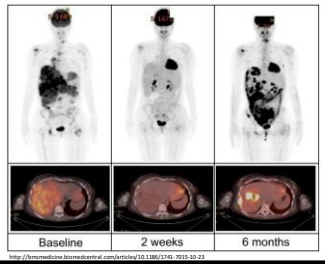


- Very high mutation burden in melanoma
- Mutation profile groups (BRAF, RAS, NF1)

- **Most of the mutations are present also in melanocytic nevi**

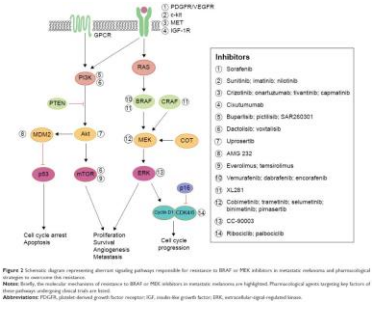
BRAF inhibitor treatment in melanoma

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



http://bmcmedicine.biomedcentral.com/articles/10.1186/1741-7015-10-23

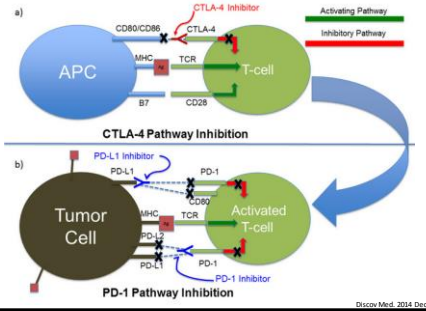
Small molecular inhibitors in melanoma therapy



Drug Des Devel Ther. 2015 Dec 21;10:43-52. doi: 10.2147/DDDT.S93545.

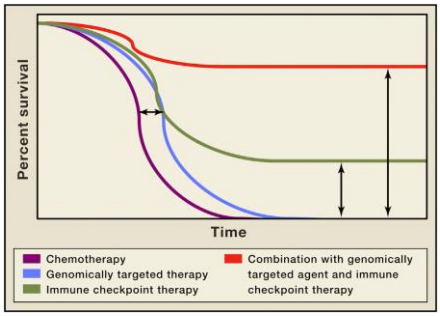
Immune checkpoint blockade for melanoma therapy

!



Discov Med. 2014 Dec;18(101):341-50

Hope for the future in melanoma therapy



http://medicalxpress.com/news/2015-04-highlights-potential-cancer-immunotherapy-therapy.html

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