**CANCER 13**

Cancer as a disease - Skin Cancer  
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Epidermis provides our first line of defence against harmful solar UV radiation. It is exposed to much higher levels of solar radiation than any other organ. This exposure increases the risk to skin cells of damage by UV and to DNA of UV-mediated mutagenesis and consequently to **UV-induced cancer**.

**Many & varied types**

Epidermis keratinocytes –basal cell carcinomas, squamous cell carcinomas

Melanocytes – malignant melanoma

Blood vessels haemangiomas, Karposi’s sarcoma. Also tumours of adnexae, etc.

# Main Causes

Genetic (rare) – familial melanoma, Gorlin’s syndrome (BCC’s), xeroderma pigmentosa, dysplastic naevus syndrome, epidermodysplasia verruciformis

Viral – Karposi’ sarcoma – human herpes virus 8, Human papilloma virus in squamous cell carcinoma

Ultraviolet Light BCC, SCC, MM,

Cases of all types of UV-induced skin cancer are increasing in the UK.

This lecture: **keratinocytes & melanocytes** – “non-melanoma skin cancer” (SCC’s, BCC’s) & malignant melanoma

# Ultraviolet Light as a Mutagen

Solar UV primarily, but also UV used in phototherapy for some inflammatory dermatoses

## Wavelengths

<280nm UVC – mostly filtered by atmosphere, little reaches earth’s surface

280-320nm UVB

320-400nm UVA

400nm+ visible spectrum

Photon wavelengths 250 to 300nm are absorbed by ring structures and linear repeats found in DNA and other complex macromolecules such as proteins. Energy absorbed by bonds in these structures makes them highly reactive and easily modified or broken.

As UVC mostly filtered out by the atmosphere, primarily UVB is responsible for this kind of DNA damage.

## Changes in DNA molecules caused by UVB

These affect pyrimidines Cytosine (C) & Thymine (T) bases

Most commonly 6-4 pyrimidones from pyrimidines, also formation of cyclobutane pyrimidine dimers from two adjacent pyrimidines *e.g.* -T-T-, -C-T-

## Other structural effects of UV (A and or B) on cells

Photon energy can cause many molecules in the cell to become reactive. Releasing, for example, highly reactive free radicals that cause oxidative damage to DNA, proteins, etc. (contribute to photoageing of skin).

## Consequences of these chemical changes - Damaged DNA!

Where one of the two strands of is damaged DNA can be removed and replaced by the cell’s normal nucleotide excision repair system. In Xeroderma pigmentosum thispathway is inactive because of mutations in genes encoding repair enzymes – DNA damage is unrepaired 🡪 skin cancer can result if mutated cells persist.

**“UV signature mutations”** Structurally-altered C and T bases are “mis-read” by DNA repair and replication enzymes and replaced with different bases. e.g. damaged CC in DNA replaced by TT, or damaged CT replaced by TT. Thus, the coding sequence of a gene is altered, the mRNA is changed and this is translated into a protein with an altered function or which does not function at all or the mRNA may not even be transcribed fully so no protein is made.

**What kinds of mutations can start a cell down the route to becoming a cancer?**

1. Mutations that stimulate uncontrolled cell proliferation e.g. by abolishing control of the normal “cell cycle” – p53
2. Mutations which alter responses to growth stimulating/repressing factors by altering structures of signalling pathway proteins e.g. pathways permanently signalling “proliferate” or rendering cells “blind” to inhibitory signals.
3. Mutations that inhibit programmed cell death (apoptosis)

Mutations in genes involved in these types of pathways may initiate or continue the pathway towards a keratinocytes or melanocytes becoming malignantly transformed.

# Melanin & Protection from UV

**Melanocytes** – neural crest origin, resident in basal layer of the epidermis

**Eumelanin** - (the dark brown/black pigment) granules shield the nuclei of keratinocytes in the basal and germinative layers from UV. Eumelanin absorbs UV.

## Tanning Mechanism: Solar UV stimulates melanin production by melanocytes.

Usually UV stimulates keratinocytes to release a number of growth factors & hormones such as αMSH which stimulate melanocytes to make more melanin.

Also, Damaged DNA/RNA can stimulate melanogenesis. Evidence from *in vitro* experiments indicates that fragments removed by DNA during excision repair, etc. in melanocytes (or released from UV damaged keratinocytes) also stimulate melanogenesis.

## Variation in Rates, Amounts and Types of Melanin Produced in response to UV

Epidemiology: fairer skin types more prone to UV induced skin cancers.

Fairer skin type skin contains less eumelanin - needed for photoprotection. Less is produced in response to UV.

One reason is genetic variation in the receptor for MSH – the melanocortin 1 receptor (MC1R). There are more than 20 known MC1R gene polymorphisms. These can affect:

Efficiency of response to αMSH (melanosome activity). Type of melanin produced in response to UV. Result is variation photoprotection.

# Efficient Immunosurveillance is Essential for Defence Against Skin Cancer

An efficient immune system is important for defeating skin and other tumours early in their development*.* Inindividuals who are immunocompetent many very early cancers are probably resolved (unknown to and undetected by us) very early by our own immune systems.

In patients who are immunosuppressed - either through long term immunosuppressive therapy (e.g. transplant patients or patients with severe psoriasis) or through disease (e.g. HIV infection); there is an increased occurrence of keratinocyte-derived skin tumours on sun-exposed sites.

# Immunomodulatory Effects of UV Light

UVA and UVB light can affect the expression of genes that are involved in various aspects of normal skin immunity – resulting in reduced skin immunocompetence.

This is the basis of some forms of UV phototherapy for treatment of some inflammatory skin diseases (e.g. psoriasis).

UV exposure: Increases expression of some down-regulatory cytokines such as interleukin 1Ra - suppresses Langerhans cell activity. Inhibits expression of adhesion molecules such as ICAM-1 (inflammatory cell adhesion molecule 1) decrease the migration of T cells, etc. into the skin. Depletes the number of Langerhans cells in the epidermis, decreasing epidermal immunosurveillance.

UV-induced immunosuppression combined with the ability of UVB to cause cancer-generating mutations further increases the cancer-causing potential of sun exposure.

# Programmed Cell Death – APOPTOSIS

Mutations leading to failure of normal PCD are generally considered to be one of the most important events in triggering transformation of a healthy cell into a cancer cell. Cells that are damaged beyond repair by normal mechanisms (e.g. by UVB) usually undergo PCD. It is an important pathway by which the immune system kills “unusual” (e.g. cancer) cells.

PCD is a normal part of our biology. It is a process by which cells are renewed or replaced and by which organs are shaped during development.

In the normal epidermis, the end stage of keratinocyte differentiation is programmed cell death.

## What is Programmed Cell Death?

This is not the same as necrosis! The apoptotic cell undergoes a series of defined steps – a specific biochemical programme is activated.

## Trigger Types

1. Severe DNA or protein damage
2. Withdrawal of survival/factors
3. Binding of specific ligands to specific cell surface receptors (e.g. Fas/Fas ligand) also known as CD95/CD95 ligand)

These events can all trigger a cascade of intracellular signals that initiate the programme.

Mutations which affect genes involved in or in responding to any of these trigger types can result in failure of a cell to follow the apoptosis programme.

**The Programme**

***Apoptosis*** is characterised by cytoskeletal disruption, cell shrinkage & formation of apoptotic cell envelope, cell membrane blebbing, nuclear fragmentation – DNA broken down into oligonucleosome fragments. Apoptosed cell phagocytosed by surrounding cells or breaks up into apoptotic cell bodies. There is no inflammatory response.

***Necrosis*** is characterised by changes that include membrane damage, cell swelling, release of cell contents; all of which are combined with an inflammatory response.

***SUNBURN – UV leads to keratinocyte cell apoptosis*** “Sunburn Cells” are apoptotic cells in UV overexposed skin. Apoptosis removes UV damaged cells in the skin which otherwise might become cancer cells. How?

**UVA** causes formation of free radicals: oxygen or superoxide anions these can damage mitochondrial membranes. This damage triggers PCD.

**UVB** induced DNA damage stimulates apoptosis: e.g. DNA damage activates transcription factor p53 and AP1. p53 stimulates expression of the Bax gene which initiates the PCD pathway. AP1 stimulates expression of Fas ligand. FasL binds to Fas which initiates PCD.

***Mutations in p53*** have been associated with keratinocyte cancers – failure of p53 expression results in loss of one DNA damage-activated pathway, damaged/mutated & potentially cancerous cells may survive!

***Mutations which lead to Fas L overexpression*** has been found in malignant melanoma and other cancers. Expression of FasL enables the malignant cells to avoid immune attack: The FasL binds to Fas-bearing lymphocytes triggering lymphocyte PCD.