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內文：

Purpose

To shed some light on the relationship between exposure to UV and cutaneous squamous cell carcinoma, basal cell carcinoma, and melanoma, and to discuss some aspects of the biopathology of these cancers.

Background

1. The skin of the head and face is habitually exposed to sunlight
2. Ultraviolet (UV)-induced chronic damage：solar elastosis, actinic keratosis and lentigo → development of cutaneous squamous cell carcinoma, cutaneous basal cell carcinoma and cutaneous melanoma
3.

	Origin
SCC	Stem/progenitor cells of the basal cell layer of the epidermis
BCC	(1) The bulge region of hair follicle which is rich in keratinocyte stem cells (2) stem/progenitor cells of the basal cell layer of the epidermis
melanoma	Unknown → proposed from (1) dedifferentiated melanocytes or from melanocyte progenitors in the bulge region of hair follicles (2) neural crest-derived Schwann cell precursors

4.

	Association
SCC	(1) frequent moderate chronic UV exposure →preceded by premalignant actinic keratosis or by Bowen disease (2) non-healing wounds or scarring, have been preceded by chronic immuno-inflammatory processes
BCC	intermittent, infrequent, intense UV exposure → *de novo*
melanoma	intermittent, infrequent, intense UV exposure → *de novo* 30 % → from pre-existing sites of melanotic pigmentation

5.

	Metastasis
SCC	Very likely
BCC	Seldom
melanoma	Very likely

6. Variants of the highly polymorphic melanocortin 1 receptor (MC1R) gene are associated with increased risk of these malignancies
7.

	pathogenesis
SCC	dysregulation

	(1) the cell cycle, apoptosis (2) DNA repair, cellular differentiation (3) telomerase activity with evasion of cellular senescence (4) expression of the enzyme cyclo-oxygenase 2 (COX-2)
BCC	(1) genetic mutations causing uncontrolled activation of the hedgehog intracellular pathway → enhanced proliferative capacity of basal cells (2) molecular alterations in the p53 tumour-suppressor gene (3) rare heritable basal cell nevus syndrome in association with germline molecular aberrations of the hedgehog intracellular signalling pathway
melanoma	aetiopathogenesis of melanoma is complex (1) Skin melanoma cells show molecular alterations of the RAS-BRAF-MEK-ERK mitogen activated protein kinase (MAPK) signalling pathway, mediating uncontrolled proliferation of the affected malignant melanocytes; genetic alterations in the CDKN2A gene encoding the p16INK4A tumour suppressor protein; and MC1R genetic polymorphism (2) pre-existing melanotic hyperpigmentations such as lentigo, freckles or pigmented naevi (3) UV by itself does not necessarily cause melanoma

Melanocortin 1 receptor (MC1R)

1. The MC1R gene plays an important role in melanin production and in skin pigmentation.
2. Pro-opiomelanocortin (POMC) and its derivatives, particularly α-melanocyte stimulating hormone (αMSH)
   → agonistic ligands of MC1R on melanocytes
   → mediating the biosynthesis of both red-yellow pheomelanin and brown-black eumelanin
3. Melanins are synthesized in melanosomes which are transported to the extremities of the melanocytic dendrites
   → transferred to neighbouring keratinocytes
   → protect keratinocytes from UV-induced DNA damage
4. The MC1R gene is highly polymorphic among White people
   → mediating the production of more pheomelanin and less eumelanin
   → resulting in the phenotype of red hair, blue eyes and fair skin
   → greater risk of UV-induced skin cancers
   (1) pheomelanin provides less effective protection against UV
   (2) generates more mutagenic free radicals in response to UV
5. Non-pigmentory functions of MC1R mediated via the αMSH /MC1R pathway include regulation of local immuno-inflammatory responses
   (1) modulation of NF-κB which is an important regulator of the production of inflammatory mediators
   (2) mediation of the proliferation and survival of melanocytes
   (3) induction of DNA repair
   (4) diminution of oxidative stress
6. DNA damage caused by UV
   → stimulation of the keratinocytic p53 gene → activation of αMSH
7. In melanocytes, UV induces both the upregulation of expression of MC1R and the

production of αMSH, that via the MC1R/αMSH/cAMP pathway
→ Activates DNA repair mechanisms and diminishes oxidative stresses

8. MC1R variants have a lower DNA repair capacity, more DNA mutagenic photoproducts, increased oxidative DNA damage, and decreased apoptosis

Cutaneous squamous cell carcinoma

1. UV induces two major classes of mutagenic photoproducts
   Cyclobutane-pyrimidine dimers (CPDs), and 6,4 pyrimidine-pyrimidine
   → genetic mutations C→T and/or CC→TT
2. UV generates of highly reactive oxygen species → cause DNA damage
3.

Damage to DNA	Outcomes
oncogenes	uncontrolled cell proliferation
tumour-suppressor genes (anti-oncogenes)	dysregulated oncogenic activity
cell cycle checkpoints	(1) prevent arrest of the cell cycle that is necessary to allow DNA repair (2) prevent apoptosis in response to DNA damage which exceeds the cellular DNA repair capacity → propagation of the altered DNA by cell division of the transformed cells

   Transformed cells have a selective growth advantage → clonal expansion
   → Precancerized epidermis comprising cytogenetically-altered keratinocytes
   → May exhibit actinic keratosis which is a precursor lesion of cutaneous SCC
4. Basement membrane → between epidermis and dermis/stroma
   → Prevents the tumor from invading the underlying connective tissue
5. Degradation of collagen, particularly collagen type IV, in the basement membrane
   → infiltration of the underlying connective tissue by the tumour cells
   → achieved by the matrix metalloproteinases (MMP)-2 and 9
6. Increased expression of MMP-2 in SCC than BCC
7. Collagen IV → fibrils which anchor the basement membrane to the dermis
   If depletion → invasion and epithelial-mesenchymal transition of keratinocytes
8. basement membrane has been breached by the tumour cells → metastasis
   cancer-associated (myo-) fibroblast (CAF) occurs profusely
   → production of chemokine ligand 7
   → restructuring of the extracellular matrix which facilitates invasion
9. In head and neck SCC → connective tissue growth factor (CTGF)
   → Transition and suppresses invasiveness

Cutaneous basal cell carcinoma

1. most common cancer in White people
2. slow-growing cancer, rarely metastasizes
3. increased risk for cutaneous SCC and cutaneous melanoma
4. Cutaneous BCC at sites not exposed to UV is unexplained
5. hedgehog signalling pathway
   → organogenesis
   → regulating proliferation and differentiation of keratinocyte stem cells
   → development of hair follicles and sebaceous glands
   patch 1 (PTCH1) → a tumour suppressor gene
   → inhibiting the activity of the proto-oncogene, smoothened (SMO)
6. Clonal expansion of dysregulated cells within the keratinocytes stem cell niche
   → favoured by loss-of-function mutation in PTCH1

→ gain of function mutations in the SMO gene
→ render SMO protein resistant to inhibition by PTCH1
Escape of cancer precursor cells from the niche to colonize other cellular compartments in the skin → BCC

7. molecular alterations
   (1) germline origin
   (2) subsequent to UV-induced DNA damage
   (3) rarely arise spontaneously
8. dysregulated in hedgehog signalling pathway
   → fail to undergo cell-cycle arrest in response to the p21 cell cycle inhibitor
   → enhanced proliferative capacity
9. Loss of function of PCTH1, enhanced function of SMO
10. 50 % BCC → mutations in the p53 tumour suppressor gene
11. Treatments → vismodegib and other hedgehog pathway antagonists
12. Cutaneous BCC express bone morphogenetic protein (BMP) 2 and 4
    GREMLIN 1 → a BMP antagonist
    → counteracts growth-inhibitory effect of BMPs
    → BCC proliferation & survival
13. Those who do have BCC show reduced clearance of mutagenic photoproducts from UV-induced DNA lesions

Cutaneous melanoma

1. aggressive skin tumour
   (1) superficial spreading
   (2) nodular
   (3) lentigo maligna
   (4) acral melanoma
2. Lentigo maligna
   (1) affects long-term chronically UV-exposed skin of the head and face
      → other subtypes are relatively rare
   (2) increases with age, peaks in 60~70
   (3) atypical melanocytes
      → ill-defined brown macule which slowly expands centrifugally
   (4) breach the basement membrane & invade the connective tissue
      → melanoma
3. factors are implicated in the pathogenesis
   (1) family history
   (2) phenotypic characteristics such as pale skin and red hair
   (3) many episodes of sunburn especially in youth
   (4) the presence of numerous melanotic nevi or freckles
   (5) pre-existing dysplastic nevi
   (6) MC1R genetic polymorphism
4. rare in Black persons
   → affects body sites not habitually exposed to UV
5. tumour-suppressor gene p53
   → not frequent in UV-induced cutaneous melanoma
6. oncogenic mutations in either NRAS or BRAF
   BRAF mutations：early genetic event, up to 60 %
   CDKN2A gene which encodes for p16INK4a tumour suppressor protein
7. BRAF and CDKN2A mutations → indirect UV-induced oxidative damage
8. arising from melanocytes residing in the basal cell layer of the epidermis

→ 2 histopathological patterns

Phase	patterns
radial growth phase	(1) Proliferation of atypical melanocytes within the epidermis (2) Small breaches of the basement membrane
Vertical growth phase	Basement membrane is breached → Invade the dermis in a nodular pattern

9. further third pattern → originates from melanocyte precursors
   → epidermal melanocytes have no contribution
10. loss of integrity of membranes of the melanosomes in melanoma cells
    (1) consequent leakage of reactive oxygen species (ROS)
    (2) metabolic by-products of melanogenesis
    → Cytotoxic

UV-induced immunosuppression

1. T cell-mediated immune responses
   (1) against tumour-specific antigens → lysis of tumour cells
   (2) activated inflammatory cells may non-specifically destroy tumour cells by producing and secreting active biological mediators
2. UV can cause local immune suppression
   → altering antigen presentation by Langerhans cells
   →expression of immunosuppressive neuropeptides, melanocortins, cytokines and inflammatory mediators
3. Diminish the capacity to detect and to eliminate immunogenic initially transformed keratinocytes and melanocytes

Conclusion

1. cutaneous BCC, cutaneous SCC and cutaneous melanoma is associated with UV exposure
2. relationship between the patterns of exposure to UV and the pathogenesis of these skin cancers is yet to be explained.

題號	題目
1	有關 basal cell carcinoma 的敘述下列何者錯誤 (A) 最常見的皮膚癌症 (B) 由 basal cell layer 發展而來，與長期陽光曝曬有關 (C) 好發於 30~40 歲男性 (D) 與染色體 PTCH 異常有關
答案(C)	出處：Oral and Maxillofacial Pathology, 3rd edition
題號	題目
2	有關 melanoma 的敘述下列何者錯誤 (A) 有四種 subtype : superficial spreading、nodular、lentigo maligna、acral melanoma (B) lentigo maligna melanoma 又稱作 Hutchinson's freckle (C) 最常出現在口腔的 subtype 是 nodular melanoma (D) 與急性的紫外線暴露有關
答案(C)	出處：Oral and Maxillofacial Pathology, 3rd edition