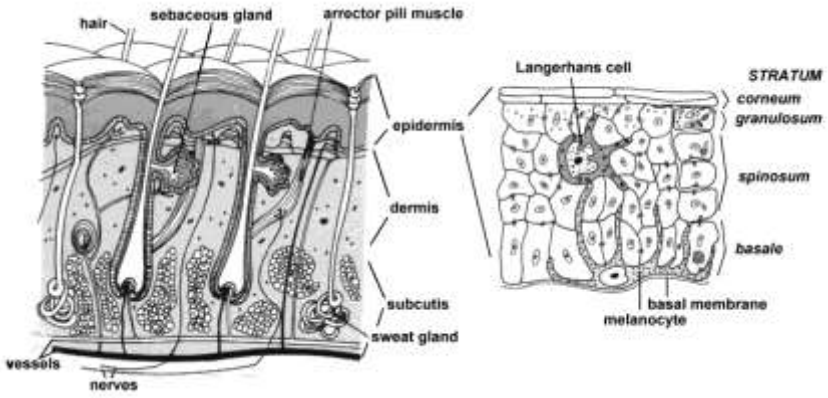
INTERGUMENT LEVEL 200 (Biochemistry)

OCK HAGAN

Objectives

- Composition of the skin
- Melanin synthesis, function and regulation
- Biochemistry of skin aging
- Clinical correlations

Structure of the skin



- the *epidermis*, which provides waterproofing and serves as a barrier to infection;
- Main cellular components – keratinocytes and melanocytes

- the *dermis* is responsible for the tensile strength of skin. Its main functions are to regulate temperature and to supply the epidermis with nutrient-saturated blood
- Main cell type is fibroblast. Metabolism of collagen, elastin, GAGs etc

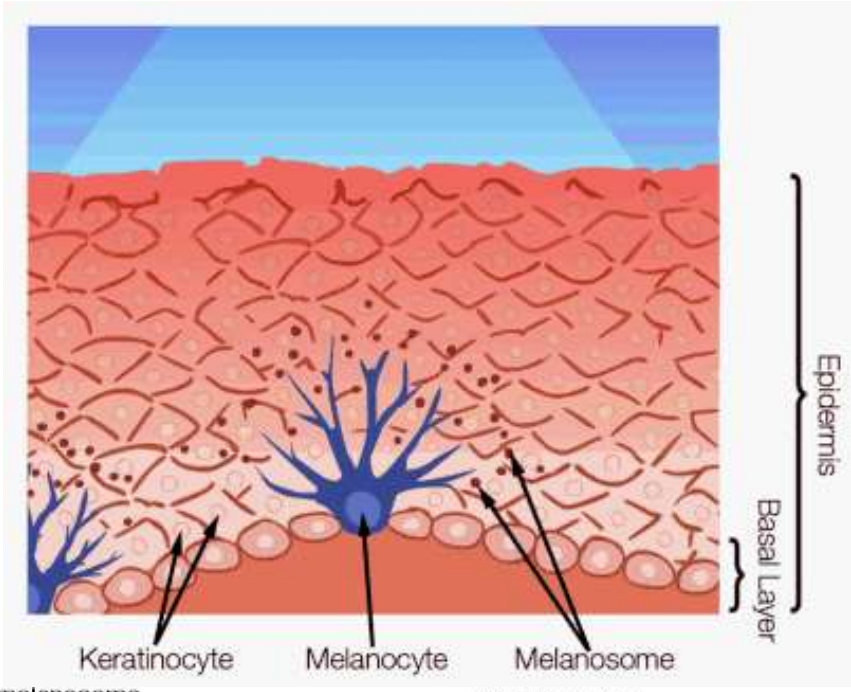
Extracellular matrix (please refer to last semester)

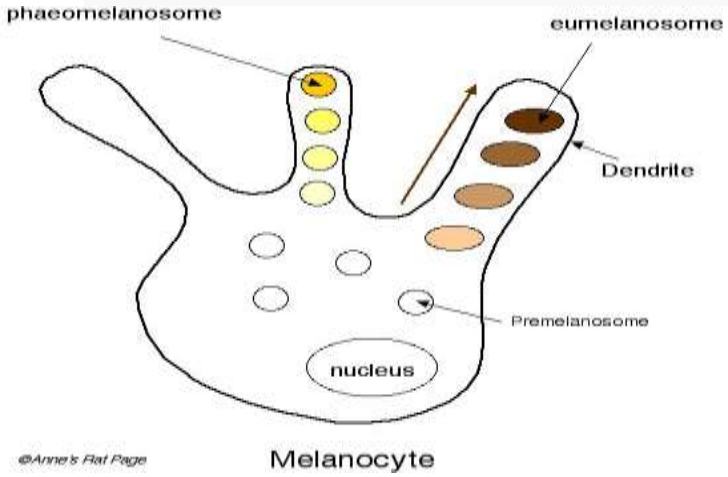
- Secreted by fibroblast
- Collagen- type I makes about 90%. Type 3 makes up about 9%. Others include type V and VI
- Collagen is responsible for skin tensile strength and tissue integrity
- Elastin- Provides the skin with elasticity and resilience. Microfibrils (review notes on microfibrils and Marfan syndrome)
- Glycosaminoglycans- predominantly chondroitin sulfate, dermatan sulfate, keratin sulfate, heparan sulfate, and heparin
- Proteoglycans- Predominantly Vesicans and perlecans

Skin Pigmentation

Melanocytes

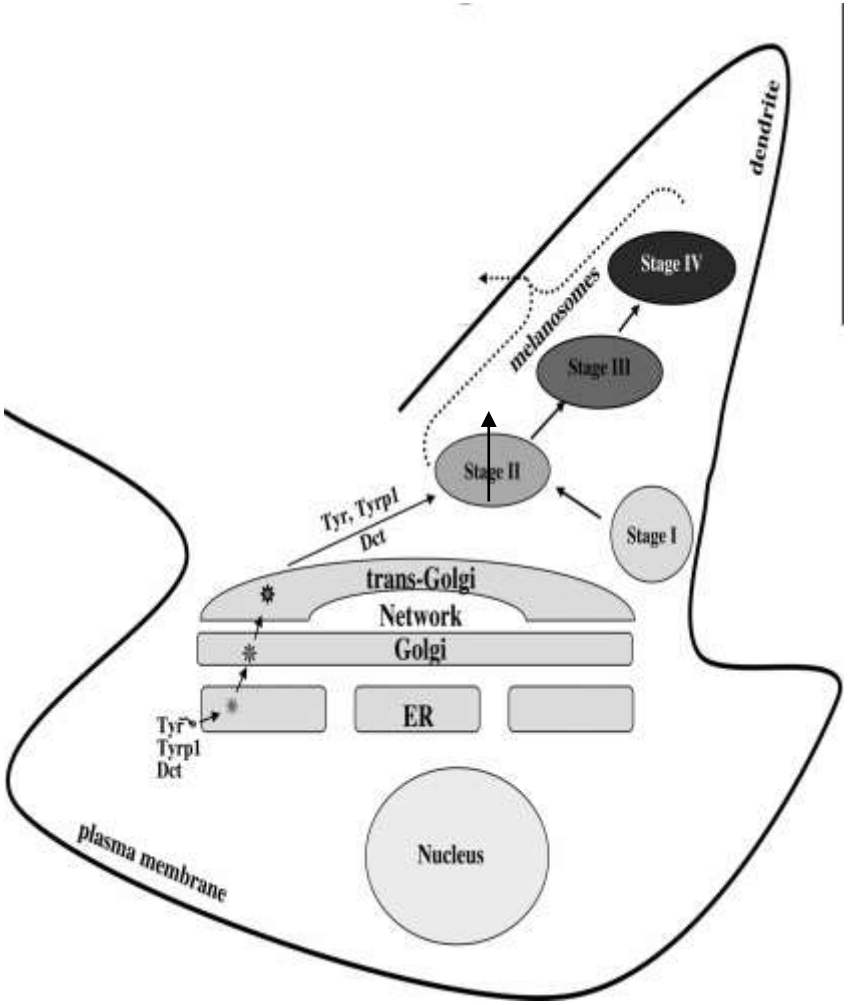
- Specialised cells for producing melanin derived from neural crest
- Precursor-melanoblast
- Found in association with keratinocytes.
- 1 melanocyte in contact with ~ 40 keratinocytes. This is called epidermal melanin unit





Formation of melanosomes

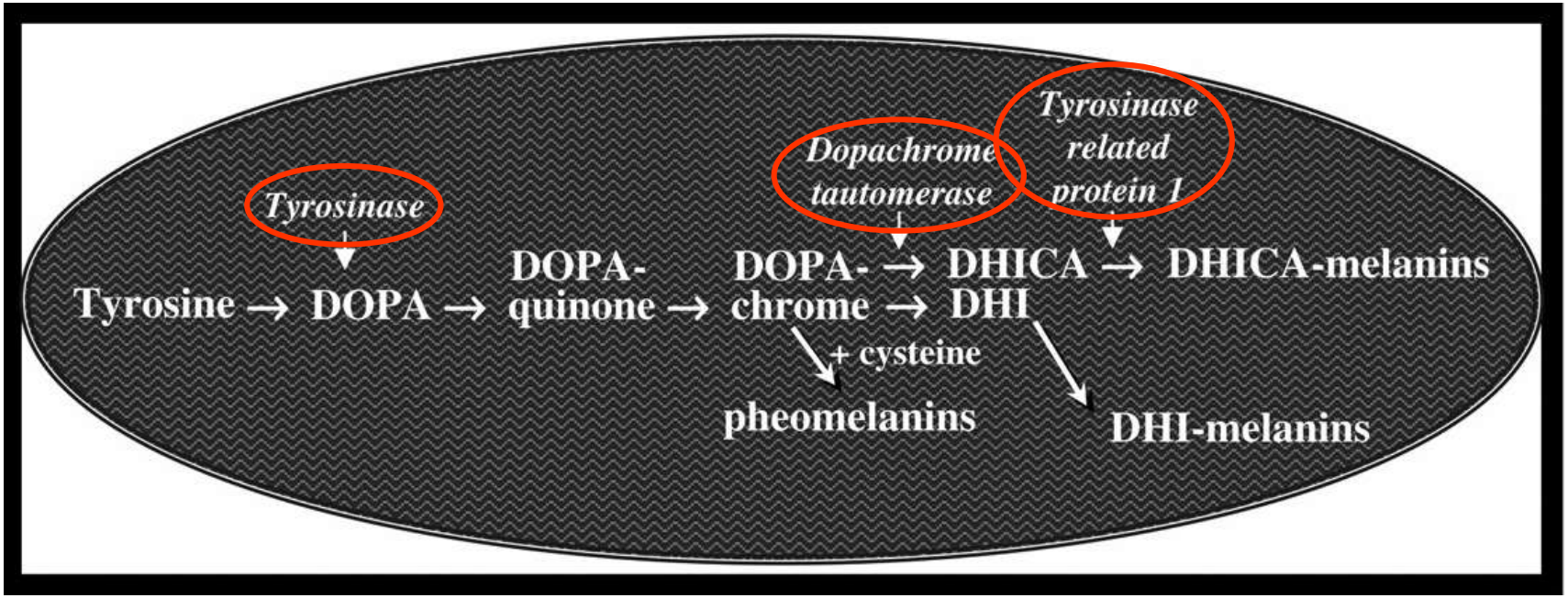
- Melanosomes - *elliptic membrane-bound organelles* (melanin synthesis).
- Synthesis of matrix proteins and *tyrosinase* (TYR) on the rough endoplasmic reticulum.
- TYR undergoes post translational modification in the form of glycosylation in the Golgi apparatus.
- Fusion of premelanosomes with coated vesicles containing tyrosinase - formation of the melanosome.
- Melanosome migrates into one of the dendrites of the melanocyte → transfer to a neighboring keratinocyte.



Production of Melanin

- Three enzymes in melanosomes whih absolutely required for different melanin type synthesis
  - *tyrosinase* (TYR) – responsible for critical step of melanogenesis (tyrosine hydroxylation)
  - *tyrosinase-related protein 1* (TYR1) and *DOPAchrome tautomerase*

(DHI = 5,6-dihydroxyindole; DHICA = 5,6-dihydroxyindole-2-carboxylic acid)



Reaction Summary

- Tyrosine → DOPA → dopaquinone

- Dopaquinone can combine with cysteine by two pathways to benzothiazines and pheomelanins

- Dopaquinone + cysteine → 5-S-cysteinyldopa → benzothiazine intermediate → pheomelanin
- Dopaquinone + cysteine → 2-S-cysteinyldopa → benzothiazine intermediate → pheomelanin

Also, dopaquinone can be converted to leucodopachrome and follow two more pathways to the eumelanins

- Dopaquinone → leucodopachrome → dopachrome → 5,6-dihydroxyindole-2-carboxylic acid → quinone → eumelanin
- Dopaquinone → leucodopachrome → dopachrome → 5,6-dihydroxyindole → quinone → eumelanin

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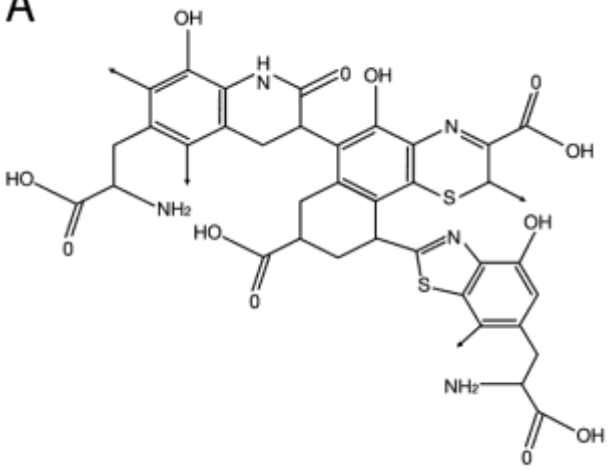
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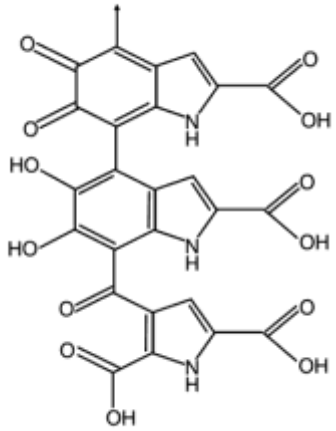
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Melanin

- Melanins are polymorphous and multifunctional polymers of eumelanin, pheomelanin, mixed melanins (a combination of the two); and neuromelanin

Eumelanin Brown-black.

Black eumelanin produces black colour when in abundance and grey

when rare. Found mainly in non-European

Brown eumalanin.

Mainly in people of European descent. Gives brown colour (hair) in abundance and in small amounts light brown or blonds

- Phaeomelanin – Produces reddish colour. In hair it is the main colouring agent in ginger hair. Protective to the body by binding cation, anions, drugs and chemicals

- Neuromelanin is produced in dopaminergic neurons of substantia nigra. It can chelate toxin like Cd, Pb, Hg

Number of melanocytes in human skin of all types is essentially constant, the number, size, and manner in which melanosomes are distributed within keratinocytes vary-leading colour variations in humans and also different parts of the body

Factors Involve in Melanin Production

- The melanin granules accumulate above the nuclei of keratinocytes and absorb harmful UV-R before it can reach the nucleus and damage the DNA.

- Quick responds of the melanocyte-keratinocyte complex to a wide range of environmental stimuli (paracrine and/or autocrine) - to UV-R, melanocyte-stimulating hormone (MSH), endothelins, growth factors, cytokines, *etc.*

- UV-R exposure → melanocytes increase their expression of proopiomelanocortin (POMC, the precursor of MSH) and its receptor melanocortin 1 receptor (MC1-R), TYR and TYRP1

- Fibroblasts (possibly other cells in skin) - produce cytokines, growth factors, and inflammatory mediators that can increase melanin production and/or stimulate melanin transfer to keratinocytes by melanocytes.

- Certain drugs can cause hyperpigmentation of the skin eg chloroquine, levodopa (parkinson's), antibiotics (sulfonamides, tetracycline)

Melanin and Humans

- Has photochemical properties that helps to protect human tissues from harmful UV light
- When a human skin is exposed to sunlight-it initially turns reddish to brownish as more melanin is synthesised. Tanning
- UV light causes mutations in DNA especially pyrimidine dimers eg C-C, T-T, C-T. These mutations can lead to formation of melanomas when unrepaired

- Lack of melanin that result from lack of enzymes leads to a recessively inherited oculocutaneous albinism

- Freckles, birth and moles result from over concentration of melanin at particular spots.
- Reduced levels of neuromelanin is found in Parkinson's disease

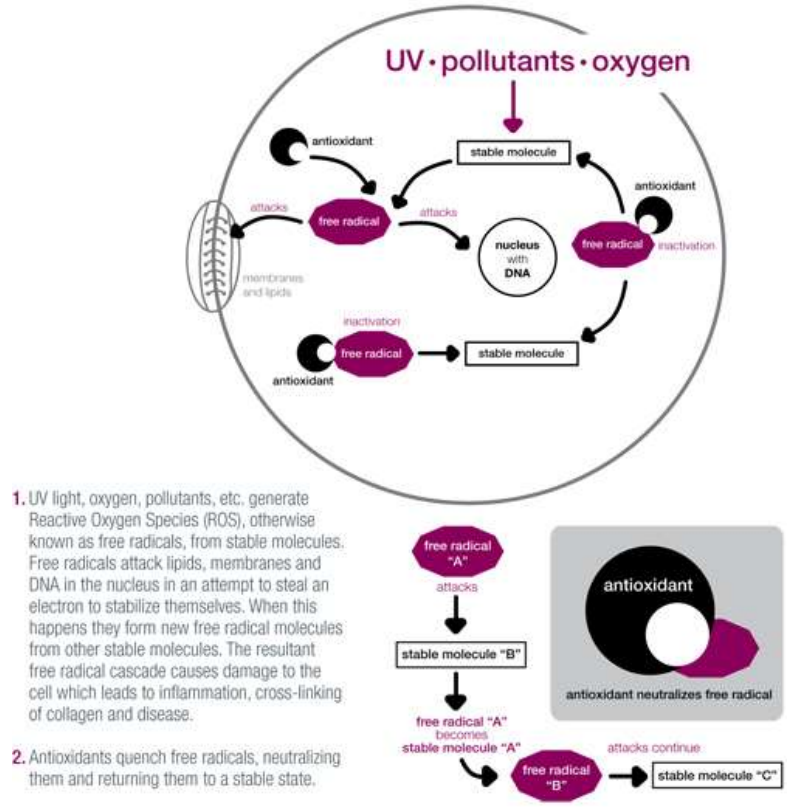
- Higher levels of eumelanin can cause Vit D deficiency especially for dark skinned individuals in temperate regions

SKIN AND AGING

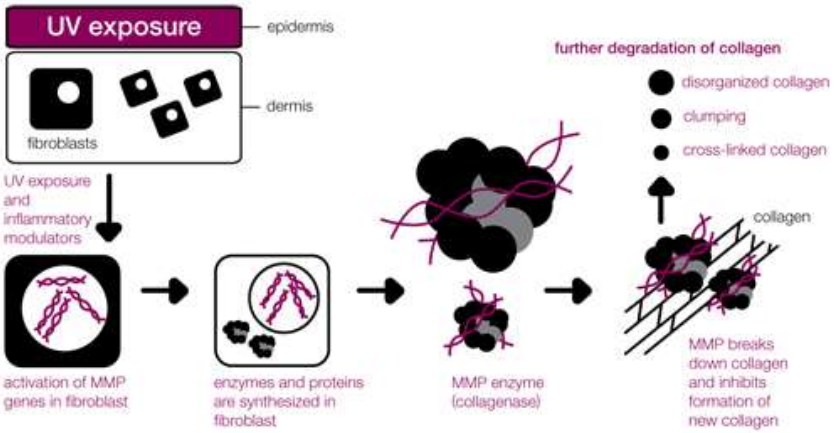
Biochemistry of skin aging

- Age related skin aging is due to
- 1. intrinsic factors (genetically programmed cell changes. Reactive oxygen species. Glycated proteins- Advance glycation end-products AGEs)
- 2. Extrinsic (about 90 due to UV, others include pollutants, oxygen species

UV light and ROS

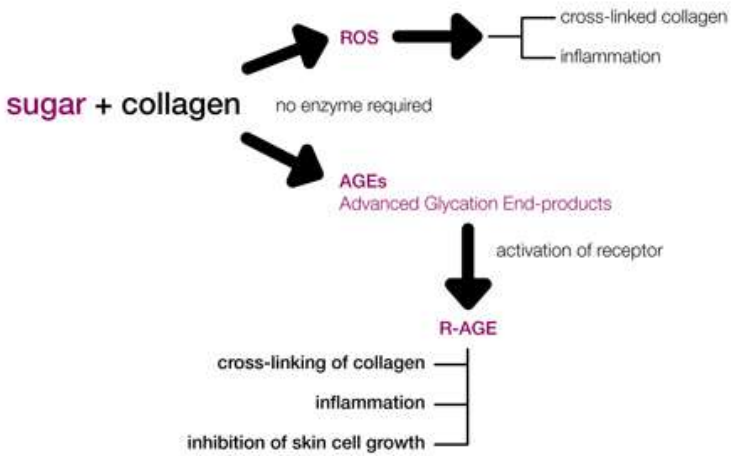


Matrix Metalloproteinases



1. MMP enzymes are activated within the fibroblast nucleus by UV light or inflammatory modulators.
2. MMPs, such as collagenase, are synthesized in the fibroblast.
3. MMPs (collagenase) break down collagen and inhibit formation of new collagen.
4. Collagen is degraded into gelatinous peptides that are further degraded by other MMPs. Cross-linking of collagen also occurs, causing wrinkling and stiffening of skin.

AGEs



1. When sugar comes in contact with a protein (such as collagen), it immediately reacts. This generates Reactive Oxygen Species (ROS – free radicals), which leads to a cross-linking of collagen and inflammation.
2. Advanced Glycation End-products (AGEs) are formed, and bond with a Receptor on the cell to form Receptor-AGE (R-AGEs).
3. This causes inflammation, inhibits skin cell growth and contributes to cross-linking of collagen.

Effect of aging on the skin

1. Wrinkle. Due to loss of collagen in dermis. Increased fibroblast synthesis of MMP which destroys collagen and elastin+reduced synthesis of collagen by senescent fibroblast
2. Slackness- due to loss of skin elasticity+resilience due to elastin destruction

3 .Increased transparency-reduced melanocytes= reduced melanin

4. Dehydration-reduction in synthesis of GAGs like hyaluronic acid (that bind water). Also due to loss of subcutaneous fat

5. Increased susceptibility to tumours eg melanomas due to diminshed protection from UV

6. Reduced numbers of melanocytes, but the remaining becomes larger in size. They also become erratic leading to hyperpigmentation

7.