Introduction to the Skin

The Skin – Prof Tony Chu (t.chu@imperial.ac.uk)

- The skin is the largest organ of the body, forming the outermost surrounding layer; separates the body from the surrounding environment
- It is a complex organ which interacts with most other organs in both physiological + pathological ways, therefore its function is essential for survival
  - Failure of the skin is incompatible with life, e.g. can be seen in burn victims

Basic structure
- There are 3 components to the skin:
  - **Epidermis** – stratified squamous epithelium, consists of mainly keratinocytes
  - **Dermis** – forms the structural foundation of the skin, supporting its superficial + deep layers
  - **Subdermis** – deep subcutaneous adipose layer; acts as a fat + heat store
- As well as the true resident skin cells, a large variety of different cell types migrate through the different layers of the skin. The components of the skin are intimately linked with this migration, and the “cross-talk” between the layers
- This shows that the skin is a dynamic organ

Basic function
- Barrier – prevents fluid loss, protects against toxic + infections agents, radiation etc
- Temperature control
- Acts as the peripheral outpost of the immune system
- Also involved in an organ of sexual attraction

Skin disease
- The skin is intimately linked to other organ systems of the body, therefore systemic disease may also affect the skin (e.g. jaundice). Skin disease can also be local.
- There are >2000 recognised skin diseases; everyone will develop at least 1 at some point in their life (can affect neonate → elderly). These range from trivial cosmetic problems to acute + chronic diseases which may be disfiguring, itchy, painful and may even rapidly fatal

Examples
Necrolytic migratory erythema – often occurs in groin area. It is a red, blistering rash that spreads across the skin. It is strongly associated with glucagonoma, but also liver disease + intestinal malabsorption.

Common warts – common skin disease caused by HPV which causes rapid growth of cells on the outer layer of your skin.

Contact dermatitis – direct inflammation of the skin in contact with a particular irritant, causing swelling, itching + redness, e.g. latex causing contact dermatitis on breast

Psoriasis – chronic non-contagious disease characterized by inflamed lesions covered with silvery-white scabs of dead skin. Can be associated with a lot of stigma

Pyoderma gangrenosum – rare + serious skin disease in which a painful nodule or pustule (caused by primary bacterial invasion) breaks down to form a progressively enlarging ulcer which has a purulent surface and a blue-black edge. This is easily treatable, but patients often do not go and see a doctor straight away because of stigma.

Skin cancer – e.g. basal cell carcinoma, angiocarcinoma + melanoma – all common
**Dermatology**

- The study of skin disease
- 20% of a GP workload with be dermatological. However in the UK there are only about 500 dermatologists to serve 60 million
- The incidence of skin diseases varies from country to country:
  - Infections are most common in developing countries
  - Inflammatory dermatoses + skin cancers are more common in western countries
- Dermatology is a visual specialty which relies highly on pattern recognition + diagnosis based on clinical features
- Additional tests are also used to confirm the diagnosis:
  - Biopsy + histology/immunohistochemistry
  - Skin scrapings for fungus
  - Swabs for infection
  - Gene arrangement studies for malignancies
  - Patch testing for allergy
- Subspecialties of dermatology:
  - Dermatological surgery or lasers
  - Contact + industrial dermatology
  - Photodermatology
  - Region specific e.g. the vulva + pelvis
  - Skin tumours

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Structure of the epidermis + adnexal structures

The Skin – Fernanda Teixeira (f.teixeira@imperial.ac.uk)

**Development of the Skin**

- Arises by juxtaposition of the ectoderm, that will give origin to the epidermis + adnexae, as well as the mesoderm which will form the dermis
- The mesoderm is also essential for inducing the differentiation of some epidermal structures, such as the hair follicles
- Melanocytes of the epidermis originate from the neural crest (which is derived from the ectoderm) and migrate to the epidermis by the 10th/11th week of embryonic life
- By week 3 of gestation, the epidermis consists of a single layer of glycogen-filled cells
- By week 6, two layers can be distinguished:
  - The outer layer or periderm
  - The inner layer of basal layer
- By week 21, the periderm disappears whereas the basal layer will form the epidermal cells throughout life
- The hair follicles are first distinguished by week 9 in the following regions: Eyebrows, Upper lip + chin
- The primordial of hairs appear as a cluster of cells in the basal layer of the epidermis, which begin to grow downwards into the dermis as “hair pegs”
  - At the same time, they are associated with fibroblasts + other mesenchymal cells, which are going to form the hair papilla
- The tip of the hair peg becomes progressively bulbous and surrounds the dermal papilla.
  - At this point, 3 bulges appear on the posterior wall of the follicle:
    - The lower one – which will be attached to the arrector pili muscle
    - The middle one – which will soon lose glycogen + accumulate intra-cytoplasmic fat and become large and functional sebaceous glands by week 16
    - The upper one – which gives rise to the apocrine glands and ducts
Apocrine glands + ducts will be numerous in the whole body surface of the foetus, but most will disappear during the 3rd trimester; persisting only in some areas e.g. the axillae, perineum + genitalia

- The dermis is then formed by the proliferation of mesodermal cells that will give rise to a whole range of vessel + connective elements, including several types of collagen + elastic fibres
- Before the end of month 3, all the elements of the mature dermo-epidermal junction will be recognizable

The Epidermis

- Constituted by keratinizing, stratified squamous epithelium
- Keratinocytes form 95% of the epidermal cells; the other 5% form the melanocytes, Langerhans cells + Merkel cells
- Keratinocytes
  - Cells that act as skin stem cells; they are located on the basal lamina
  - Here they divide, migrate upwards acquiring a large amount of cytoplasm and many desmosomes
- Functions of the epidermis:
  - Serve as a barrier to harmful exogenous substances, chemicals + pathogens
  - Fundamental as a retainer of tissue proteins + fluids
- Diseases of the epidermis:
  - Toxic epidermal necrolysis occurs when the epidermis is detached in large sheets from the body as a result of a cell-mediated response
    - This could be due to the administration of drugs
  - Some patients with TEN have to be treated in a burn unit to decrease the risk of sepsis, to correct the fluid loss + avoid the loss of body heat
- The epidermis can be subdivided into 4 layers of keratinocytes:
  - Stratum basale
  - Stratum spinosum
  - Stratum granulosum
  - Stratum corneum

The layers of the epidermis

- **Stratum basale** – continuous layer which is 1-3 layers of cuboidal cells (~12µm in diameter) which have large nuclei ad dense cytoplasm
- **Stratum spinosum** – in this layer, the cells enlarge + acquire numerous desmosomal connection plaques that will stabilize the network of cells.
  - Prickle cells are rich in tonofilaments, that are constituted by intermediate filaments of keratin that attach themselves to the desmosomes
  - Diseases that affect the desmosomes can lead to breaks in the fabric of the keratinocytes with formation of vesicles
    - In pemphigus, auto-antibodies are directed against desmosomal proteins, leading to their destruction + lack of cellular adhesion
- **Stratum granulosum** – here, the cells become flat and accumulate dense, basophilic granules in the cytoplasm = keratohyalin granules
  - These granules contain precursor of filaggrin, a protein which when activated is so called because it promotes the aggregation of filaments of keratin
    - By the influence of filaggrin, the keratin filaments align into the disulphide cross-linked macrofibres
  - At the same time, the nucleus + cytoplasmic organelles disappear, and the keratinocyte is reduced to a flat squame of keratin = the corneocyte; will be shed on the surface
- **Stratum corneum** – the outermost layer is the major layer responsible for the barrier function of skin; epidermis is actually devoted to its production.
  - It is composed of 15-20 layers of flattened, non-nucleated keratinized cells; filled with filaments of keratin
  - The surface cells of the stratum corneum are continuously desquamated (i.e. shed = skin flaking)
  - The cornified envelope surrounds each corenocyte (includes involucrin, loricrin, keratolinin, pancornulins + cornifin)

**Clinical correlation:**
- **Pemphigus vulgaris**
  - Autoimmune blistering disease affecting the stratified epithelium particularly in the upper trunk, head, neck + intertriginous areas
  - Begins with mouth lesions, which are covered by fibrino-purulent pseudomembrane. Development + spread then occurs over weeks or months.
- **Pemphigus foliaceus**
  - Idiopathic or rifampicin induced blistering disease

**Keratinocytes**
- Are labile cells, where the basal cells are continuously dividing to replace the corneocytes that are continuously shed to maintain the thickness of the epidermis
- The mechanisms that control the cell division in the basal layer are the result of the balance between stimulatory (growth) factors and inhibitory factors:
  - Stimulatory signals:
    - Epidermal growth factor
    - Transforming growth factor alpha (TGF-α)
    - IL-1, IL-6
    - Granulocyte-Macrophage Colony-stimulating factor (GM-CSF)
  - Inhibitory factors:
    - Transforming growth factor beta (TGF-β) – this inhibits the division of basal cells, but stimulates the fibroblasts’ growth + collagen production
    - Interferons (IFN) alpha + gamma
    - Tumour necrosis factor (TNF) alpha
  - Cytokines + growth factors are produced by keratinocytes, Langerhans cells + lymphocytes within the dermis and epidermis
- As keratinocytes move upwards in the epidermis, they undergo a complex process of differentiation to produce the stratum corneum. They first lose their ability to divide, then the types of keratin changes as the cells evolve into keratinocytes

**Cytoskeleton**
- The cytoskeletons of all mammalian cells comprise:
- **Microfilaments** – approx. 7nm in diameter + composed of actin
- **Microtubules** – approx. 20-25nm in diameter + composed of tubulin
- **Intermediate filaments** – between 7-10nm in diameter; 6 types as follows:
  - Vimentin (mesenchymal cells)
  - Glial fibrillary acidic protein (in astrocytes)
  - Neurofilaments (in nerve cells)
  - Desmin (in muscle)
  - Laminins A, B, C (in the nuclear matrix)
  - Keratins
- **Keratins** – present in all epithelial cells from many different organs including the epidermis, pancreatic ducts, the cells the line the interstitial lumen, the hepatocytes + so on
- They are a family of approx. 20 members, each a product of a different gene.
- Weight between 40-70kD
- Divided into 2 groups:
  - Basic keratins (numbered 1 to 8) – gene = 12q11-q13
  - Acidic keratins (numbered 9 to 19) – gene = 17q12-q21
- Filaments are formed by the assembly of one acidic + one basic keratin type into pairs, which stabilise each other. At each layer of the skin, keratinocytes express one pair of keratins in equimolar amounts.
- Specific keratin pairs are synthesised in microscopically distinct epidermal cell layers:
  - Keratins 4 + 15 are synthesised in the basal layer
  - Keratins 1 + 10 are synthesised in the more differentiated spinous and granular layers
- The function of the keratin seems to be to maintain the 3D architecture of the epidermis

Other epidermal cells

**Langerhans cell**
- Highly specialised macrophage originating from the bone marrow
- It settles in the epidermis, working as an antigen-presenting cell with a branched or dendritic morphology that forms a horizontal network of approximately 300-800 cells per square millimetre in the middle layers of the epidermis
- They are mobile cells, and therefore lack desmosomes + tonofibrils

**Melanocytes**
- Originate from the neural crest + migrate into the lower epidermis
- Role is melanin synthesis

**Merkel cell**
- Located in the basal layer of the epidermis
- They are in close proximity to the axonal processes and are believed to be involved in sensory perception
- They can be found on the whole surface of the skin, but they are more numerous on more sensitive areas e.g. tip of nose, fingertips, lips
- Merkel cells are not seen in routine histologic preparations – their identification requires electron microscopy and immunostaining
- Under transmission electron microscopy, Merkel cells are seen to contain dense granules that are morphologically identical to the chromaffin granules in the adrenal medulla
  - These granules contain substances including metencephalin, ACTH, substance P, bombesin + vasoactive intestinal polypeptide
- Neurofilaments can also be found in perinuclear balls
- There is controversy regarding the origin of Merkel cells, i.e. whether they are ectodermal or neuroectodermal
  - They seem to contain keratin filaments + desmosomes; therefore are likely to be epithelial derivations. It is believed that traction of the epidermis is transmitted to Merkel cells which stimulate the nearby axons, so contributing to local sensation

**Adnexal structures**
- The dermis contains mostly extracellular matrix, providing support for nerves, vasculature + adnexal structures e.g. the hair follicles, the sebaceous glands, and sweat gland
- These adnexal structures are in continuity with the epidermis + develop during embryonic life through complex epithelia-mesenchymal interactions
Different areas of the body have different proportions of adnexal + hair follicle structures
- Dense hair on the scalp vs none on the palms
- Intense sweating from the armpits, palms + soles vs everywhere else

Hair + nails are “epidermal appendages” – specialised structures formed by the direct extension of the epidermis

Hair follicles are associated with sebaceous glands + arrector pili smooth muscle (responsible for goose bumps)

**Glands**

**Sweat glands**
- There are 3 types of sweat glands:
  - Eccrine
  - Apocrine
  - Apoeccrine

**Eccrine glands**
- These are found over the whole skin, but are more numerous on the soles, forehead + axillae
- Their secretory portion is a convoluted tubule located at the junction between the dermis and the subcutaneous fat
- There are 3 types of cells in this tube: dark cells, clear cells + myoepithelial cells
- The excretion of sweat is accomplished through straight duct that crosses the dermis, and is continued by an intraepidermal portion called the acrosyringium which opens onto the surface of the skin
  - Functions:
    - Thermoregulation – through evaporation of superficial moisture; eccrine sweat is colourless + odourless (composed of water + electrolytes)
    - The precursor of sweat is produced in the coil as an isotonic solution but undergoes reabsorption of sodium chloride in the duct, producing a hypotonic sweat
    - Cholinergic nerves of SNS discharge acetylcholine, which controls sweat production. Thermal + emotional factors also involved.
  - Ingested drugs can also be delivered to the skin
  - The ductal epithelium also contributes to wound healing

**Apocrine glands**
- These are more numerous in some locations, such as the anogenital skin, axillae + around the umbilicus
- Their secretory coil is up to 10x larger than the eccrine gland (up to 5mm diameter)
- The secretory glands are located in the deep dermis or subcutaneous fat and are lined by large cells
  - They shed part of their apical cytoplasm into the lumen
- They are also surrounded by myoepithelial cells
- The apocrine duct does not open onto the surface of the skin; instead it ends in the hair follicle above the sebaceous duct
The apocrine secretion is milky-white and sterile; its distinctive smell is due to the action of bacteria present on the surface of the skin.

Its function is believed to be a leftover from other mammals, where it has identifying or sexual roles.

Axillary apocrine glands regress with age and produce less odour.

**Apoeccrine glands**

- These are present in the human axillae.
- They have a secretory portion indistinguishable from that of apocrine glands, but their duct opens on the surface of the skin.
- They develop from eccrine glands during puberty, and account for approx. ½ of all axillary sweat glands.

**Sebaceous glands**

- These are holocrine glands where the secretions are produced by the disintegration of cells.
- They are found on the whole body surface except the palms + soles.
- Sebaceous glands are lobulated + contain small, germinative basophilic cells at the periphery.
  - The daughter cells migrate into the centre of the gland, and accumulate lipid droplets in the cytoplasm until they disintegrate.
  - They then discharge cellular debris into the sebaceous duct at the lower part of the infundibulum.
- Sebum production is at its greatest in early adulthood and decreases with age.

**Structure of the dermis + dermo-epidermal junction**

The dermis is the structural “foundation” to the epidermis, bound externally by the junction with the epidermis and internally by subcutaneous fat.

It contributes 15-20% of total human body weight.

It varies in thickness, thick in the back + thighs to thin on the eyelids.

Consists of cellular elements (fibroblasts, mast cells, histiocytes, Langerhans cells, lymphocytes, eosinophils) with a supporting matrix/ground substance embedded with protein fibres (collagen, elastic fibres + microfibrillar components). There are also embedded nerves, blood vessels, lymph vessel, muscles, apocrine units + eccrine units.

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**Acne Vulgaris**

**Cause:** Androgens (principally testosterone) induce increased sebum production and follicular retention hyperkeratosis. P. acnes subsist in the sebum, produce chemotactic factors, and PMNs help induce wall rupture. Women have 1/10 the testosterone level of men and hence less acne.

**Clinical:**

- Closed comedo: “Whitehead”
- Inflammatory (red) papules and pustules: “Zits”

**Relative Efficacy of Acne Treatments on Pathogenic Factors**

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<th>Therapy</th>
<th>Decreases Abnormal Follicular Keratinization</th>
<th>Reduces Sebum Production</th>
<th>Decreases P. Acnes</th>
<th>Reduces Inflammation</th>
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P. Pochi M.D. Management of Acne
Development of the dermis

- The dermis arises from the mesoderm, which is brought into contact with the inner surface if the epidermis during gastrulation
  - The mesoderm not only provides a dermis, but is also essential for inducing differentiation of epidermal structures e.g. the hair follicle
- The embryonic dermis is at first very cellular, and the interface with the epidermis is very flat.
  - By 12 weeks, the interface is undulated (known as the rete-ridge pattern) + fibrillar components are evident.
  - By 24 weeks, dermal papillae develop

Structure

- The dermis is divided into:
  - The superficial thin papillary dermis = ADVENTITIAL DERMIS— this interdigitates with the ridged underside of the epidermis
    - Histologically appear pale; consists of abundant ground substance with a highly developed microcirculation but thin irregular collagen fibres, delicate elastic fibres + numerous fibroblasts
  - The larger underlying reticular dermis = RETICULAR DERMIS – this blends with the subcutaneous fat
    - Makes up the bulk of the dermis – consists of irregular course elastic fibres, thick regular collagen bundles, fewer fibroblasts, microcirculation + ground sustance
  - In specialised regions, e.g. the nipples, penis, scrotum + perineum – there are also smooth muscle fibres within the reticular dermis

The supporting matrix

Made up of ground substance with protein fibres including collagen, elastic fibres + microfibrillar components.

- **Collagen**
  - Most abundant protein of the body, accounts for 70% dry weight of the dermis
  - High tensile strength protein
  - There are >20 different collagens identified. Skin collagens can be subdivided into:
    - Fibrillar collagens – type I + II
      - Type I forms the course fibres found in reticular dermis
      - Type III forms the fine loosely arranged fibres of the adventitial dermis
    - Basement membrane collagens – type IV, VII +XVII
    - Non-fibrillar, non-basement membrane collagens – type XVI
  - Fibrillar collagen formation
    - Produced by fibroblasts – initially as procollagen chains which form triple alpha helices intracellularly. In the extracellular space, the triple helices self-assemble into irregular overlapping staggered fibres.
      - Prior to helix formation, prolines within procollagen → hydroxyproline occurs. This is the rate-limiting step in collagen synthesis and stabilises the conformation of the triple helix.

- **Elastic fibres**
  - Produced by fibroblasts; highly branches structures consisting of elastin core and peripheral microfibrils making up <1% dry weight of dermis
  - Confer elastic properties to the dermis, important in deformation
  - Elastic fibres are absent in scars + stretch marks (striae)

- **Ground substance**
  - Amorphous extracellular material produced by fibroblasts – consists of water, electrolytes, plasma proteins + mucopolysaccharides
  - Surrounded both fibrillar + cellular components of dermis
- **Function:**
  - Sodium + water balance
  - Support for other components of dermis
  - Regulation of connective tissue metabolism by promoting cell growth, migration + differentiation

- **Mucopolyssacharides – in the dermis:**
  - Hyaluronic acid
  - Dermatan sulphate
  - Chondroitin 6 sulphate
  - Heparin sulfate

### Cellular components

#### Fibroblasts
- These are the most numerous cell of the dermis – arise from mesenchymal cells.
- Highly metabolically active cell involved in the production of ground substance, collagen + elastin
- Most numerous in the papillary dermis
- Are able to differentiate to myofibroblasts, smooth muscle cells, chondrocytes + osteoclasts
- As an early response to skin injury, dermal fibroblasts synthesise + secrete prostaglandins, leukotrienes and a number of cytokines and pro-inflammatory mediators
  - They also synthesise growth factors to promote subsequent healing
- Fibroblast proliferation is stimulated by platelet derived growth factor, TGF-beta + fibroblast growth factor
- Synthesis of collagen is induced by platelet derived growth factor + TGF-beta
- After skin damage, fibroblasts are activated + migrate onto fibronectin + fibrin, synthesise new colla and induce healing tissue formation. As collagen matures the wound then contracts.

#### Most cells
- These are of bone marrow origin – contain multiple granules containing a large number of preformed inflammatory mediators e.g. histamine, leukotriene C4, prostaglandin D2, 5-HETE, thromboxane A2, platelet activating factor + interleukin 4 5 6 + 8, TNF, tryptase, carboxypeptidase, heparin
  - Also synthesise new mediators on activation
- Ovoid or spindle shaped
  - Most numerous in subpapillary dermis, close to blood vessels + nerves

### Ageing of the Skin

- Senescent in the skin is a gradual process, which has input from intrinsic ageing as well as the effects of environmental insults, including ultraviolet radiation
  - In women, the hormonal changes at menopause also have effects
- **Environmental factors** are of obvious importance in certain communities living in particular parts of the world
  - 90% of age associated cosmetic problems on exposed skin are caused by ultraviolet radiation rather than intrinsic ageing of the skin
  - Cumulative damage of the DNA caused by UV radiation = photoageing
    - Dermis principally affected by UVA, Epidermis by UVB
- **Intrinsic ageing falls into two categories**
  - Those engendered within the skin itself
  - Those that result as alterations by senile changes in other organs
- **Dermis**
  - Wrinkling of the senescent skin is mostly the result of changes in the dermis
  - Collagen decreases with age; there is also a steady decrease in the number and size of fibroblasts
  - Elastic fibres gradually disintegrate with age
    - After the age of 70, most fibres appear abnormal
Collagen bundles become fragmented and disorientated, leading to progressive loss of tensile strength and elasticity in the skin, sagging of the dermis and wrinkle formation.

**Epidermis**
- With age, the rete ridge pattern of the derma-epidermal junction becomes flattened and in general, the epidermis becomes thinner with age.
- Permeability of the skin changes with age.
- This does not seem to affect the capacity of isolated horny layer to a straight water loss but does alter percutaneous absorption through the skin.
- With age, the skin progressively gets drier and flakier and this is partly due to a reduced water-binding capacity of the corneum but also a reduction of the sebaceous glands.

**Pigmentation**
- Irregular pigmentation occurs in old skin.
- Melanoctyes undergo localised proliferations at the derma-epidermal junction, giving rise to yellow or brown spots, known as liver spots or senile lentigines.

**Greying of Hair**
- Greying of hair becomes evident at about the age of 50.
- The bulbs of grey hair lack tyrosinase activity, which is the enzyme necessary for melanin synthesis.
- Fully white hairs completely lack melanocytes.

**Hair Follicles**
- With age, the density of hair follicles steadily reduces in the scalp.
  - Most marked on the vertex.
  - Least marked on the occiput.
- Scalp hair also becomes visibly finer with age.

**Sebaceous and Apocrine Glands**
- Sebum production is at its greatest in early adulthood and decreases with old age.
- Sebum excretion declines steadily faster in women than in men.
- Axillary apocrine glands also regress with age and produce less odour.

**Eccrine Glands**
- Spontaneous sweating on the fingertips declines in old age due to a combination of a reduction in the number of glands and reduction in output per gland.

**Nail Growth**
- The rate of linear nail growth increases progressively until about the age of twenty five after which, it progressively decreases.
- Before the age of seventy, nail growth in men is greater. After the age of seventy, nail growth in women is greater.

The Dermo-epidermal junction
- This is the transition between the stratified squamous cells of the epidermis and the dermis, between which lies the basement membrane with associated structural proteins.
- The main adhesion unit between the basal layer of the epidermis and the dermis is called a hemidesmosome.
  - Key role in epidermal cell anchorage, adhesion, migration + differentiation.
  - They have an important role in the control of permeability across the dermis.

Structure
- Just underneath the plasma membrane of the basal keratinocytes is the first layer of the basement membrane called the lamina lucida.
  - This is composed of laminins, glycosaminoglycans + proteoglycans.
- The lamina densa lies under this and mainly consists of type IV collagens and heparin sulphate proteoglycan.
- Underneath the lamina densa, there are anchoring fibrils, which are composed of collagen type VII, and are attached to structures called anchoring plaques located in the superficial dermis.

**Hemidesmosomes**
- Specialised complexes that contribute to the attachment of epithelial cells to the underlying basement membrane in stratified + other complex epithelia.
In the skin, they act as the major adhesion units at the dermal-epidermal junction

- Composed of electron-dense inner + outer plaques that bind to intracellular keratin filaments, which in turn, bind to the lamina densa + anchoring fibrils in the superficial dermis
- Keratin intermediate filaments are made up of keratins 5 and 14, and are found within the keratinocyte cytoplasm
  - They are capable of binding both plectin + the 230-kDa bullous pemphigoid antigen within the hemodesmosomal inner plaque
  - Plectin + 230kDa BP antigen (both part of the plectin family) interact with the two major transmembrane molecules, integrin alpha6-beta4 + type XVII collagen
- Integrin 16b4 is the receptor for the extracellular ligand, laminin 5, which in turn binds to Type VII collagen, the major component of anchoring fibrils in the superficial dermis
- In addition, laminin 5 is linked to Type IV collagen, which forms a network in the lamina densa
- Other roles of the protein components:
  - Integrin 16b4 is able to transduce signals from their extracellular matrix to the interior of basal cells, modulating the organisation of their cytoskeleton and their proliferation, apoptosis + differentiation
  - Interactions between Type VII collagen + laminin 5 have been shown to play a role in tumour cell invasion in epidermal neoplasia

Skin disorders

Many skin disorders are associated with the structural proteins of hemidesmosomes. These may be classified as inherited (involving gene mutations → loss of functional protein) or acquired (autoimmune response to the autoantigenic epitopes of the proteins)

Inherited

- Mutations in the genes encoding proteins associated with hemidesmosomes → skin fragility disorder = epidermolysis bullosa (EB)
- There are different subtypes of EB, each of which have identified different genes (10 identified), including mutations that affect:
  - Keratins 5 + 14
  - Plectin
  - Collagen types VII + XVII
  - Alpha6-beta4 integrin
  - Laminin 5
• The level of blister formation occurs close to the dermo-epidermal junction, but depends on precisely which gene/protein is mutated
• Several forms of EB also have extracutaneous features which reflect the tissue distribution of the abnormal protein, e.g. plectin = skin + muscle therefore also presents with muscular dystrophy
• There are no known inherited skin conditions with typer IV collagen, but mutations in certain subtypes → Alport’s syndrome
  o This causes haematuria, proteinuria + progressive renal failure (i.e. involves the abnormal collagen effect in kidney)

Acquired
• Many of the components serve as “target autoantigens” in acquired autoimmune diseases e.g. Bullous pemphigoid
• In BP, autoantibodies target the autoantigens present on epitopes within the type XVII collagen protein → bullae (blister) formation
  o However the formation also dependent on the activation of complements + generation of neutrophil-rich infiltrates. It is in fact the activity of neutrophil elastase (which is generated via the autoantibody targeting) that degrades the collagen producing the subdermal blisters
• Other proteins targeted by autoantibodies include
  o laminin 5 in mucous membrane pemphigoid
  o type VII collagen in EP aquisita or bullous systemic lupus erythematosus
• there are no known acquired skin conditions with antibodies targeting type IV collagen at the cutaneous basement membrane; however in Goodpasture’s syndrome – lung haemorrhage + glomerulonephritis are caused by antibodies to Type IV collagen in the lungs + kidneys respectively

summary of skin disorders relating to hemidesmosomes
Blood vessels and Nerves

The Skin 4 – Dr Rakesh Patalay (r.patalay@imperial.ac.uk)

1. Understand the size, structure + organisation of blood vessels in the skin
2. Understand the different mechanisms to control skin perfusion
3. Recognise the different nerve endings in the skin and function
4. Recognize the role of the sympathetic nervous system in efferent nerves

Blood vessels

Structure

- The circulation consists of:
  - Aorta ~24,000 µm (2cm)
  - arteries
  - Arterioles ~20-200 µm
  - Capillaries/RBC ~ 6 µm
  - Venules 20-500 µm
  - Veins
  - Vena cava ~34,000 µm

- The different vessels form a vascular network within the skin formed by frequent anastomoses = vascular plexus

- Arteries branch from the aorta, and their corresponding arterioles enter the skin from the fascial network into the subcutis
  - From here, further arterioles branch and rise to the border between the subcutaneous adipose tissue + the dermis – the point at which the vessels anastomose at the border = deep plexus

- The deep plexus gives arteriolar branches to the various cutaneous appendages (E.g. sweat glands + hair follicles), but also provide the ascending arterioles to supply the epidermis

- The point at which these arterioles meet the epidermis = superficial plexus. The superficial plexus then forms capillary loops in the papillary layers between the ridges of the dermo-epidermal junctions

- Venous drainage is very similar to the arrangement of the microcirculation in the skin, but blood flows in the opposite direction

- The vascular supply is more elaborate than would be necessary solely for nutrition; important in thermoregulation

Vessel wall

- The vessel walls can be divided into 5 layers:
  - Tunica intima – consists of the endothelium which lines the lumen
  - Internal elastic tissue
  - Tunica media – consists of the smooth muscle
  - External elastic tissue
  - Tunica adventitia – consists of fibrous connective tissue

- The thickness of these layers are different in veins + arteries
  - Remember capillaries are just formed by the single layer of endothelial cells
**Cellular components**
- Endothelial cells – form single layer in endothelium within tunica intima
- Pericytes – contractile cells which maintain static vascular architecture
  - These are multilayers in venules
- Basement membrane components - Type IV collagen, laminin
- Smooth muscle cells – within the tunica media
- Veil cell – unique to the skin; function unknown

**Control of skin perfusion**
- **Pre-capillary sphincters** – band of smooth muscle that adjusts the blood flow into each capillary at the point where the capillary originates from the arterioles
  - can cause a 1000x difference in cross sectional area, and therefore flow ($A \propto r^2$)
- **Arterial-venous (AV) shunts** – anastomoses directly between an artery + vein
  - There are mainly found in the deep plexus
  - They are usually only ~60% open
  - They are found in the acral sites, such as hands feet + earlobes
- **Vascular tone** – arterioles have a thick smooth muscle wall which can adjust constriction of the vessel to adjust flow
- Control is under autonomic, sympathetic control + can respond to local factors such as vasodilation due to ischaemia
- Skin perfusion is used for thermoregulation

**Function**
- **Coagulation**
  - Weibel-palade bodies are storage granules within endothelial cells which store + release von Willebrand factor involved in haemostasis
- **Angiogenesis** following injury
  - Can be induced in chronic inflammatory conditions e.g. psoriasis + cancer
- **Inflammation**
  - Weibel-palade bodies also store + release P-selectin which is involved in leukocyte recruitment in inflammation
  - Cell trafficking - Endothelial cells express adhesion molecules for white blood cells, e.g. P-selectin + E-selectin for adhesion, ICAM 1+2 and VCAM for cell migration out of the vasculature
  - Nerves can also respond to local stimuli by inducing a local chemotactic response, involving blood vessels = localized neurogenic inflammation

**NB:** the **lymphatic system** – serves to transport cells and liquid material from the extracellular compartment of the dermis to regional lymph nodes and thus back to the circulation

**Nerves + Sensory Organs**
- The skin is innervated by approx. 1 mil afferent nerve fibres, which form a branching network (usually accompanied by blood vessels) to form a mesh of interlacing nerves in the superficial dermis. The distribution of these afferent nerves depends on body sites, but most terminate in the face extremities + genitalia with relatively few on the back
- Cutaneous nerves contain axons with cell bodies in the dorsal root ganglia. The main nerve trunks then enter the subdermal fatty tissue and divide into small bundles.
  - Groups of myelinated fibres then fan out in a horizontal plane to form branching network
  - Throughout their course the axons are enveloped in schwann cells
- Sensory endings are of two kinds:
- Corpuscular – which embrace non-nervous elements and are subdivided into encapsulated + non-encapsulated
- Free – which are derived from non-myelinated fibres and do not embrace non-nervous elements

**Free nerve endings**
- Occur in the superficial dermis + in the overlying epidermis
- Those in the dermis are arranged in a tuft like manner and are called penicillate nerve endings
- Hair follicles have nerve terminals of varying degrees of complexity
  - Fine nerve filaments run parallel to and encircle the follicle forming a palisade
- These are the most common nerves found in the skin and are polymodal, i.e. can transmit multiple sensory modalities

**Corpuscular nerve endings**

*Meissner’s Corpuscle*
- Lammellated, encapsulated unmyelinated nerve ending found in the superficial dermis
- Concentrated in non-hair bearing skin
- It is found more superficially, therefore mediates light touch

*Pacinian corpuscle*
- Encapsulated, ovoid structure about 1mm in length found within the dermis
- The corpuscle is laminated in cross-section like an onion, and is innervated by myelinated sensory axons.
- It is found deeper in the dermis, thus mediates deep touch including pressure + vibration
  - Particularly in the dermal papillae of the hands and feet
- NB: Efferent nerves from the sympathetic nervous system innervate vasculature, eccrine glands, arrector pili muscles of the pilosebaceous unit

**The Merkel Cell**
- Located in the basal layer of the epidermis, in close proximity to the axonal processes
- Involved in sensory perception
- Most numerous on sensitive areas of the skin e.g. tip of nose, lips, around hair follicles or fingertips
- Not seen in routine histological preparations; require immunostaining + EM
- See earlier lecture for more detail

**Sensory pathway**
- Afferent nerves ascending via the spinothalamic tracts, either:
  - Contralaterally (both sides) from the level of insertion to the spinal cord to the thalamus or dorsal column tracts
  - Ipsilaterally (one side) from the level of insertion to the spinal cord to the thalamus, crossing the midline

<table>
<thead>
<tr>
<th>Modality</th>
<th>Nerve ending</th>
<th>Nerve fibre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Touch</td>
<td>Meissner Pacinian free</td>
<td>Aβ</td>
</tr>
<tr>
<td>Pressure</td>
<td>Merkel Free (also ruffini)</td>
<td>Aβ, Aδ</td>
</tr>
<tr>
<td>Vibration</td>
<td>Meissners pacinian</td>
<td>Aβ</td>
</tr>
<tr>
<td>Temperature</td>
<td>thermoreceptor</td>
<td>Aδ, C</td>
</tr>
<tr>
<td>Pain</td>
<td>Free nociceptor</td>
<td>Free, Aδ, C</td>
</tr>
</tbody>
</table>
Normal skin colour depends on several types of pigment, including haemoglobin + melanin.

Melanocytes

- Melanocytes are the cell which synthesises melanin, which is then transferred to keratinocytes involving the transfer melanosomes
- Melanocytes originate in the neural crest of the embryo, and migrate into the skin by the 8th week of gestation. By the 10th week, production of melanin is already evident
- Melanocytes can be found in many tissues, but in the epidermis they form a network among the basal keratinocytes + suprabasal position
- Melanocytes can undergo cell division within the epidermis under stimuli, although the mitotic rate is much lower than that of keratinocytes
  - One of the most important stimuli = UV radiation exposure

Melanin

- The melanin pigment can be of 2 main types:
  - Eumelanin – black/brown + insoluble
  - Phaeomelanin – yellow/reddish-brown, soluble in alkalis
    - Found in red hair + feathers of red hens
- Both are derived from tyrosine, and share the same initial steps of synthesis

Melanin synthesis

- Initial common steps:
  - Tyrosine oxidised to DOPA (enzyme = tyrosinase)
  - DOPA further oxidised to dopaquinone (enzyme = tyrosinase)
- Synthesis of eumelanin:
  - Dopachrome is rearranged to form DICA (in the presence of Zn, Cu, Co or Ni catalysts)
- Synthesis of phaeomelanin:
  - Involves addition of the SH group of cysteine/glutathione to dopaquinone to form cysteinyldopa/glutathionedopa respectively
- Regulation of melanin synthesis
  - By melanocyte-stimulating hormone (alpha MSH)
  - This is a peptide derived from POMC in pituitary gland (pro-opio melanocortin)
  - MSH taken up by membrane receptors on melanocyte, and this proceeds to activate cyclicAMP + tyrosinase
  - Darkening of the skin is seen in patients who have excessive MSH – e.g. Addison’s disease; damage to the adrenal glands

Formation of a melanosome

- Melanin is packaged in the cytoplasm of melanocytes in granules = melanosomes
- These granules are classified into 4 stages, according to their tyrosinase activity and amount of pigment:
  - Stage 1 – spherical vesicle with no melanin deposition
  - Stage 2 – oval shape with numerous melanofilaments; show minimal deposition of melanin + high tyrosinase activity
- Stage 3 – same as stage 2 with increased melanin deposition
- Stage 4 – oval shape, heavy deposition of melanin with minimal tyrosinase activity

Transfer of the melanosome
- The melanosome is produced + matures in golgi apparatus
- It is moved into the melanocyte cell processes
- Keratinocyte then phagocytoses the tips of the melanocyte cell processes, incorporating the melanosome into a cytoplasmic phagosome
- Each melanocyte is in contact with ~36 keratinocytes, and each such group = epidermal melanin unit

Functions of melanin
- Avoids damage to DNA of keratinocytes by UV radiation
- Decreases cutaneous carcinogenesis
- Eliminates genetically damaged cells
- Prevents photo-ageing of the skin

Tanning
- Our normal skin colour is called our constitutive skin colour; polyallelic genetic determination
- Depends on the amount + distribution of melanin in the skin
  - There is no significant difference in the number of melanocytes between races. People with darker skin have an increased melanin production, distribution + retention
  - The size of melanosomes also correlates with darkness of skin; larger melanosomes = darker skin
  - In very fair people, melanosomes are in clusters enclosed by lysosomes, which break them down
- Under the sun, many individuals will develop a tan – this is their inducible skin colours. There is a classification of 6 skin phototypes, which categorise people based on their sensitivity to the sun.

<table>
<thead>
<tr>
<th>Type</th>
<th>Sun sensitivity</th>
<th>Inducible skin colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Burns easily</td>
<td>Never tans</td>
</tr>
<tr>
<td>2</td>
<td>Always burns</td>
<td>Minimal tan</td>
</tr>
<tr>
<td>3</td>
<td>Burns moderately</td>
<td>Tans gradually (light brown)</td>
</tr>
<tr>
<td>4</td>
<td>Burns minimally</td>
<td>Tans easily (brown)</td>
</tr>
<tr>
<td>5</td>
<td>Rarely burns</td>
<td>Always tans (dark brown)</td>
</tr>
<tr>
<td>6</td>
<td>Never burns</td>
<td>Always tans (black)</td>
</tr>
</tbody>
</table>

- There are two types of tanning:
  - Immediate pigment darkening
    - Within 5 mins of exposure to UVA (320-400nm)
    - Oxidation of pre-formed melanin
    - Short-lived
  - Delayed tanning reaction
    - Within approx. 24 hour exposure to UVB (290-320nm)
    - Results from proliferation of melanocytes
    - Increased tyrosinase activity
    - Increased production + transfer of new melanocytes
    - Long-lived
Effects of UV on the skin

- UV radiation causes dermal elastosis, a decrease in the number of Langerhans cells, mutations in keratinocytes + production of free radical
- Effects of exposure include:
  - Damage to skin – sunburn, premature photoageing + cancer
    - Photoageing – responsible for 90% of aging; thin skin, solar lentigos, wrinkles, solar elastosis, flattening of rete ridges, decrease in blood vasculature
  - Damage to eyes – keratitis + cataracts
  - Suppression of immunity
  - Predisposition of bacterial + viral skin infections
  - Exacerbates pre-existing solar keratosis
  - Prevents rejection of skin tumours

UVR levels are effected by:

- Angle of the skin (higher = higher)
- Latitude (closer to equator = higher)
- Cloud cover (clear sky/scattered cloud = higher)
- Altitude (higher = higher)
- Ozone thickness
- Reflection

Penetration of UVR

_UVR can be subdivided depending on its penetrance_

- UVC: \( \lambda < 290 \text{ nm} \) - absorbed by atmosphere
- UVB: \( 290 < \lambda < 320 \text{ nm} \) – blocked by glass
  - Responsible for burns, tumours.
- UVA: \( 320 < \lambda < 400 \text{ nm} \) – penetrates glass
  - Responsible for ageing of the skin

Sun Protection

- Regulated by FDA
- SPF – the dose of UVR required to produce minimal erythema on the skin protected with 2mg/cm\(^2\) of sunscreen/UVR required to produce a faint blush on unprotected skin
- Water-resistant = able to maintain SPF level after 40 mins of water immersion
- Very water-resistant (previously waterproof) = able to maintain SPF level after 80 mins of water immersion
- Broad/full spectrum = provides both UVA + UVB protection (UVA 1+2)
- Adequacy of UVA1 protection in sunscreens questioned; individuals relying on sunscreens as sole form of photoprotection may now be subject to greater cumulative sun exposure
- Sun avoidance + sunscreen application 15-30 mins prior to exposure = best
  - Particular attention to back of neck, ears + scalp
- Clothing also provides good protection, with large brimmed hats + dark clothes providing best protection
1. Understand the structure + function of hair
2. Recognize the different types of hair
3. Understand the hair cycle + influences to it
4. Understand the anatomy and growth of finger/toe nails

Hair

Function

- Protection of the skin
  - Physically e.g. eye lashes
  - Against UV damage e.g. scalp
- Thermoregulation
  - Piloerection when cold/sacred
  - Evaporation of sweat from hair when hot (increases SA)
- Communication
  - Provides sexual attraction
  - Suggests info about health, youth + fertility
  - Conveys threatening behaviour or fear when erect
  - Camouflage (colour of animals)
- Provides sensation
  - Amplifies movement, therefore sensation is more sensitive e.g. movement from the wind

Development

- All hair follicles develop in utero. Initially 2 hairs grow from each follicle = lanugo hair
- Lanugo hair develops during 3rd trimester + shed by 8 months
- The 2nd hair is shed 3-4 months postpartum, with ~500 mil follicles at birth

Types

- Hair density: the size of a hair follicle varies with time and where it is in the hair cycle. They are present all over the epidermis except the palms, soles + mucous membranes. Only 5% is present on the scalp.
  - Caucasian density ~250-320hairs/cm²
  - African density ~180 hairs/cm²
- Lanugo hair – the fine, soft, usually unpigmented + unmedullated prenatal hair which may be seen in premature babies
- Vellus hair – post natal hair; soft + occasionally pigmented usually <2cm long and unmedullated, covers most of the skin
- Terminal hair – post natal hair; longer than vellus hair, pigmented, course + medullated
  - Prior to puberty, terminal hair is limited to the scalp, eyebrows + eyelashes
  - Under the influence of sex hormones, vellus hairs can transform into terminal hairs e.g. axillae, pubic hairs (+facial and chest hair in men)

Structure and Anatomy of the Hair + Hair follicle

- Hair is the keratinized product of the hair follicle
- Keratin is an intermediate filament of the cytoskeleton of cells, which is intermediate in size between actin and microtubules (8-10nm diameters)
  - The basic structural unit consists of dimers of type I (acidic) and type II (basic) intermediate filaments
These then form alpha helical structures that further polymerise into protofibrils and finally make the cortex of the hair

- Cross section through a terminal hair – consists of a medulla, cortex + outer cuticle
- **Cross section through an active hair follicle** – can be divided into 3 segments:
  - **Hair bulb**: the expanded lower end of the follicle which includes the dermal papillae
  - **Suprabulbar region**: the region between the hair bulb and the isthmus
  - **The isthmus**: short portion between entry of sebaceous ducts + attachment of the arrector pili muscle.
    - Hair follicle stem cells are thought to reside in the lower part of the isthmus close to the insertion of the arrector pili muscle
  - **Infundibulum** – skin surface to point of entry of sebaceous duct
    - Has same epithelial structure as the skin surface

**The hair bulb**

- Consists of dermal papilla + hair bulb matrix
- **Cells of matrix** have high mitotic rates + produce the various parts of the hair
  - Lower more lateral cells – inner root sheath
  - Upper more central cells – hair shaft
- In pigmented hair follicles, melanocytes are situated in the cells destined to become the cortex and they give rise to pigment in the hair shaft
- Langherhans cells may also be found in the hair matrix
- The **dermal papilla** is made up of specialised fibroblast-like cells embedded in an ECM rich in BM proteins and proteoglycans
  - It also contains blood vessels
  - Importance in the induction + maintenance of follicular epithelial differentiation
  - The volume of the dermal papilla may be responsible for controlling the size of the hair follicle + fibre
- At the level of the hair bulb there is an outer root sheath surrounding the inner root sheath
  - Surrounding both of these is a dermal sheath – a collagenous layer
- As the hair growth cycle changes, communication between the hair bulb and the dermal papilla means that the vasculature to the hair follicle grow + shrunk in response to metabolic needs of the follicle

**Hair shaft**

- The **cortex** forms the bulk, will cells consisting of hair specific keratins + proteins
- The **cuticle** consists of 5-10 overlapping cell layers, with compact cuticular keratins associated with sulphur containing proteins e.g. cysteine
  - Has a protective role
With wear + tear, gradual degradation of the cuticle occurs, with breaking + lifting of the free margins exposing the cortex

- The **medulla** is the variable structure

- **Hair root**
  - **Inner root sheath** – consists of three layers: Henle’s, Huxley’s and the cuticle
  - Cells have specific keratin + it hardens before the hair shaft within it, controlling the shape
  - **Outer root sheath** – forms the most peripheral layer of the hair follicle epithelium, enclosing the inner root sheath

### Hair cycle

- **Anagen** – the period of active hair growth
  - Duration determines the final length of hair, e.g. scalp hair remains in anagen for 2-8 years, eyebrows for 2-3 months
  - As each cycle occurs, the anagen phase shortens and the telogen phase elongates

- **Catagen** – the brief period where the proximal part of the hair shaft keratinizes to form a club-shaped structure and the lower part of the follicle involutes by apoptosis
  - The base of the follicle moves upwards to lie below the level of the arrector pili muscle insertion

- **Telogen** – the phase when hair is not being produced and the club hair is shed. This period lasts about 3 months for scalp. Human follicles re-enter anagen prior to shedding the club hair

- The maximum hair length for a given body site is determined by the length of time the hair is in anogen and the speed of body growth for that body
  - Over time, there is asynchronous pattern of growth and regression → shedding of hair in diffuse pattern and no “apparent” focal areas of hair loss

- **Influences on the hair cycle**
  - Pregnancy, testosterone, prolactin, oestrogens + melanin
  - Increased anagen duration
    - Hypertrichosis
• Trichostasis
• Spinulosa
• Pregnancy

• Decreased anagen duration
  • Androgenic alopecia
    ▪ Polygenic cause leading to genetic sensitivity to androgens
    ▪ >80% of men over 70 yrs – male pattern balding (Hippocratic balding)
  • Alopecia areata
    ▪ Bald patch
  • Telogen effluvium
    ▪ Premature termination of anogen, causing diffuse hair loss
    ▪ Causes include severe physiological stress including starvation, major surgery + blood loss
    ▪ Regrows over 3-6 months

Hair colour
• Fully differentiated melanocytes can be found mainly in the hair bulb of the skin (but also in the infundibulum)
  ▪ They secrete melanosomes into the keratinocytes leading to melanised hairs:
    ▪ Eumelanin = brown/black hair
    ▪ Phaeomelanin = red/blond hair
• Greying hair is the most familial manifestation of the ageing process, with onset being determined largely by hereditary factors, usually occurs in 40-50 yrs
• In senile grey/white hairs, there is a reduced number of melanocytes + cells show little activity with few melanosomes
• In addition, alpha-MSH binding sites normally present in pigmented human scalp follicles are absent

Diseases of hair
• Telogen Effluvium
  ▪ There is premature termination of the anogen stage of the hair cycle
  ▪ There is diffuse hair loss but regrowth occurs over three to six months
• Hirsutism
  ▪ This is development of terminal hair in the beard area and body in females
  ▪ This may or may not be part of a generalised disorder known as virilisation
• Hypertrichosis
  ▪ This is growth of terminal hair in areas which are not meant to be hairy
  ▪ This can be localised like in Becker’s naevi or generalised due to prophyria or drugs
• Hypertrichosis Lanuginosa
  ▪ This could be congenital or acquired
  ▪ It results due to the persistence of fetal lanugo hair which grows excessively and is renewed throughout life
  ▪ It could also result due to a normal hair follicle reverting to producing hair with lanugo characteristics
  ▪ Excessive hair growth is generalised but does not involve the palm or soles
  ▪ The congenital form is often autosomal dominantly inherited
  ▪ The acquired form is often seen in association with malignancy of the gastrointestinal tract, breast, gallbladder, uterus, bladder or other organs
  ▪ The excessive hair growth in the acquired form may precede the diagnosis of malignancy by several years
• Androgen Alopecia
  ▪ This is the pattern of hair loss due to testosterone influence
  ▪ The pattern is different in men and women
  ▪ 80% of the men above 70 years of age will have signs
  ▪ It has a polygenetic cause but most lie on the X chromosome
Nails

Functions
- Touch
- Protection
  - Chemical
  - Physical
  - For the finger
- Communication
- Weapon

Structure
- Composed of 80% hair keratins and 20% cytokeratins
- Also has calcium deposits
- The nail unit can be divided into a number of distinct areas
- Its strength is contributed by longitudinal ridging between the nail plate and the nail bed. This provides immense resistance to sheering forces. It is also curved longitudinally + laterally

Distinct areas
- Germinal Matrix
  - This ranges from 4 to 9mm in length
  - Most of it is located under the proximal nail fold
  - The distal end of the nail matrix is visible in most people and is represented by the distal end of the lunula
  - It is formed from a thick epithelium consisting mostly of matrix cells
  - There are some poorly developed melanocytes present
- Nail Plate
  - This originates from the nail matrix
  - The proximal portion is usually white and defined as the lunula
  - The middle section overlies the nail bed
  - The distal part is the free edge of the nail plate
  - It is made from closely packed, fully keratinized, multilayered lamella or cornified cells
  - It is only smooth on the dorsal surface
  - Over 80% of the nail plate is formed from the proximal 50% of the nail matrix
  - The ventral surface shows longitudinal folds and grooves that adhere to the nail bed
- The Cuticular System
  - This ensheathes the nail plate from both above and below
  - It acts as a barrier to the external environment
  - It includes the proximal eponychium and the deeper and more distal cuticle
  - The hyponychium is more superficial
Features

- **Rate of Growth**
  - The rate of nail growth is determined by a number of factors
  - The fingernails grow at about 0.1mm/day with toenails growing half as fast

- **Thickness**
  - The thickness of the nail varies from 0.6 to 1mm
  - The surface of the nail is produced by the proximal nail bed
  - The undersurface of the nail is produced by the distal nail bed

Diseases of the Nails

- Nail changes may be non-specific or characteristic of specific processes
- **Psoriasis**
  - This condition involves the apical and/or the dorsal matrix, resulting in pitting of the nail plate through loss of cells from the upper layer of the plate
  - When paraheratotic cells appear in the distal third of the matrix, onycholysis (separation or loosening of a nail from its nail bed) may occur
  - A third of patients will show with nail changes
- **Sudden Illness**
  - Illness or trauma can lead to an arrest of the apical nail growth
  - This results in Beau’s lines, which are transverse depressions along the nail plate
- **Systemic disease**
  - Horizontal and longitudinal curvature of the nail (clubbing) can occur in response to a number of systemic diseases including lung disease, cyanotic heart disease and inflammatory bowel disease

Nail Pigmentation

- Linear pigmented streaks can be caused by a number of things
  - Melanonychia striata has benign causes
  - Melanoma is malignant
  - The above two conditions cannot be distinguished easily by clinical examination alone

Hair + nail diagnostic tools

*The hair + nails can be used diagnostically in:*
- Cystic fibrosis
- Drug compliance investigation
- Illicit drug intake
- Environmental exposure

Organisation of the skin immune system

The Skin 7 - Professor Tony Chu (t.chu@imperial.ac.uk)

**Key players involved:** keratinocyte, Langerhans cell, T cell, monocyte/macrophage, endothelial cell, mast cell

**Keratinocytes**

- 98% of epidermis; act as stem cells. Their morphology thus changes as they mature:
  - Basal layer – cuboid cell, involved in division + repair
  - Prickle cell layer – polygonal, appearance of lamellar bodies
  - Granular layer – flattened, highly granular = Keratohyalin granules
  - Stratum corneum – flat, no nucleus, “dead” = protective barrier
• **Role in immunity** – initiation/control of inflammation, modulation of immunity + interaction with melanocytes, Langerhans cells, memory T-cells + cytotoxic T-cells

• Major factors for the production of cytokines, e.g. IL 1 (produce more cytokines than any other cell in the body)

• **Phagocytic**

• Can be induced to express **MHC Class II** (in inflammatory conditions, induced by INFγ)
  - Expression is a cardinal feature of APC – debate as to whether they are APC; but they lack co-stimulatory molecules + studies have failed to show antigen presentation

• Express **toll-like receptors**
  - Respond to highly conserved motifs on micro-organisms, expressing TLR 1,2,4 +5
  - These stimulate “danger” signals

• Produce **antimicrobial peptides**
  - E.g. produce cathelicidin peptide IL37 under inflammatory conditions
  - Also produce human beta defensins 1,2 + 3

• Express growth factors, chemoattractant cytokines, down-regulatory cytokines

*Langerhans cell*

• 2% of epidermal cell population
  - Localised in the basal and suprabasal layers of the epidermis
  - Forms a regular with their protrusions/dendrites spanning the epidermis (all dendrites on same plane)

• **Ultrastructure** – interdigitating shape, lobulated nucleus + clear cytoplasm containing Birbeck granules but lacking tonofilaments + desmosomes

• Migrant from **CD4+ bone marrow precursor**, but also locally self-replicating
  - Mitosis extremely slow
  - In severe damage to the skin, e.g. burns, there is a feedback mechanisms to stimulate more production from bone marrow

• **Role in immunity** – recognition of danger signals, orchestration of inflammation, antigen presentation, transport of antigen to regional lymph nodes, expression of additional stimulatory molecules/stimulation of naïve T-cells
  - Also interacts with keratinocytes, endothelium, naïve + memory T-cells

• Dendritic APC of the skin

• Express a unique combination of **surface antigens**: HLA-DR, CD1a (non-polymorphic class I molecule – important in lipid presentation, but role unknown), Langerin (surface glycoprotein)

• Stimulated to mature by GM-CSF, TNFalpha, IL4 and TGFbeta

• Possess a unique intracytoplasmic organelle – **Birbeck granule**
  - This has a trilaminate structure with an extended terminal end (like tennis racket)
  - Important in receptor-specific endocytosis; langerin is a lectin present within the Birbeck granule

• Precursors are able to get into the skin via **CLA receptor**, using the **E-selectin** on endothelial cells as a ligand
  - The langerhan cell expresses **CCR6 receptor for CCL20** (produced by keratinocytes)
  - Adhesion to keratinocytes then via **E-cadherin**

• Following stimulation, the cells change their chemokine receptor to CCR7, lose their E-cadherin + migrate out of the epidermis to the dermal lymphatics:
  - These then up-regulate CD80 + CD86 and migrate to the para-cortical zone of lymph nodes to interact with CD4+ T cells
  - NB: the Langerhans cells start to apoptose when they leave the epidermis
Melanocyte

- 2% of epidermal cells
- Localised in the basal layer
- Branching cells which interact with keratinocytes
- **Role in immunity** – produce melanin, protects body from UV radiation + prevents UV-induced immune suppression

Mast Cells

- 10,000mm$^3$ found in the skin near blood vessels, hair follicles + sweat glands – within the dermis
- Rounded/ovoid structure containing secretory granules
- Express **IgE receptors, TLR + complement receptors**
- Activation is mainly during Type 1 IgE mediated hypersensitivity (involved in parasite reactions + allergy)
  - **Role in immunity:**
    - Recognition, phagocytosis + killing of bacteria
    - Produces cytokines IL4, 5, 6 + 13
- Express TLR 2,4,6 + 8
- Express C3a + C5a receptors

T cell

- Lymphocytes, 7-12µm in diameter (nucleus occupies most of cell)
- Infiltrate skin from blood + leave through lymphatics
- T cells that go into the skin express the skin homing antigen CLA
  - In the steady state, the main T cell is CD8+
  - In inflammatory skin conditions, the major T cell is CD4+ helper T cell (which interact with Langerhans cells)
- Dermal T cells represent 98% of T cells involved with the skin, and are predominantly CD4+
- **Role in immunity** – memory cells survey skin for recurrent infections + provide help to boost immune response, cytotoxic killing + peripheral tolerance

Monocytes/macrophages

- Macrophages: 15-18 µm in diameter, irregular shaped nucleus + phagocytic vacuoles
- Arise from myeloid precursors in the bone marrow
- Circulate as monocytes, migrate into various tissues including the skin where they activate into macrophages – resident in the dermis
- phagocytes
- Can act as APC + express TLR (therefore important in innate immune response)
- Produce a large range of pro-inflammatory cytokines, growth factors + down-regulatory cytokines – important in adaptive immune response
  - Provide costimulation of T cells by IL12 generation

Endothelial cells

- Prevent clotting under normal circumstances
- Allow cells to adhere and migrate through them involving E-selectin
- Express number of cytokine receptors, as well as producing a number of cytokines including basic fibroblast growth factor
Neutrophils

- 12-15 µm in diameter, multi-lobed nucleus, granular
- Circulate in blood then migrate into dermis
- Short-lived
- Role in immunity:
  - Elimination of pathogens
  - Phagocytic (Increased phagocytic function following opsonisation)
  - Killing by oxidative burst OR by antimicrobial peptide/granule release

Function of the Skin
The Skin 8 - Professor Tony Chu (t.chu@imperial.ac.uk)

- Organ of sexual attraction + social interaction
- Barrier to loss or absorption of fluid and molecules
- Barrier to infection
- Protection against UV + other radiations
- Temperature control
- Reaction to infection, cancer + foreign substances

Role in social and sexual interactions

Sexual interactions
- To display sexuality or to exert social status it is necessary to have skin + hair which looks, feels + smells attractive
- The importance of the skin in sexual interactions is highlighted by the effect of disfiguring skin conditions. People will often then perceive themselves to be unattractive and this will impact their quality of life + their confidence
- This may lead to general loss of confidence; unwillingness to partake in various activities which may display the disfigured areas of skin, reclusiveness, depression + suicidal ideation

Quality of life issues
- Dermatological conditions are visible and may have profound impact on quality of life
- Facial dermatoses may have result in loss of confidence, reclusiveness, depression + social isolation
- Scaly skin conditions may make staying overnight difficult
- Itching may result in bleeding onto clothes and bedding
- Employment – patients with acne were found to have a 50% greater employment rate, and patients with significant acne cannot joined the armed forces
  - Pathogenesis of acne – humidity increases blockage of pores, may lead to increased infections
- Patients with psoriasis are often thought to be infectious, and are often asked to leave public amenities
  - Also problems wearing certain clothing + interpersonal relationships
- Patients with significant disease on arms + legs will not wear clothing that exposes those areas
- Patients with significant acne or psoriasis on the body will not undress in public, e.g. trying on clothes, swimming baths, going to the beach
- Social stigma - In certain countries, vitiligo, where the skin develops white patches, is a major social stigma
  - Kaposi sarcoma is a very visible sign of AIDS + can lead to patients being ostracised by areas of society
Barrier functions

- The skin acts as a 2-way barrier to prevent inward + outward passage of water + electrolytes
- The dermis is durable (type I collagen), the stratum corneum are selectively permeable + there is regional variation in absorptive capacity
- Shedding of the epidermis \(\rightarrow\) shedding of surface bacteria
- The skin limits water loss from the body, and regulates penetration of water + other chemicals into the body
- Most of the barrier function resides in the epidermis within the stratum corneum
  - The lipid barrier is also important
- Keratinocytes synthesise fibrous proteins of keratin + histidine rich proteins (keratohyalin + filaggrin)
- Odland boddies develop in keratinocytes close to the golgi apparatus + migrate to the cell periphery
  - Within the bodies, uni-laminar liposomes rich in sphingolipids and nural lipids become arranged in a disc form
  - In the stratum granulosum, the odland bodies fuse with the cell membrane and the contents are discharged \(\rightarrow\) this acts as a lipid barrier
  - After discharge from the granules, the discs become arranged parallel to the cell membrane + fuse to produce uninterrupted sheets consisting of 2 lipid biolayers in close apposition
    - These intercellular lamellae are the main barrier to trans-epidermal water loss + prevent absorption of water through the skin
- Ceremides are essential in the formation of the bilaminar lipid membrane – they contain essential fatty acids
  - Deficiencies of these, especially linoleic acid \(\rightarrow\) results in poor barrier function
- In atopic eczema, there is an enzyme deficineyc of delta-6-desaturase: this results in poor incorporation of linoleic acid into ceramides
  - The patients thus have dry skin with poor barrier function
  - The dry skin is irritable + adds to the itch of the eczema

Percutaneous absorption

- Skin is slightly permeable to water, and this permeability increases with lipid solubility
- Drugs that penetrate the skin are generally soluble in lipids or contained in a lipid containing medium
  - Topical therapy can be used in treatment for both skin disease, as well as disease of other organs
- Certain areas show increased absorption: scrotum, face, forehead + dorsum of hands
- The principle pathway of percutaneous absorption is through the stratum corneum
  - There is also absorption through the pilosebaceous apparatus or sweat ducts – these play a minor role in providing rapid route of entre for ions, polyfunctional polar compounds + very large molcules
- Absorption is through the corenocytes rather than between them. In an infant and old skin, the absorptionis greater due to reduced thickness of the skin
  - In disease, barrier function may be lose and absorption is thus greater
- Pharmacological relevance \(\rightarrow\) important in delivering drugs to other organs other than the skin, e.g. nicotin replacement patches, hormone replacement therapy, topical NSAIDs, nitroglycerine

Protection against micro-organisms + destructive chemicals

- Intact stratum corneum prevents invasion by microorganisms
- Sebum has anti-bacterial properties + glycophospholipids/free fatty acids are bacteriostatic

sebum

- Sebum – holocrin excretion produced by sebaceous glands
- Excreted into the hair follicle + gains access to the surface of the skin
- Sebaceous gland is active from 26weeks gestation; contributes to venix caseosa on newborn babies
- Excretion mainly controlled by androgens: maternal in the foetus, adrenal glands ovaries in women, testes in men
- Minor role in regulating ambient temperature
The Skin

- In animals, it has an important function in coating/waterproofing hair + fur – role in man is more speculative
- Possible role in reducing moisture loss but not a major part of barrier function
- Lipids have antibacterial + anti-fungal properties

Thermoregulation

The Skin 9 – Dr Sangeeta Punjabi (s.punjabi@imperial.ac.uk)

**Definition:** the ability of an organism to keep its body temperature within certain boundaries, even when the surrounding temperature is very different

- Homeothermy – the maintainance of a high temperature constant and independent of that of the surrounding air (shown by mammals/birds)
- Poikilothermy – the display of a variation of body temperature dependent on their surroundings

Why is thermoregulation important?

- Important aspect of human homeostasis – enabling humans to live under the extremes of temperature ranging from the cold Antarctic to hot deserts
- A temperature of ~37°C is essential for normal function – normal mental functions are dramatically impaired outside the 35-40°C range

Temperature regulation

- Temperature can be subdivided into core or peripheral temperature
- Core temperature – represents the balance between heat generated by organs, and heat loss
- Peripheral temperature – homeostasis assisted by the skin; does this by reacting differently to hot/cold conditions
  - Vasodilation + sweating are the primary modes by which humans attempt to lose excess body heat
- Under normal conditions, core temperature is a few degrees higher than skin. Skin temperature is a function of the heat that reaches it from the core + external temperature
- Core temperature – there is a diurnal variation around 37°C, which is influences by age, external temperatures, exercise + ovulation
  - Within 24 hours of ovulation, women experience an elevation of 0.15-0.45°C – due to the increased metabolic rate caused by sharply elevated levels of progesterone
- Sensors may be deep or superficial:
  - Deep sensors present on the preoptic area of the anterior hypothalamus + the spinal cord, great veins + abdominal viscera
  - Peripheral sensors are present in the skin
- The hypothalamic centre (preoptic area) sensors are set at critical temperatures = set point
  - This is more finely controlled than the thermoreceptors of the skin. (a fall as small as 0.3°C in the blood reaching the sensors, produces an effect similar to a drop of 10°C on skin).

Heat production/heat loss

- Sources of heat: BMR, muscle activity, thyroxine + effects of adrenaline/noradrenaline/sympathetic stimulation
- Sources of heat loss: 18% conduction, 60% radiation + 22% evaporation
- Insulation – fat is a poor conductor of heat, therefore subcutaneous fat is an excellent insulator
- A lot of heat loss is via eccrine sweat glands
Role of skin in thermoregulation

- If the skin temperature > surroundings, the body can lose heat by radiation + conduction
- If the temperature < surroundings, the body gains heat by radiation and conduction
- In such conditions, the only means by which the body can rid itself of heat is by evaporation

Dermal capillary network

- Vascular supply to the skin far outweighs its metabolic needs
- There is a network of arterioles + venules that form the dermal capillaries – the blood supplied to these through muscular arteriovenous anastomoses
- These are under sympathetic nervous control – blood flow can thus vary from ~0-30% of cardiac output
- When dilated, larger volumes of blood reach the surface of the skin (via deep + superficial vascular plexus branches) – heat is then conducted from the core more efficiently
- Heat is conducted less in cold weather, as less blood reaches the superficial vascular capillaries

Sweating

- For every g of water that evaporates, 0.58 calories of heat is lost
- Insensible water loss from the skin + lungs account for 12-16 calories/hr (~600ml/day)
- This loss cannot be controlled + is affected by ambient humidity and the surrounding movement of air
- Sweating is under nervous control and can respond to changes in core and ambient temperature
  o Sweat ducts are innervated by sympathetic cholinergic nerve fibres – they also respond to adrenaline/noradrenaline
- A sweat gland consists of 2 parts:
  o Coiled subdermal component – produces the sweat; consists mainly of protein-free filtrate of the plasma and is secreted actively
  o Sweat duct passages – pass through the dermis + epidermis to open onto the skin as a sweat pore
    ▪ Mpst Na, Cl + H2O reabsorbed here, leaving sweat as predominantly urea, lactic acid + K+
    ▪ The Na+ content can vary depending on amount of sweat produced

Responses to change in temperature

- The preoptic area in the anterior hypothalamus, thermoreceptors in skin + some deep thermoreceptors monitor the temperature of the core/blood/skin
- The posterior hypothalamus processes the peripheral + central signals and co-ordinates the body’s responses:
  o Signals from the preoptic area have a greater effect on the autonomic regulation
  o Peripheral signals have a greater effect on the “set point” of the hypothalamus
- If cold:
  o Vasoconstriction – sympathetic vasoconstriction of the dermal capillaries
  o Piloerection – sympathetic stimulation of arrector pili muscle
  o Shivering – peripheral muscle tone is increased leading to shivering
  o Chemical thermogenesis – cellular metabolism can be increased by adrenaline/noradrenaline. Brown fat (found in infants) is important in this context. Thyroxine is also upregulated.
  o Behaviour – move, wear more clothes etc.
- If hot:
  o Vasodilation – sympathetic vasoconstriction of the dermal capillaries
  o Sweating
  o Decrease heat production – inhibition of shivering and chemical thermogenesis
  o Behaviour – move, wear less clothes, drink cold drink
Determinants of body temperature

- Production of heat by metabolic processes
- Thermoreceptor mechanisms
- Warming/cooling mechanisms
- Mechanisms for exporting heat through lung + skin
- Mechanisms for conserving body heat

Set point

- A fever is one of the body's immune responses which attempts to neutralize a bacterial or viral infection.
- When you have a fever it is as though the body has temporarily reset its thermostat. During a fever, pyrogens in the circulation cause the set point to increase. The body then behaves as if it were cold until the newer, higher set point is reached
- People develop higher temperatures with activities but this is not considered a fever as the set-point is normal
- Extremes of deviation from set point = heat stroke, anhidrotic + hypothermia

Wound Healing

Introduction to Healing

- After injury to the skin, 2 broad types of healing can occur:
  - Regeneration – the epidermis regenerates; result of the lability of the cells
  - Repair + formation of fibrotic scar; the dermis must undergo repair, as cleansing of necrotic tissue, demolition of the clot, stimulation of blood vessels + collagen synthesis are all required processes

Phases of healing

Healing is the result of the interaction of many events, and can be divided into 3 phases: inflammatory, proliferative + maturation

1) Inflammation

- Following a cut in the skin, there will be disruption of the normal structures, rupture of the blood vessels + bleeding
- When bleeding stops, a clot will form at the site of damage.
- The clot contains WBC that contain growth factors – important for cell proliferation + increased cell activity
- Platelets + mast cells produce histamine – produces vasodilation + increased post-capillary venule permeability (this leads to swelling + erythema)
- Trauma causes cell damage – may leave cell debris, e.g. cell membrane debris. The cell membranes contain phospholipids; these stimulate the production of prostaglandins, which also help to dilate the arterioles to the skin
- Macrophages present in the clot (migrate to site of damage through dilated blood vessels) + start actively phagocytosing dead cell products
  - These also then secrete collagenases + elastases – break down damaged tissue
  - Also secrete growth factor, especially Platelet-derived growth factor (PDGF) – important as stimulates fibroblast migration + proliferation
  - Macrophages also produce angiogenesis factors, promoting endothelial cell proliferation + formation of new blood vessels
The new tissue formed during the inflammatory phase of healing is composed of many fibroblasts, numerous blood vessels + soft matrix (rich in collagen T2 + GAGs – GRANULATION tissue; forms 3-5 days after injury)

- Epithelial repair during inflammatory phase – clot forms a scab. The dead epithelium also produces many cytokines esp EGF (stimulates basal cells on the margins of the scab to proliferate + migrate under the scab
  - This occurs at 7 micrometers/hr
  - Newly formed epithelium subsequently becomes thicker by the proliferation of basal cells + formation of intermediate/superficial layers of the epidermis
  - When the scab finally detaches, a new epidermis is found underneath it

2) Proliferation

- After 5 days of granulation tissue formation, collagen Type 1 begins to replace the collagen type 2
- Collagen consists of 3 polypeptide chains, each twisted into a L-hand helix
- 3 chains aggregate by covalent bonds, and twist into R-hand superhelix
- Every 3 amino acid is glycine
- Collagen rich in hydroxylysine + hydroxyproline – enable to form cross-links
- The hydroxylation of proline + lysine residues depends on the presence of oxygen, Vit C, ferrous ion and alpha-ketoglutarate
- Deficiencies of oxygen + vit C result in unhydroxylated collagen that is less capable of forming strong cross-links and therefore is more vulnerable to breakdown
- Collagen is secreted to the EC space in the form of procollagen; this is then cleaved of its terminal segments \(\rightarrow\) tropocollagen
- Tropocollagen can aggregate with other tropocollagen molecules to form collagen filaments; arranged in a staggered fashion + joined by intermolecular cross links
- Filaments are then aggregated to form fibrils, which aggregate to form fibers

3) Maturation

- Collagen Type 2 is replaced again by Type 1
- The number of newly formed blood vessels decreases
- The amount of GAGs of the matrix diminishes
- As a consequence, the soft ref appearance of the early scar is progressively replaced by a harder, white scar
- Myofibroblasts; cells with the appearance of fibroblasts BUT also contain actin filaments.
  - These appear in the maturation phase. Their function is to contract the scar
- The full maturation of a scar in the skin can take up to 12 months, and even so, the tensile strength of the scar will never be the same as that of the uninjured skin (max 80%)

Closure by primary + secondary intention

- A wound is said to be closed by primary intention when it is approximated, usually by suturing
  - This will approximate the borders, and promote faster healing with a smaller scar
- In closure by secondary intention, the wound is left to heal by itself
  - This occurs, for example, when the wound is infected
  - It is not advisable to close this area
  - Produces larger scars

Complications in the process of healing

Vitamin C deficiency

- Vitamin C is essential for collagen synthesis
- Deficiency \(\Rightarrow\) difficulty in healing
Diabetes
- In diabetes, glucose molecules are attached to all types of protein – a process called non-enzymatic glycosylation
- This makes proteins less active, including proteins important for the defence against bacterial infection
- Healing thus takes much longer in diabetics, and the risk of infection is high

Keloids
- These are dermal fibrotic lesions that a variation of the normal wound healing process
- They usually occur during healing of a deep skin wound, because of excessive production of ECM proteins, collagen, elastin + proteoglycans – i.e. the result of a prolonged inflammatory response in the wound
- Formation can occur within a year after injury, and enlarge well beyond the original scar margin
- The most frequently involved sites are areas subjected to high skin tension e.g. anterior chest, should, anterior neck (+ any wounds that cross skin tension lines)

Hypertrophic scars
- These are raised, erythematous, fibrotic lesions that usually remain confined within the borders of the original wound.
- They occur within months of the initial trauma and have a tendency to remain stable or regress with time

Risk factors/Causes
- The most important risk factor for the development of abnormal scars is a wound healing by secondary intention, especially if the healing time is >3 weeks
  o Wounds subjected to a prolonged inflammation, whether due to a foreign body, infection, burn or inadequate wound closure
  o Areas of chronic inflammation, e.g. earring site
  o Also, rare spontaneous keloids without history may occur
- After the initial insult to the skin + formation of a clot, the balance between granulation tissue degradation + tissue biosynthesis = key to adequate healing
  o Keloids have an increased blood vessel density, a thickened epidermal layer, and increased mucous ground substance
  o The presence of myofibroblasts are also important for contraction of scars, and these a few/not present in keloids
- The collagen fibrils in keloids are more irregularly + abnormally thick
  o Biochemical differences in collagen content in normal scars + keyoids have been examined in numerous studies
  o Collagen synthesis is 20x > normal scars, but cross links in normal scars > keloids (scars are less stable)
- These changes seem to be mediated by cytokines:
  o Keloids demonstrate an amplified production of TNF-alpha, INF-beta + IL-6
  o Also diminished production of INF-alpha, INF-gamma + TNF-beta
- The abnormal cytokine production is possibly due to genetic predispositions involving HLA + blood group A; however there is no consistent pattern

NB: Why do foetuses heal without scarring?
- Sterile amniotic fluid
- Rapid epithelialization
- More HA
- Nonsulfated GAGs
- TGFβ 3 isoform
- More fibroblast migration
- High proportion PCIII
- No inflammatory effector cell

**Cytokines**

*These are important mediators of wound healing events, including the following:*

- **Epidermal growth factor (EGF)**
  - Potent mitogen (stimulates mitosis) for epithelial cells, endothelial cells + fibroblasts
  - Also stimulates fibronectin synthesis, angiogenesis, fibroplasia + collagenase activity

- **Fibroblast growth factor (FGF)**
  - Mitogen for mesenchymal cells, endothelial cells, fibroblasts, keratinocytes + myoblasts
  - Stimulus for angiogenesis
  - Stimulates wound contraction + epithelialisation
  - Stimulates production of collagen, fibronectin + proteoglycans

- **Plasma derived growth factor (PDGF)**
  - Released from platelets
  - Stimulates neutrophils, macrophages + production of TGF-beta
  - Mitogen + chemotactic agent for fibroblasts + smooth muscle cells
  - Stimulates angiogenesis + collagenase

- **Transforming growth factor beta (TGFβ)**
  - Released from platelets; regulates its own production in an autocrine manner
  - Important stimulant for fibroblast proliferation + proteoglycans, collagen + fibrin
  - Promotes accumulation of ECM + fibrosis
  - Reduces scarring

- **Tumour necrosis factor alpha (TNFα)**
  - Produced by macrophages, mitogen for fibroblasts
  - Stimulates angiogenesis + collagen/collagenase synthesis

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**The Skin in innate + acquired immunity**

The Skin 11 – Paul Seldon (p.seldon@imperial.ac.uk)

**The Innate Immune System**

- The old concept of the skin's innate immune response consisted of 3 elements:
  - **Skin** as a barrier function to keep microorganisms out
  - **Sebum** – fatty acids + acid pH inhibit growth of microorganisms
  - **Sweat** – lysozyme damages cell wall of bacteria

- The innate immune system is responsible for the detection and control of an initial immune insult. It is a simple mechanism of protection that occurs rapidly without required refinement of receptors or prior exposure. Features of the innate immune response include:
  - Initial response to bacteria, fungi and viruses
  - Broad spectrum
  - Prevents infection
  - Damages cell wall of micro-organism
  - Removal by ingestion

- The **functions** of the innate immune response are:
  - Danger signal
  - Chemotaxis
  - Phagocytosis + opsonisation
  - Oxidative burst
- Inflammation
- Induction of acute phase proteins
- Complement mediated lysis

- Recognition of pathogens – pathogens have pathogen associated molecular patterns (PAMPs). These are recognised as non-human and stimulate cellular response to the non-self-organisms
  - Several families of receptors exist, including Toll-like receptors, complement receptors (CR3), and lipopolysaccharide binding protein

**Toll-like receptors**
- These are cell surface pattern recognition receptors which recognise evolutionary conserved proteins within cell walls of bacteria/fungi.
- In humans there are 10 TLRs with different binding specificities – they are found on mast cells, macrophages, dendritic cells + epithelial cells
- They are transmembrane proteins, with cytoplasmic domains that are similar to IL-1R1
- Binding causes activation of the cell to produce chemokines + cytokines
  - Also leads to the stimulation of antimicrobial peptides + induction of immune response genes through NK-xB activation
- TLR 1/2 = heterodimer which recognises triacylated lipoproteins
- TLR 2 also recognises peptidoglycan from Gram + bacteria
- TLR 4 – recognises lipopolysaccharide from Gram – bacteria
- TLR 5 – recognises flagellin
- NB: Keratinocytes express TLR 1, 2 (4) + 5, and Langerhans cells express TLR 2 + TLR4

**Complement components**
- The complement cascade may be activated in the innate immune response by either the Lectin or alternative pathway
- It has 3 roles within the innate immune response:
  - Assembly of Membrane attack complex (MAC) → cell lysis
  - Chemotaxis
  - Opsonisation of microbes to assist phagocytosis

**Lipopolysaccharide-binding protein**
- LPS is a pathogen specific pattern molecule
- It binds to lipopolysaccharide binding protein, stimulating CD14 + TLR4
- These leads to the generation of a “danger signal” + production of cytokines

**Antimicrobial peptides (AMP)**
- First line of defence against infectious agents; act both as natural antibiotics + signalling activation of host immune cells
- Directly kill bacteria, fungi + some viruses
- Include the cathelicidin + defensin gene families
- **Cathelicidins** – single gene = Hcap18
  - Have broad spectrum antimicrobial activity, but also chemoattract to neutrophils, macrophages, mast cells + T cells
  - Observed in human epidermal keratinocytes under inflammatory conditions e.g. psoriasis + contact dermatitis
- **Defensins** – comprise 3 families: alpha, beta and omega
  - Only human beta defensins (HBD) have been identified in the epidermis
  - HBD may be upregulated in psoriasis
    - They have broad spectrum antimicrobial activity
- Bind to CCR6 + are chemotactic for immature DC and memory T cells
- HBD2 promotes histamine + PGD2 release by mast cells
- In resting conditions, AMP are produced in the skin at potential sites of entry by bacteria – follicular openings, sweat ducts
  - After injury/inflammation – there is a rapid increase in AMP production
  - The chemotactic activity of IL-37 + HBD2 also increase leukocyte recruitment
- In atopic dermatitis, there is an increased susceptibility to bacterial and viral infection, with a reduced HDB2 + IL37 (increasing susceptibility to Staph + Herpes infections)

The acquired immune response

- Responsible for the establishment of immunological recognition + memory of a specific pathogen
- Its initiation requires signals from the innate system, and the rearrangement of receptor DNA to generate specific recognition receptors
- The system requires: specificity, diversity, memory, self-limitation + tolerance
- Features of the acquired immune response:
  - Secondary response initiated by innate response
  - Generation of specific receptors to recognize bacteria, fungi or viruses
  - Response to peptide/antigen polypeptide sequence
  - Provides help for prolonged immune response
  - Eliminates infected cells
  - Creating of “memory cells”
- B cell receptor stimulation results in B-cell maturation into an antibody producing plasma cell
- T cell receptor stimulation results in the activation of naïve T cells and their proliferation/differentiation into effector cells
- Functions:
  - Recognition of danger signals
  - Generation of foreign peptides
  - Transport + presentation of foreign peptides
  - Maturation of T + B cells
  - Life-long surveillance + response to subsequent infection
- The key players in the skin involved in the acquired immune response: keratinocytes, Langerhans cells, T cells

Keratinocytes

- Efficient factory; phagocytic – constitutively secreting/induced to secrete a large number of cytokines
  - Also can be induced to express HLA-DR (by INF-gamma + IL-8)
  - CD54 expression can also be induced (also known as ICAM-1 – induced by IFN-gamma + TNF-alpha)
- Also role in antigen presentation, but unable to present to T cells
  - In fact, suggest the HLA-DR+ keratinocytes induce intolerance in T cells

Langerhans cell

- Bone marrow derived cell from CD34+ + CLA+ precursor, resident in the suprabasal area of the epidermis
- Represent 2% of the epidermal cells
- Flattened dendrites extend horizontally (covering 25% of the skin surface without interconnecting)
- Role in immune surveillance in the skin; central to sensitisation + elicitation phases of contact allergic dermatitis
  - Therefore target for allogenic skin graft rejection + graft vs. host disease
- Consist of:
The Skin

- CD1a – non-polymorphic, MHC class I like molecule – role in lipid presentation to T cells
- Birbeck granules – rod or racket shaped intracytoplasmic organelles implicated in the endocytic pathway – express Lag antigen
- Langerin CD207 – mannose specific C type lectin expressed on the cytoplasmic membrane and in the Birbeck granule

- In the skin in resting state, the langerhans cells are immature, and lack CD80 +CD86 expression
  - They are activated in antigen processing – uptake antigen by endocytosis + micropinocytosis
- Maturation is stimulated by cytokines, and involves reduced antigen uptake, expression of co-stimulatory molecules, up-regulation of HLA-DR, down-regulation of CD1a + migration to draining lymph nodes
  - Also lose E-cadherin expression
- Cancer surveillance – Langerhans cells are sensitive to UV radiation with a dose-dependent reduction in APC ability
  - UV suppression may cause skin cancer (photocarcinogenesis), and reduces the risk of autoimmune disease to UV-generated neo-antigens in the skin

Contact dermatitis

- This is an acquired sensitivity to haptans (small molecules e.g. Nickel)
- The immune system is triggered to respond at site of contact once memory T cells have been generated
- Summary of pathogenesis:
  - Haptans disguise normal proteins → Langerhans cells see protein as foreign
  - Langerhans cell migrate to lymph nodes and stimulate naïve T cells → production of memory cells
  - Dermal circulating memory cells then respond to the Haptan disguised proteins → attack of normal proteins + damage to surrounding cells

Graft vs Host Disease

- Host dendritic cells expressing self-proteins are involved in the maintenance of tolerance to graft
- In GVH, donor naïve T cells are stimulated to mature by the host DC → mount immune response against host

Failure of skin functions

The Skin 12 – Fernanda Teixeira (f.teixeira@imperial.ac.uk)

Our knowledge of the function of the skin comes from the conditions in which there is partial or total skin failure. While this is not exhaustive, it allows us to build a picture of the important functions of the skin:

- Prevent infection – bacterial, viral, fungal, cancer
- Maintain a barrier – against physical/chemical agents + UV radiation
- Repair injury
- Provide nutrition – Vitamin D, oxygen to the skin
- Thermoregulation – dermal capillaries
- Attraction
- Communicate information about the environment – nerves, chemokines, hormones

Twenty nail dystrophy

- Idiopathic nail dystrophy
- Appears in early childhood.
- Presents with: Excessive ridging, with longitudinal striations and discolouration.
- The nails very slowly return to normality.
- This condition is not seen in adults.
Hypohidrotic ectodermal dysplasia
- X-linked recessive or autosomal dominant (2q11-13)
- Diagnosis: skin biopsy (rudimentary sweat glands)
- Presents with:
  - Hypotrichosis – hair loss
  - Anodontia – absence of teeth
  - Hypohidrosis – diminished sweating
  - Prominent supraorbital ridge
  - Thin lower face
- In infants, may present with intermittent hyperperexia (which may lead to seizures + neurological sequelae)
- Mortality rate ~30%

Albinism
- Cause
  - Disruption of melanocyte migration
  - Disruption of melanin synthesis (oculo-cutaneous albinism)
  - Disruption of melanosome formation
  - Disruption of transfer of melanosomes to keratinocytes
- There are 4 types of oculocutaneous albinism, 40% caused by mutations in tyrosinase genes + 50% in P gene (“yellow albinos”)

Vitiligo
- Caused by Mutations in the NALP1 gene (17p13)
- Role of gene: Regulates inflammation and cell death
  - NALP 1 expressed in T lymphocytes and Langerhans cells
  - Products: Caspases 1 and 5, that activate IL 1 - an inflammatory cytokine
- Presents with patches of discoloration of the skin

Toxic Epidermal Necrolysis (TEN)
- Acute severe bullous cutaneous disease characterised by extensive areas of skin necrosis
- Potentially life-threatening – most commonly drug induced (95%)
- Other aetiologies include infection + malignancy
- Clinical presentation:
  - Associated with an 8-12day acute phase – persistent fevers, generalised epidermal sloughing + mucous membrane involvement
    - Complications include stomatitis + mucositis – both painful and hinder oral intake (increases risk of dehydration + malnutrition)
  - The conjunctivae are commonly affected 1-3 days prior to appearance of skin lesions (red macules blisters → sheetlike epidermal detachment)
  - All mucous membranes can become denuded (loss of epidermis), including buccal, nasal, pharyngeal, tracheobronchial, oesophageal, perineal, urethral + anal mucosa
  - Common complications: skin infection, excess electrolyte loss + dehydration, hypothermia, protein loss, bacterial sepsis + renal tubular necrosis
- Treatment: remove underlying cause + supportive measures to prevent possible complications
  - Treated like burns patients
- Pathophysiology: (not fully understood) – immune-related cytotoxic reaction aimed at destroying keratinocytes expressing a foreign antigen
Also associated with over expression of TNF-alpha in the epidermis → direct or indirect (via cytotoxic T cell) epidermal apoptosis

**Prognosis:**
- 10-70% mortality, depending on quality of care + rapidity of treatment initiation
- Morbidity depends on treatment aggressiveness
- Associated with slow healing + recovery of 3-6 weeks

**Erythroderma**
- **Definition:** an erythematous dermatitis involving 90% or more of the cutaneous surface
  - Associated with extensive desquamation in some cases, which may develop as a result of primary dermatitis.
- **Causes** include: idiopathic, drug allergy, lymphoma/leukaemia, atopic dermatitis, psoriasis, contact dermatitis, seborrheic dermatitis (order of decreasing prevalence)
- **Pathophysiology:** the erythema is due to an increased skin blood perfusion from dilation of the dermal capillaries
  - This results in temperature dysregulation and possible cardiac failure
  - BMR rises to compensate for heat loss, with fluid loss increasing in proportion to this
- **Clinical presentation:** The situation is similar to that observed in patients following burns – negative nitrogen balance characterised by edema, hypoalbuminaemia + loss of muscle mass
- **Treatment:**
  - Discontinue all unnecessary medications
  - Monitor/control fluid intake
  - Monitor body temperature
  - Institute systemic antibodies if signs of secondary infection
  - Antihistamines reduce pruritus (itchiness)
  - Plasma infusion + possible nutritional intervention
- **Prognosis:** depends on underlying aetiology. Overall mortality 20-40%