Biochemistry of Skin

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Objective

- Structure and Function of skin biomolecules
- Skin junction and diseases
- Skin Melanogenesis: mechanism and functions
- Skin Melanogenesis and associated disorders
- Skin ageing
- Nutrition and skin
Functions of Skin

Protection:

Sensation:

Heat regulation:

Control of evaporation:

Storage and synthesis:

Excretion: Absorption:

Water resistance:
This figure shows the conversion of 7-dehydrocholesterol to vitamin D in the skin and its transfer to the blood where it is complexes to a Vitamin D binding protein (DBP).
A heparan/chondroitin sulfate proteoglycan form of CD44, Epican, is expressed on the surface of keratinocytes from the basal layer to the granular layer of the epidermis.

Intercellular spaces between keratinocytes

- **Lipid leaflets** (barrier lipid) → **Glycolipids, Sterols, Phospholipids**

- **Proteoglycans** → Epican; HS/CS proteoglycan,

  Epican is a heparan/chondroitin sulfate proteoglycan form of CD44 and is expressed on the surface of keratinocytes from the basal layer to the granular layer of the epidermis.
One way to understand the barrier function of the stratum corneum is to consider it as a brick wall. The corneocytes (made of tough protein) form the bricks and between these a double layer of lipids (fatty materials) and water make up the mortar. Some lipids have a hard crystal-like structure and are impermeable to water. Others lipids do not have this structure and they allow water to percolate through. So, the barrier is semi-permeable.

http://www.hse.gov.uk/skin/professional/causes/understand.htm
Dermal Biomeolecules (Dermal ECM)
Dermal Biomeolecules (Dermal ECM)

Fibrous protein:
- Collagens
- Elastin

Ground substance:
- Glycosaminoglycans → Hyaluronan
- Proteoglycan
  - Small DSPG
  - Large CSPG
- Glycoproteins and enzymes; MMPs
Dermal collagens: a major component of skin

- type I ~ 85-90%
- type III ~ 8-11% (more prominent in fetal skin and early stage of wound healing)
- type V ~ 2-4%
- small proportions; type VI, XII, XIII
Collagen peptide

It is also called collagen hydrolysate, gelatine, gelatine hydrolysate and hydrolyzed gelatine.
Collagen peptide biological activities

Bovine hide CH(GELTA® CPB1000) stimulated cell proliferation, HAS2 mRNA expression and hyaluronan production in human dermal fibroblasts


After 4 weeks of daily ingestion of CH, it promoted stimulatory effects on skin tissue, increasing expression levels of type I and type IV collagen


Collagen hydrolysate ingestion inhibited ultraviolet B-induced decreased of type I collagen, thus improving skin conditions in mice

Side Effects of Taking Collagen Supplements

• **High Calcium Levels** ➔ hypercalcemia. Too much calcium in the body causes constipation, bone pain, fatigue, nausea, vomiting and abnormal heart rhythms.

• **Hypersensitivity Reactions** ➔ abnormal response of the immune system against allergens.
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elastic fiber

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STRETCH

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RELAX

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single elastin molecule

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cross-link
Dermal Biome molecules (Dermal ECM)

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- Elastin

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- Proteoglycan ➔ Small DSPG
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Glycosaminoglycans (GAGs)

* Jelly-like property

* Heteropolysaccharide

* No sulfate in the chain

* No covalent bonding with protein to form proteoglycan

* High content in child and gradually decrease with age
Loss of HA associated with skin aging

Skin with **high** HA content

Skin with **low** HA content
Bacterial Hyaluronidase

Bacterial hyaluronidases, enzymes capable of breaking down hyaluronate, are produced by a number of pathogenic Gram-positive bacteria that initiate infections at the skin or mucosal surfaces.
Proteoglycan
Model of human decorin with triple helix of human collagen
Decorin knock-out mice
The hypodermis is the innermost and thickest layer of the skin. It invaginates into the dermis and is attached to the latter, immediately above it, by collagen and elastin fibres.

It is essentially composed of a type of cells specialized in accumulating and storing fats, known as adipocytes.

These cells are grouped together in lobules separated by connective tissue.
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Epidermis

Dermis
Skin Junction

- Dermoepidermal Junction
- Hemidesmosomal Junction
- Desmosomal Junction
Skin Junction

- Basal keratinocytes
- Cytoskeleton
- Hemidesmosome
- Lamina lucida
- Anchoring filaments
- Lamina densa
- Anchoring fibrils
- Interstitial collagen
- Desmosome
- Keratin 5 and 14
- Envolakin, Periplakin
- Desmoplakin, Cadherins
- Simplex
- Hemidesmosomal
- Junctional
- Dystrophic
- BPAG1, Plectin
- BPAG2, α6β4 integrin
- Laminin 5, Laminin 6
- Laminin 1, Nidogen
- Type IV collagen
- Type VII collagen
Dermoepidermal Junction

Anatomy of Normal Skin

- Dead cells
- Keratinocytes
- Basal epidermal cells
- Basement membrane
- Nerve
- Basal epidermal cells
- Epidermis
- Papillary
- Dermis
- Reticular
- Fat layer

- Epithelial cell
- Macrophage
- Fibroblast
- Neutrophil
- Collagen
- Matrix (glycosaminoglycans)
- Matrix protein (fibrinectin)
Basement Membrane
Basal membrane (Basement Membrane)

Anchoring fibrils

Type IV collagen

Autoantigens

Hemidesmosome

Lamina lucida

Anchoring filaments

Lamina densa

Sublamina densa

Anchoring fibrils

Collagen bundles

Type VII collagen

Basal membrane (Basement Membrane)
Epidermolysis bullosa dystrophica (Dystrophic EB; DEB)

- The deficiency in anchoring fibrils impairs the adherence between the epidermis and the underlying dermis.

- The skin of DEB patients is thus highly susceptible to severe blistering.

- Open wounds on the skin heal slowly or not at all, and are particularly susceptible to infection.

- The chronic inflammation leads to errors in the DNA of the affected skin cells, which in turn causes squamous cell carcinoma (SCC). The majority of these patients die before the age of 30.
Epidermolysis bullosa dystrophica (Dystrophic EB; DEB)
Skin Junction
Bullous pemphigoid

Bullous pemphigoid is characterized by the presence of immunoglobulin autoantibodies specific for the hemidesmosomal bullous pemphigoid antigens BP230 (BPAg1) and BP180 (BPAg2).
Skin Junction

- Basal keratinocytes
- Cytoskeleton
- Hemidesmosome
- Lamina lucida
- Anchoring filaments
- Lamina densa
- Anchoring fibrils
- Interstitial collagen
- Desmosome
- Keratin 5 and 14
- Envolakin, Periplakin
- Desmoplakin, Cadherins

- Basement membrane zone
- Simplex
- Hemidesmosomal
- Junctional
- Dystrophic
- BPAG1, Plectin
- BPAG2, α6β4 integrin
- Laminin 5, Laminin 6
- Laminin 1, Nidogen
- Type IV collagen
- Type VII collagen
Disturbed desmosomal adhesion contributes to the pathogenesis of a number of diseases such as pemphigus vulgaris, which is caused by autoantibodies against desmosomal cadherins or viral infection such as herpes simplex infections.
Cosmetic applications of skin biomolecules: anti-wrinkle

Most fillers replace the host components of the skin: collagen, hyaluronic acid, and elastin.
Collagen: collagen makes up 75% of our skin protein. From around the age of 25 Collagen levels start to deplete at an astonishing rate of 1.5% every year.
**Bovine Collagen Fillers**

Bovine collagen is processed from the skin of cows. Approved in the 1980s as a wrinkle treatment, bovine collagen is still widely used as a cosmetic filler. It can cause allergic reactions. The body naturally breaks down injected collagen, so you need to get collagen injections two to four times per year to maintain results.

**Human Collagen Fillers**

Human collagen, made from cultures of human cells, became available in 2002. Human collagen causes dramatically fewer allergic reactions than bovine collagen. It is more expensive than bovine collagen, and injections also need to be repeated every three to six months.
Hyaluronic acid:
its molecules bind to water in the skin, hydrating and firming its structure, indicate that HA injections induce collagen production, stimulation of growth factors and inhibition of collagen breakdown, lasting for 4-12 months. Allergic reactions are very rare.

Fat Injection Fillers
Fat injections involve removing small amounts of fat from the thighs, belly, or buttocks and injecting it under the skin of the face. The fat expands the skin, shrinking wrinkles. Because it is your own tissue, there can be no allergic reaction.
Derived from Botulinum toxin type A, Botox blocks nerve impulses within facial muscles, thus smoothing wrinkles by temporarily paralyzing the muscles. It is currently being used to treat deep lines between the brows, forehead lines that cause people to always look angry or annoyed. It reduces the appearance of crow’s feet that appear at the side of the eyes. It also relaxes tense neck muscles which help diminish the extent of neck bands. Some doctors have successfully used Botox Cosmetic to lessen the downward pull of the corner of the mouth. The process takes about ten minutes and effects last about three to four months.

Botox Cosmetic is a protein that is injected into muscles to relax them, smoothing lines and wrinkles caused by repeated facial movements.
Skin Pigmentation (Melanogenesis)
Skin Pigmentation (Melanogenesis)

**MC1R**
(melanocortin-1 receptor)

**MITF**
(microphthalmia transcription factor)

**TRYP1**: Tyrosinase-related protein 1
Skin Pigmentation (Melanogenesis)

- Nucleus
- ER (Endoplasmic Reticulum)
- Golgi
- Melanosomes
- Phosphorylation
- Melanin synthesis
- Ubiquitylation
- Endosomal/lysosomal system
- Proteasome
- ER-associated degradation
- Proteolysis
Melanin formation and melanin storage

1. Melanocyte
2. Dendrites
3. Cell nucleus

Melanin
Superoxide anion elevates tyrosinase activity.
Simplified Pathway of Melanin Formation

- Tyrosine
- Dopa
- Dopaquinone
- Dopachrome
  - Dihydroxylindone-2 Carboxyl Acid (DHICA)
  - EUMELANIN
  - Glutathionedopa
  - PHAEOMELANIN

Glutathione (in increased dose)
### Complexion and Biology

#### Figure 1: Schematic of Human Skin Architecture from Light- and Dark-Pigmented Skin Types

- **Light UV** to **Dark UV**

#### Table: Melanin Mixture and Skin Types

<table>
<thead>
<tr>
<th></th>
<th><strong>African</strong></th>
<th><strong>Oriental</strong></th>
<th><strong>Caucasian</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Melanin Mixture</strong></td>
<td>Pheomelanine</td>
<td>Pheomelanine</td>
<td>Pheomelanine</td>
</tr>
<tr>
<td></td>
<td>Eumelanine</td>
<td>Eumelanine</td>
<td>Eumelanine</td>
</tr>
</tbody>
</table>

#### Table: Melanin Grains in the Epidermis

<table>
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<th><strong>Caucasian</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of Free Melanin Grains in the Epidermis</strong></td>
<td>Complexed</td>
<td>Complexed</td>
<td>Complexed</td>
</tr>
<tr>
<td></td>
<td>Free</td>
<td>Free</td>
<td>Free</td>
</tr>
</tbody>
</table>

#### Table: Melanin Grain Morphology

- **Melanin Morphology**
  - **Grain**
  - **African**: 1 x 0.5 nm
  - **Oriental**: 0.6 x 0.3 nm
  - **Caucasian**: 0.5 x 0.3 nm

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*Hypothetical schematic and data for illustration purposes.*
Target mechanism of Whitening agents
endocytotic activity of keratinocyte

niacinamide
The mechanism of skin pigmentation after UV irradiation

Expert Reviews in Molecular Medicine © 2002 Cambridge University Press
DCT = dopachrome tautomerase
Inhibition by Licorice, Kogic acid, Vit C

TRYP1: Tyrosinase-related protein 1
tyrosinase-related protein 1 (TYRP1), and dopachrome tautomerase (DCT),

http://www.nature.com/milestones/skinbio4/full/skinbio20114a.html
Melanogenesis also serves as a major antioxidant defence mechanism of skin as melanocytes, the specialised cells that produce melanins, neutralise the deleterious effects of active oxygen species and free radicals.
Hyperpigmentation

• Increase in MC-1R on melanocyte membrane
• Increase in MC-1R and melanocyte proliferation
• Activation the mechanism of action of melanogenesis
Hyperpigmentation related diseases

- Acanthosis nigricans
- Cushing's disease
- Addison's disease
- Linea nigra
- Pellagra
- Some cancer drug: cisplatin
Hyperpigmentation in Acanthosis nigricans (insulin resistance)
Hyperpigmentation in Addison's disease
(increase synthesis MSH)
Hyperpigmentation in Cushing’s syndrome
(increase synthesis MSH)
Linea nigra
Post Inflammatory Hyperpigmentation (PIH) after Photodynamic Therapy treatment for acne.
Hypopigmentation

• Decrease in the number of melanocyte
• Lack of tyrosine
**Phenylalanine hydroxylase (PAH)**

**Phenylketonuria (PKU)**

**Albinism**

* tyrosinase
Biochemistry of Skin Aging

- Intrinsic Aging
- Extrinsic or photo aging
**20s**
Free Radicals Attack Surface Environmental Damage is High

**30s**
First Signs of Aging Appear Dull, Lackless, Lifeless Skin

**40s**
Significant dullness, aging & dark spots. Skin sensitivity.

**50+**
Significant tension decrease. Moisture retention slowing.

**Constant exposure to the sun & fast life style leads to skins premature aging.**

Skin regeneration is reducing leading to dull complexion & uneven skin tone. Use of harsh skin care can become apparent. Elastin degradation can show first signs of aging.

Skin thinning can cause sensitivity, redness, dry, oily, sudden redness. Photo aging appears - dark spots - more prominent signs of aging appear.

Decrease in surface tension impairs skin structure and ability to defend itself. Barrier lessens leading to less efficiency in retaining moisture. Combined with excessive dryness sometimes accompanied by adult acne.
Biochemistry of Skin Aging

Effects on cells → Decrease in cell apoptosis

Effects on skin ECM

Effects on proteins

Effects on lipids

Effects on DNA

Effects on proteoglycans and GAGs
Skin aging

Acute effect

Activation and proliferation

Infiltrating neutrophils

ECM degeneration

Incomplete repair of the ECM

Chronic effect

Solar elastosis

Accumulation of ECM damage

Solar elastosis

Chemokines

MMPs

ROS

Elastase

MMPs

Inflammatory cells

Cytokine

Keratinocyte
Advanced Glycation Ends products (AGEs)
Exogenous / Endogenous Stress

DNA

Telomerase interactions

Mitochondrial DNA common deletion

DNA-Protein cross links

Decrease of DNA repair mechanisms
- base excision repair
- nucleotide excision repair

Immune system

Thymine derivatives

DNA replication

Altered Transcription

Genome instability

8 oxoguanine

Accumulation in mitochondrial DNA

Mitochondrial dysfunction

Energetic Crisis
Nutrition and Skin

- EFA
- Water
- Minerals
- Proteins
- Vitamins

Nutrients for healthy skin include:

- EFA (Essential Fatty Acids)
- Water
- Minerals
- Proteins
- Vitamins
Pellagra: Niacin def.
Vitamin B3, also known as Niacin or Nicotinic acid, is a water-soluble B-vitamin that plays a significant role in energy metabolism and maintaining healthy skin.

Niacin is synthesized inside the body by the liver from the essential amino acid tryptophan.

Niacin is lost with cooking. Also, alcohol inhibits vitamin B3 absorption.

*Corn is the only grain low in niacin.
Fig. 1: Principle Action of B3 Metabolism in the Body

Tryptophan

Quinolinate

Nicotinate

Nicotinamide

PRPP

NaMN

ATP

Deamido-NAD

Glutamine

ATP

NAD

ATP

NADP

H₂O

1 - Methyl nicotinamide

1 - Methyl-3-carboxamido-6-pyridone

O₂

SAM

ADPR

H₂O

NMN

PRPP

H₂O
Deficiency of vitamin B
(Vit B2, Vit B5, Vit B9 or vit B12)

• hair changes, and recurrent angular stomatitis
Hair loss (alopecia) caused by biotin (vit B7) deficiency
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Dermis