SESSION 7: SKIN HEALTH AND GENETICS

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REVIEW FROM LECTURES 1-6

- Genetics of Autism
- CYP2D6 and codeine
- MAOA – the criminal gene
- Cannabis and heart disease
- BPA and Cancer
- Endocannabinoid Deficiency
- Cannabis and addiction/food
- CYP2A6 and lung cancer
- Estrogen Metabolism
- Depression and Serotonin Genetics
- Dopamine Genetics and ADHD
- CYP2C9-Warfarin-Vitamin K
- ALDH2 genetics and alcohol flush
- Cannabinoids – THC, CBD
- Type 2 diabetes genetics
- CYP3A4 and Graperfruit juice (implications)
- COMT and Dopamine
- NAT, Red Meat and Cancer Risk

SESSIONS 1 - 8

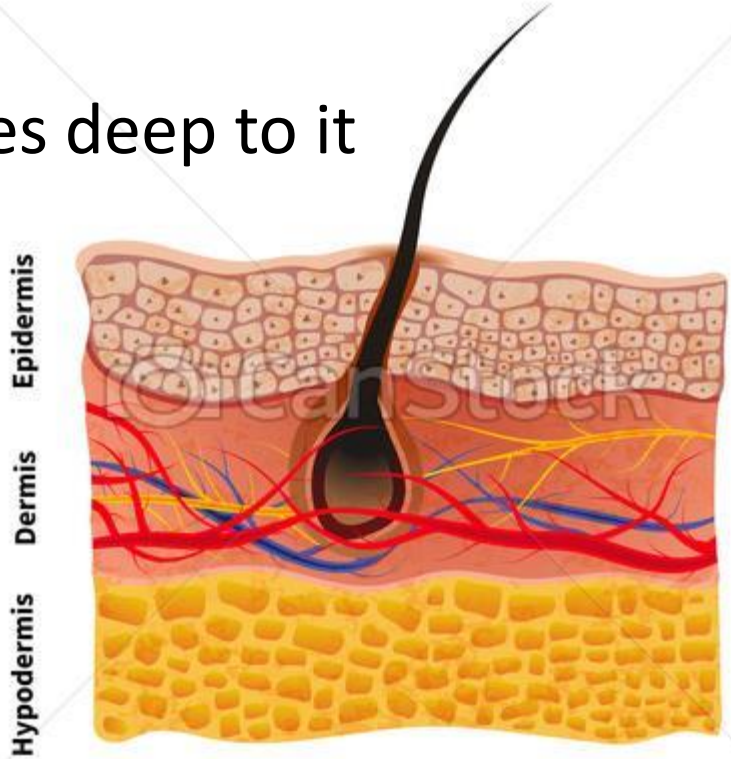
Session	Topic	Evaluations
1	INTRODUCTION TO MOLECULAR GENETICS, MOLECULAR BIOLOGY AND HUMAN GENETICS	Discussion – Participation
2	NUTRITIONAL AND DIETARY GENETICS: HOW DO OUR GENES REGULATE OUR NUTRITION AND NUTRITIONAL HEALTH?	Discussion - Participation
3.	FITNESS GENETICS AND GENETICS OF CHRONIC DISEASES: HOW DO OUR GENES REGULATE OUR RESPONSE TO EXERCISE AND HOW DO GENES REGULATE THE RISK OF CHRONIC METABOLIC DISORDERS?	Discussion - Participation
4.	DETOXIFICATION GENETICS: HOW DO OUR GENES REGULATE DETOXIFICATION WHICH INDIRECTLY IMPACTS OVERALL HEALTH AND DISEASE RISK?	Discussion - Participation
5.	NEUROGENETICS: HOW DO OUR GENES REGULATE THE SYNTHESIS AND BREAKDOWN OF NEUROTRANSMITTERS AND ITS IMPACT ON OUR HEALTH ?	Take home exam on sections 1-5, due during session 6
6.	GENETICS OF ENDOCANNABINOID PATHWAYS: HOW DO OUR GENES REGULATE THE RESPONSE TO CANNABIS?	Discussion - Participation
7.	SKIN GENETICS: HOW DO OUR GENES REGULATE OUR SKIN HEALTH ?	Take home assignment – due during session 8
8.	DISCUSSION AND PRACTICAL APPLICATIONS OF GENETIC TESTS DISCUSSED IN SESSIONS 2-7	Discussion - Participation

SESSION OBJECTIVES:

- Skin biology
- Inflammatory disorders of the skin and underlying genetics
- Skin aging and genetics
- Skin nutrition and genetics
- Skin pigmentation and genetics
- Skin genetics and cancer

The Integumentary System

- Integument is skin
- Skin and its appendages (hair, nails) make up the integumentary system
- A fatty layer (hypodermis) lies deep to it
- Two distinct regions
  - Epidermis
  - Dermis



Functions of skin

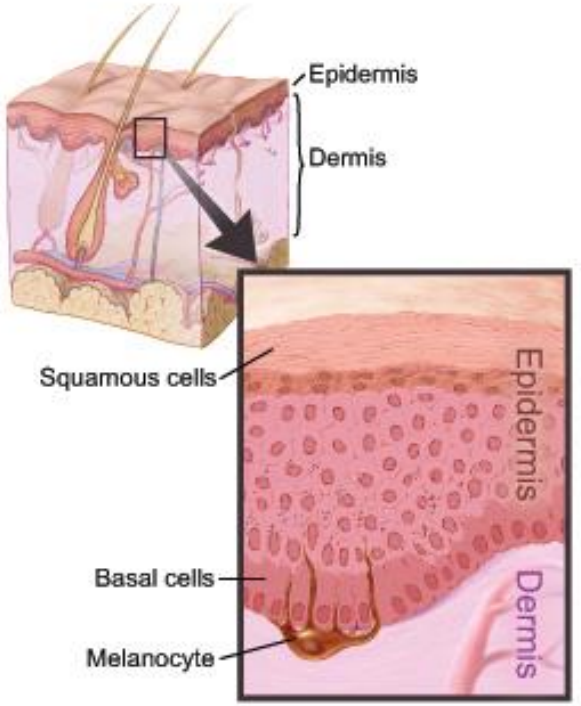
- Protection
  - Cushions and insulates and is waterproof
  - Protects from chemicals, heat, cold, bacteria
  - Screens UV
  - Largest organ
- Synthesizes vitamin D with UV
- Regulates body heat
- Prevents unnecessary water loss
- Sensory reception (nerve endings)

Epidermis and Dermis

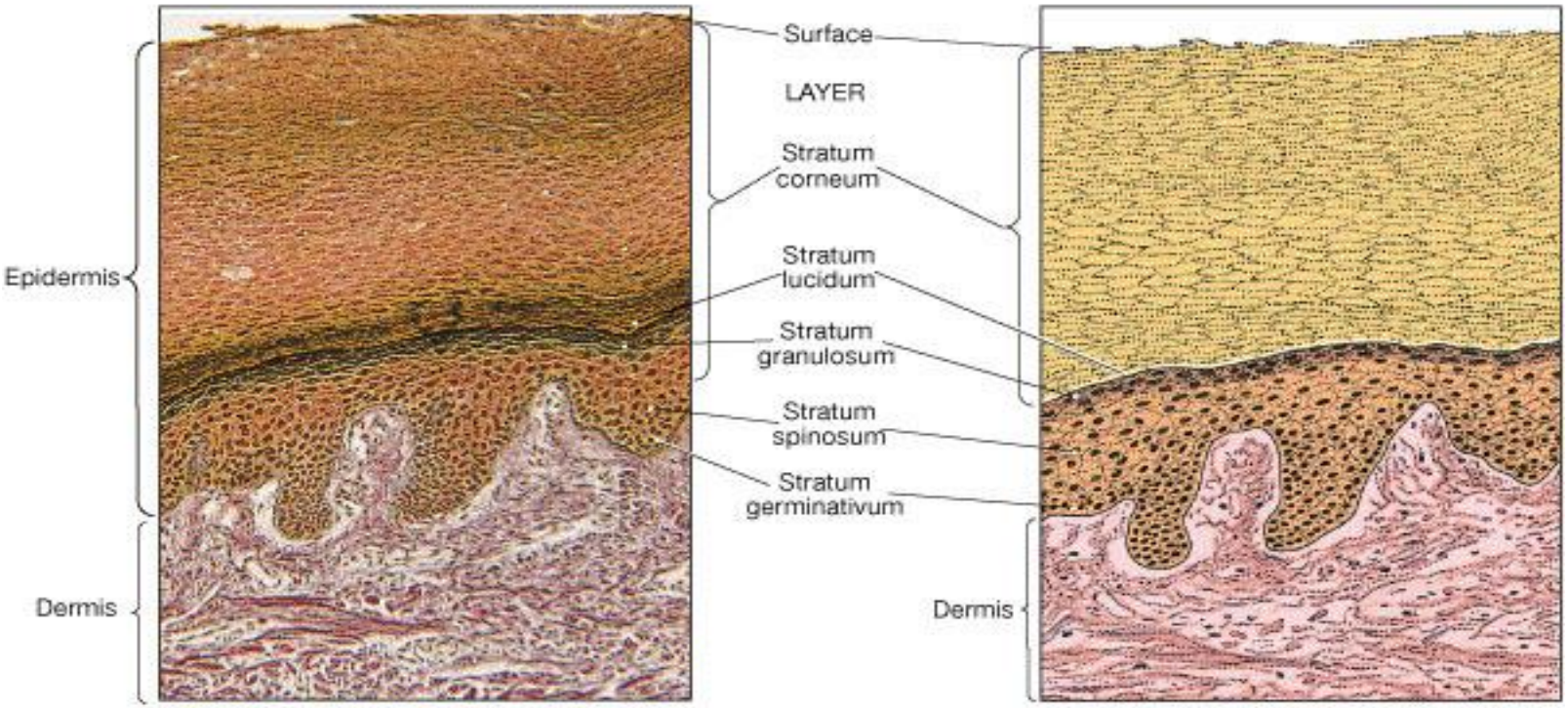
- Epidermis is avascular (no blood vessels)
- Dermis is highly vascular (has blood vessels)
- Epidermis receives nourishment from dermis
- Cells far away from nourishment die

Epidermis

- Outer layer of dead skin cells called cuticle .
- Layer you see everyday.
- “Ashiness” is caused by this layer of dead skin cells being very rough and raggedy.
- DUST you see around is made up of dead skin cells!
- Under the cuticle is another layer of living epithelial cells that make up the rest of the epidermis.

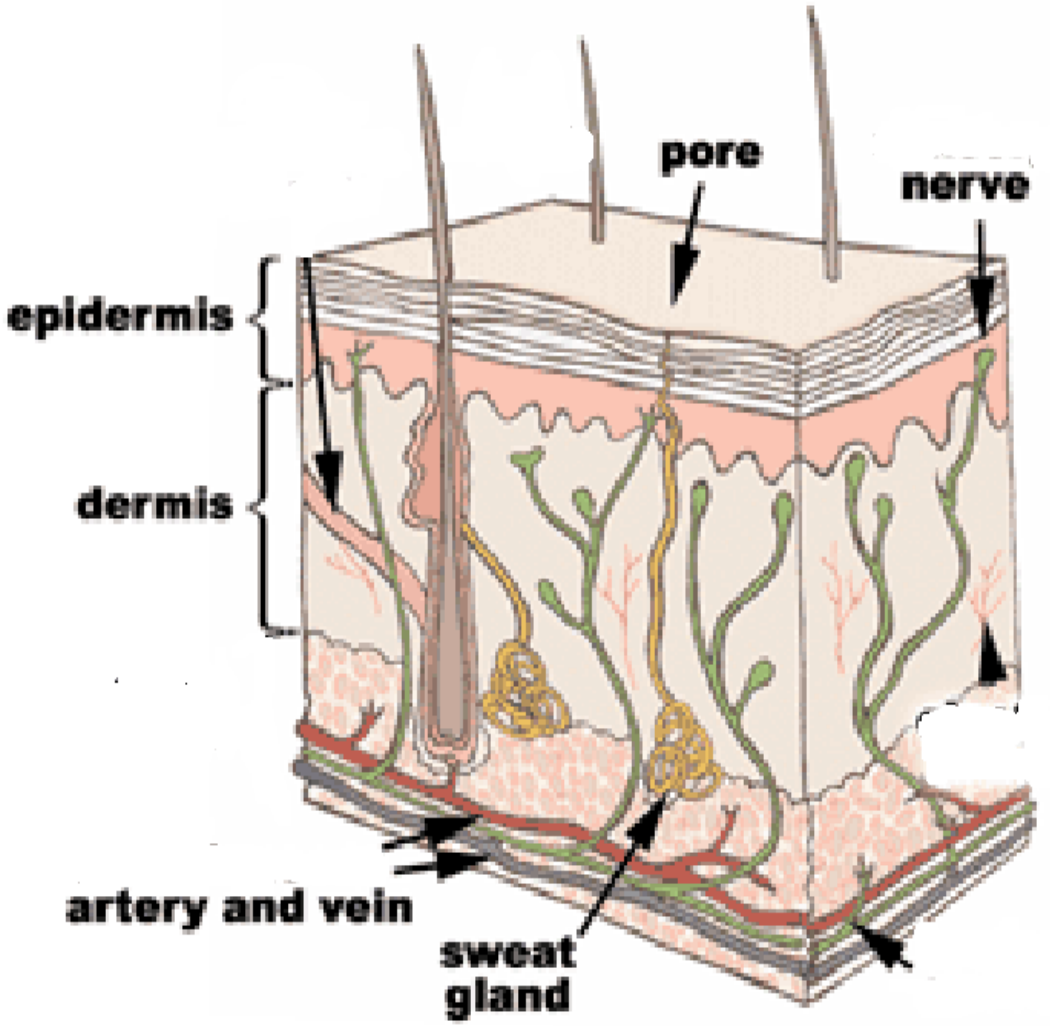


Epidermis *structure*



Dermis

- Thick layer under the epidermis
- Contains blood vessels
- Oil glands
- Sweat glands
- Hair follicles
- Fat tissue
- Nerves
- Connective tissue



Deeper Layer of the Dermis

Dense connective tissue

- Contains
  - Blood vessels
  - Glands
  - Deep pressure receptors
- Attached to underlying organs by the subcutaneous layer
  - Loose connective tissue
    - Packed with adipose cells
  - Stabilizes position of skin

Hypodermis

- “Hypodermis” (Gk) = below the skin
- “Subcutaneous” (Latin) = below the skin
- Also called “superficial fascia”
  - “fascia” (Latin) =band; in anatomy: sheet of connective tissue
- Fatty tissue which stores fat and anchors skin (areolar tissue and adipose cells)
- Different patterns of accumulation

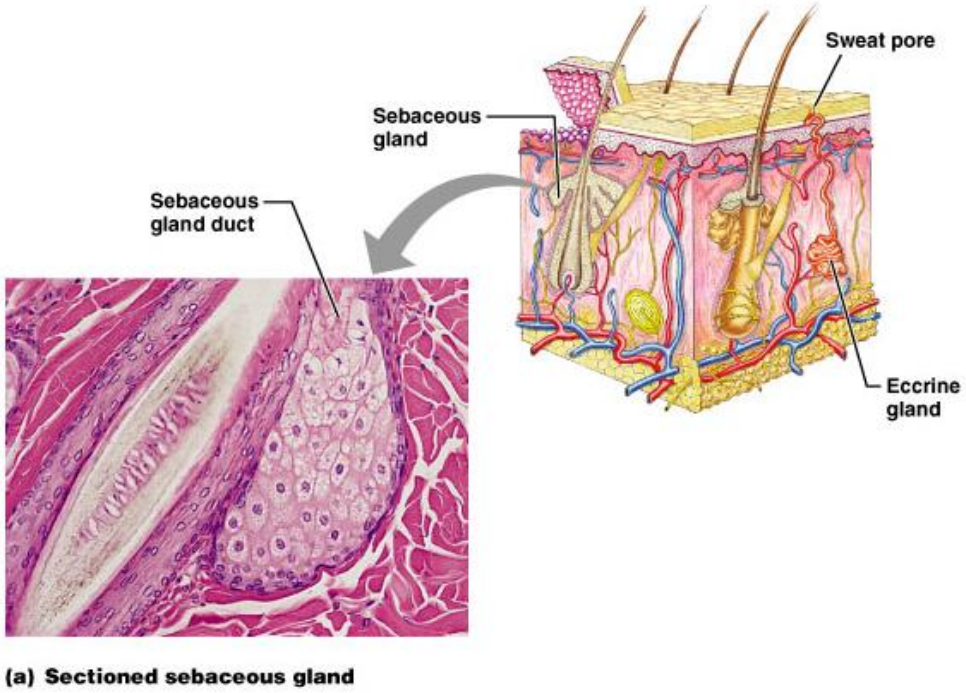
  (male/female)

Skin color

- Three skin pigments
  - Melanin: the most important
  - Carotene: from carrots and yellow vegies
  - Hemoglobin: the pink of light skin
- Melanin in granules passes from melanocytes (same number in all races) to keratinocytes in stratum basale
  - Digested by lysosomes
  - Variations in color
  - Protection from UV light vs vitamin D?

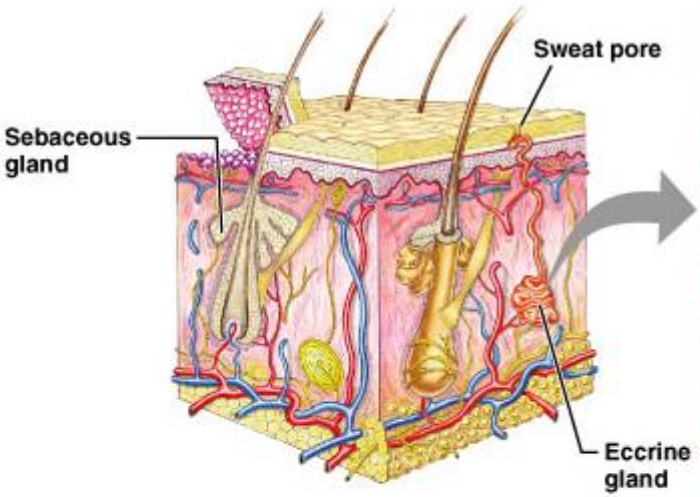
Sebaceous (oil) glands

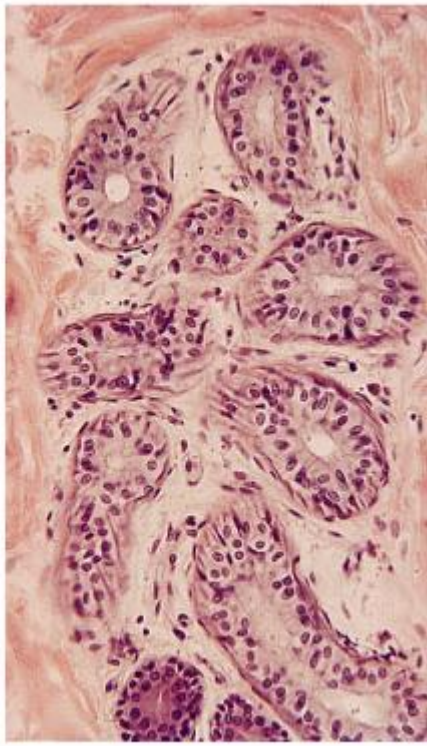
- Entire body except palms and soles
- Produce *sebum* by holocrine secretion
- Oils and lubricates
- Connected to hair follicles
- Secrete a waxy, oily substance (sebum)
- Secretion increases at puberty



Sweat glands

- Entire skin surface except nipples and part of external genitalia
- Prevent overheating
- 500 cc to 12 l/day! (is mostly water)
- Humans most efficient (only mammals have)
- Produced in response to stress as well as heat





(b) Sectioned eccrine gland

SKIN AGING

- Collagen production slows (skin gets thinner)
- Elastin fibers break down (skin loses its ability to snap back after stretching)
- Subcutaneous fat decreases (skin looks less plump and smooth)
- Turnover of skin cells slows down
- Skin becomes dryer

What causes skin to age?

- Sun (ultraviolet light)—damages elastin and collagen fibers, causing wrinkles, and producing mottling and brown spots
- Cigarette smoking—damages elastin and decreases blood flow to skin
- Gravity—pulls on our bodies and with loss of elastin and collagen, causes sagging
- Sleeping positions—cause creases
- Facial expressions—muscles produce grooves in skin which gradually become etched in face

Skin aging

AVOID ULTRAVIOLET LIGHT!!!!!

- Avoid deliberate tanning
- Stay out of sun between 10AM and 4PM
- Wear protective clothing (hats, long sleeves)
- Apply broad spectrum (UVA and UVB) sunscreen (SPF 25 or greater) year round

SKIN DEGENERATION

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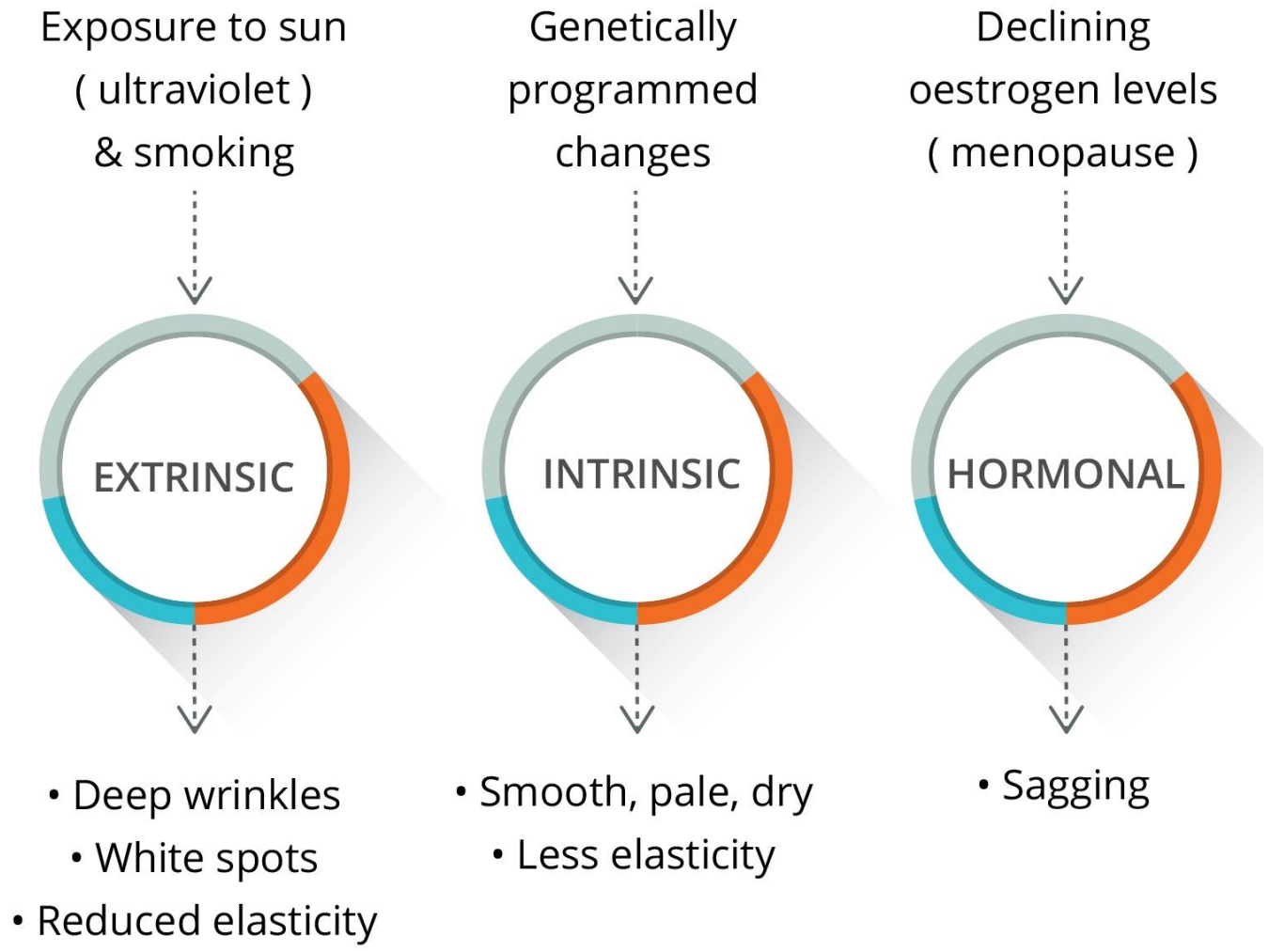
3 TYPES OF SKIN DEGENERATION



INTRINSIC SKIN AGING

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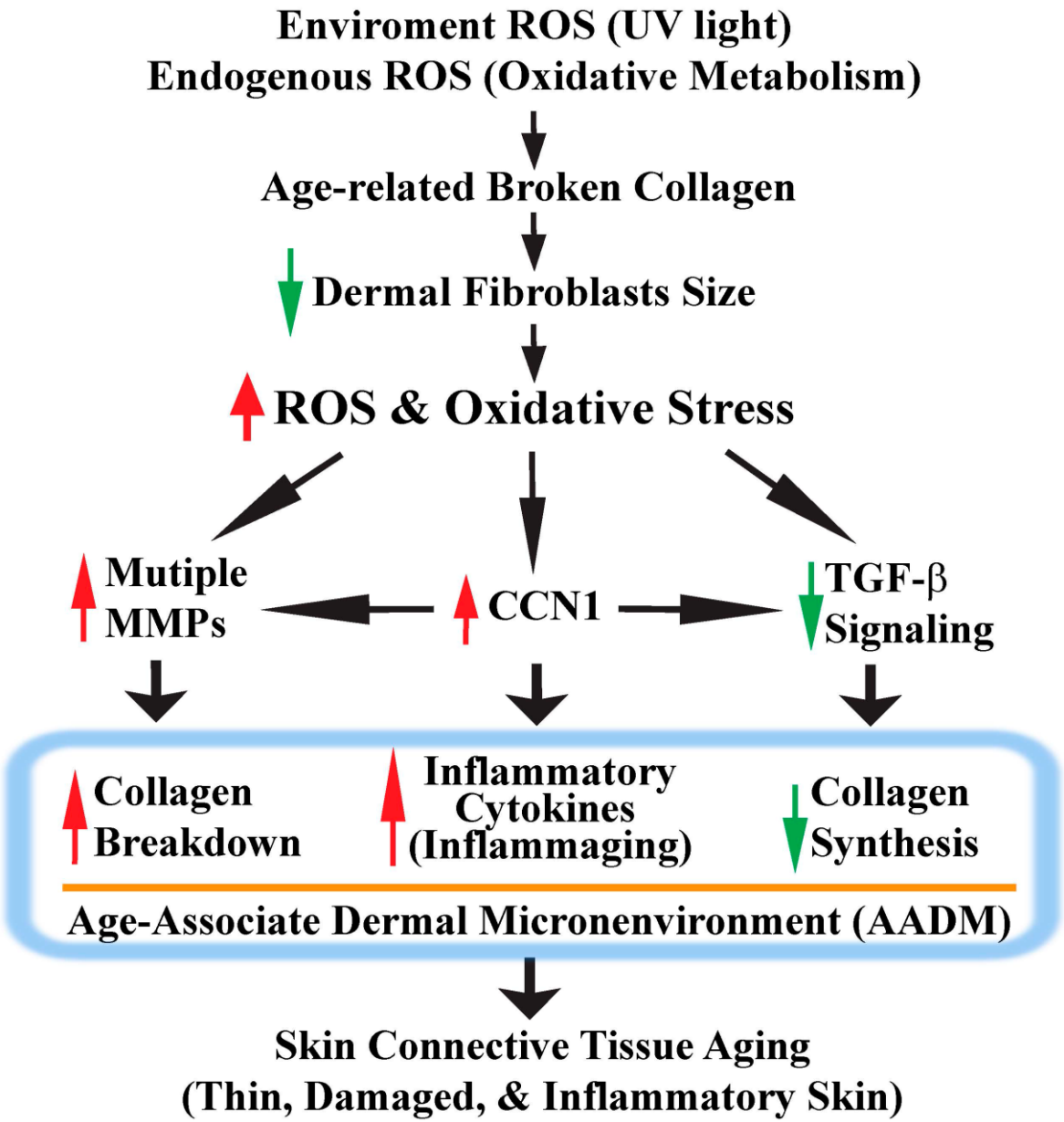
- Inevitable natural aging process that occurs in all people
- Occurs as part of a pre-programmed degeneration within cells and extracellular matrix in all skin layers.
- Although begin in 20's, visible signs are not apparent for many decades.
- Intrinsic aging proceeds at highly variable rates between different people
- Primarily determined by unique genetic make-up and underlying type of skin

EXTRINSIC SKIN AGING



SKIN INFLAMMATORY DISEASES

- Inflammatory skin diseases are the most common problem in dermatology.
- They come in many forms, from occasional rashes accompanied by skin itching and redness, to chronic conditions such as dermatitis (eczema), rosacea, seborrheic dermatitis, and psoriasis.
- Skin inflammation can be characterized as acute or chronic.
- Acute inflammation can result from exposure to UV radiation (UVR), ionizing radiation, allergens, or to contact with chemical irritants (soaps, hair dyes, etc.). This type of inflammation is typically resolved within 1 to 2 weeks with little accompanying tissue destruction.
- In contrast, chronic inflammation results from a sustained immune cell mediated inflammatory response within the skin itself. This inflammation is long lasting and can cause significant and serious tissue destruction.
- Inflammatory skin conditions affect over 35 million Americans who annually spend over $2 billion to treat their symptoms.

FILAGRRIN

- Encoded by FLG gene
- The FLG gene provides instructions for making a large protein called profilaggrin, which is found in cells that make up the outermost layer of skin (the epidermis)
- Profilaggrin is cut (cleaved) to produce multiple copies of the filaggrin protein, which is important for the structure of the epidermis.
- Filaggrin plays an important role in the skin's barrier function. It brings together structural proteins in the outermost skin cells to form tight bundles, flattening and strengthening the cells to create a strong barrier.
- Processing of filaggrin proteins leads to production of molecules that are part of the skin's "natural moisturizing factor," which helps maintain hydration of the skin. These molecules also maintain the correct acidity (pH) of the skin, which is another important aspect of the barrier.

FILAGRRIN

In the stratum corneum:

Filaggrin proteolysis releases histidine, which is then deaminated to form *trans-urocanic* acid, which is converted to *cis-urocanic* acid by ultraviolet irradiation

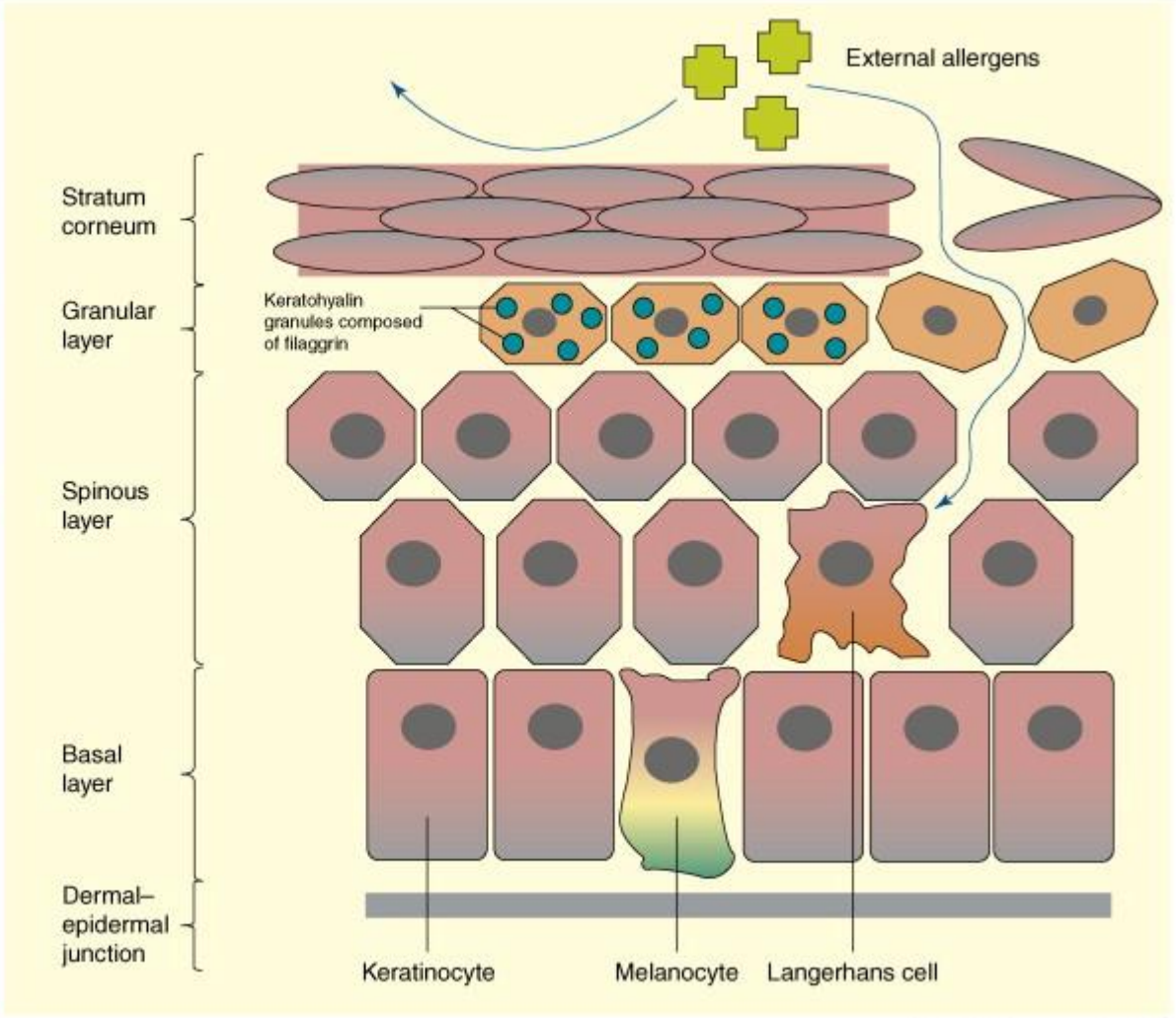
Glutamic acid released from filaggrin is converted to pyroglutamic acid which may function as a natural moisturising substance

In the granular layer:

Filaggrin is formed from profilaggrin, a highly phosphorylated, histidine-rich, very basic protein

Filaggrin aggregates keratin filamants and flattens the shape of keratinocytes

Other events include the release of lipids and cell envelope proteins from Golgi-derived organelles, known as lameller granules, to form the skin barrier



FILAGRRIN

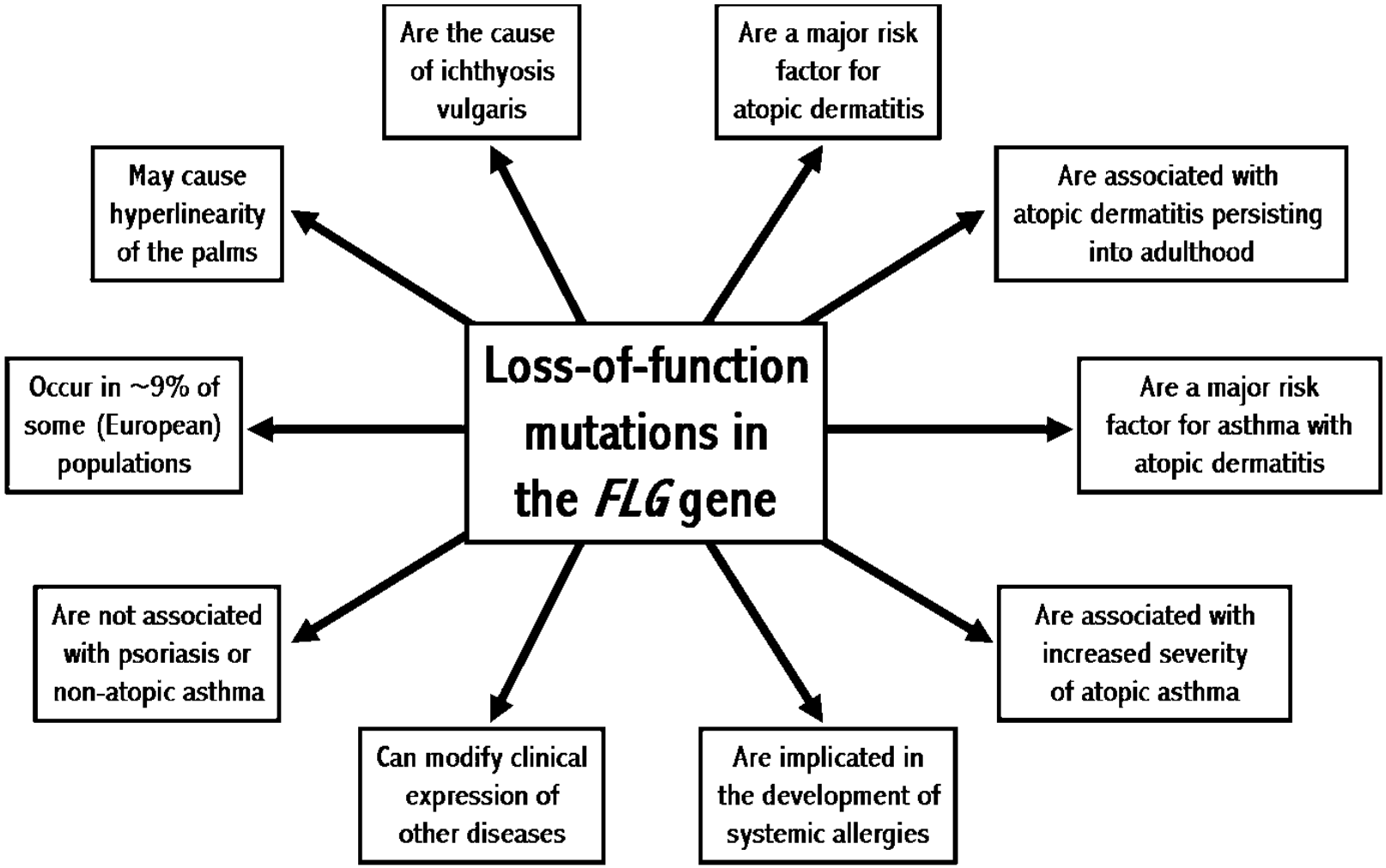


Figure 2 Clinical significance of loss-of-function mutations in the *FLG* gene. Mutations in *FLG* are directly associated with the cause

ICHTHYOSIS VULGARIS

- Commonest form and also the mildest.
- Autosomal-dominantly inherited
- Inherited disorder of keratinization associated with decreased conversion of profilaggrin to filaggrin that is characterized by fine scaling predominantly affecting the extensor surfaces of the extremities with sparing of the flexures and tendency towards improvement in the summer months.
- Filaggrin is an epidermal protein which is needed for aggregation of keratin intermediate filament and retention of moisture in the stratum corneum.
- Onset : early childhood (in between 3-12 months of age)

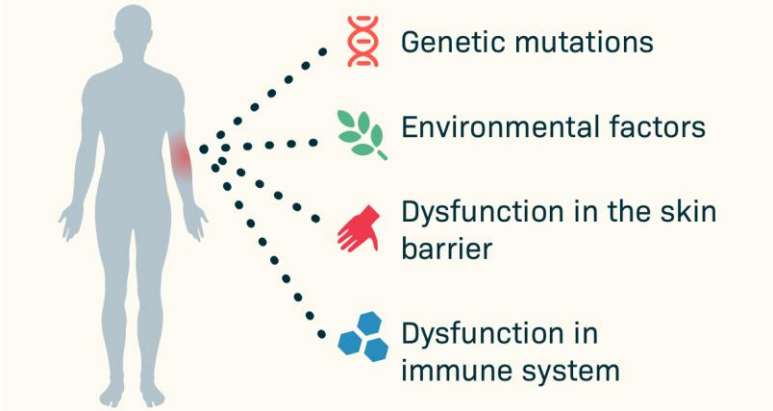
DERMATITIS

Atopic dermatitis is an inflammatory skin disease characterized by erythema, edema, pruritus, exudation, crusting, and scaling.

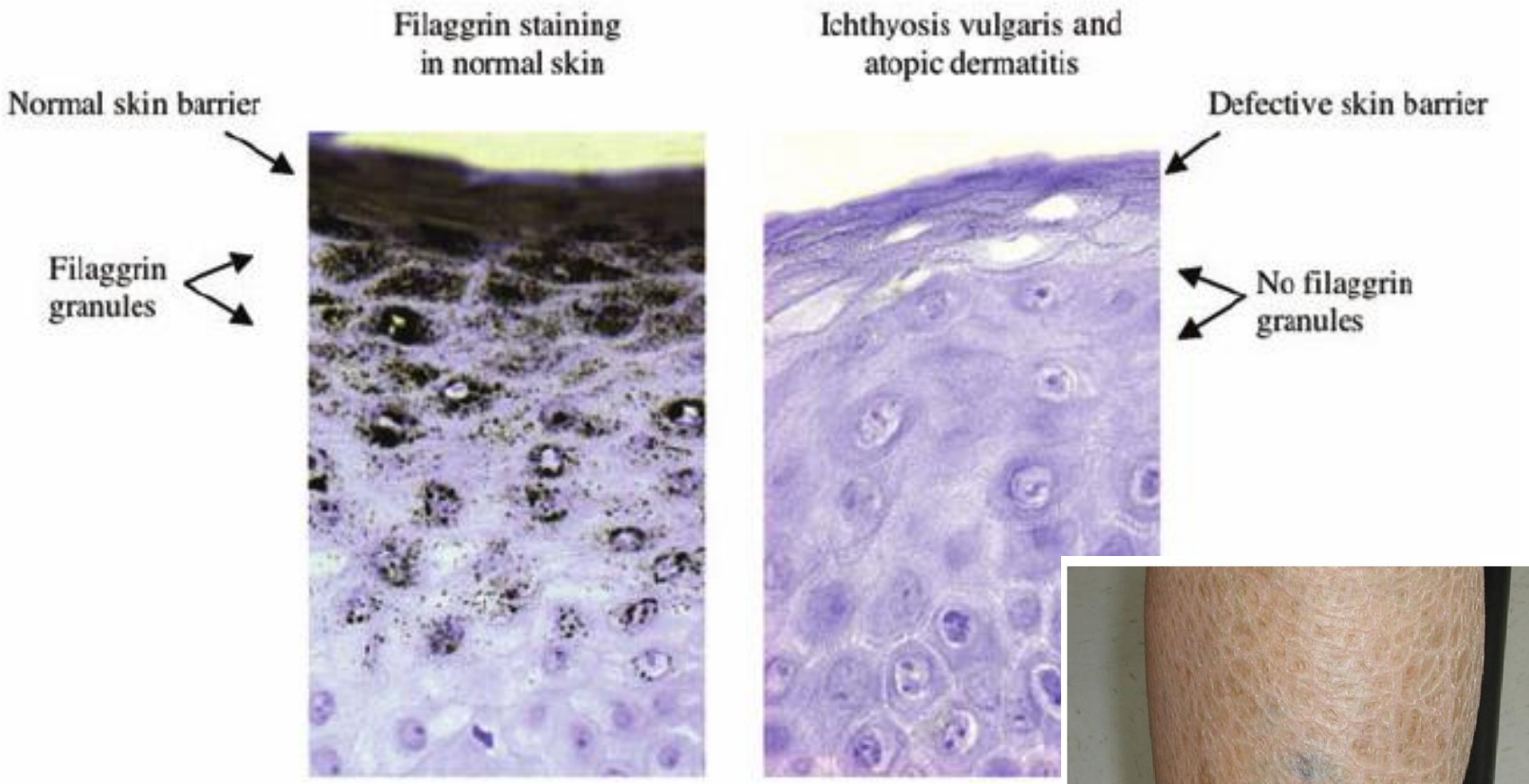
It is often referred to as the "**itch that rashes.**"

Pruritus may lead to intense scratching and secondary infection.

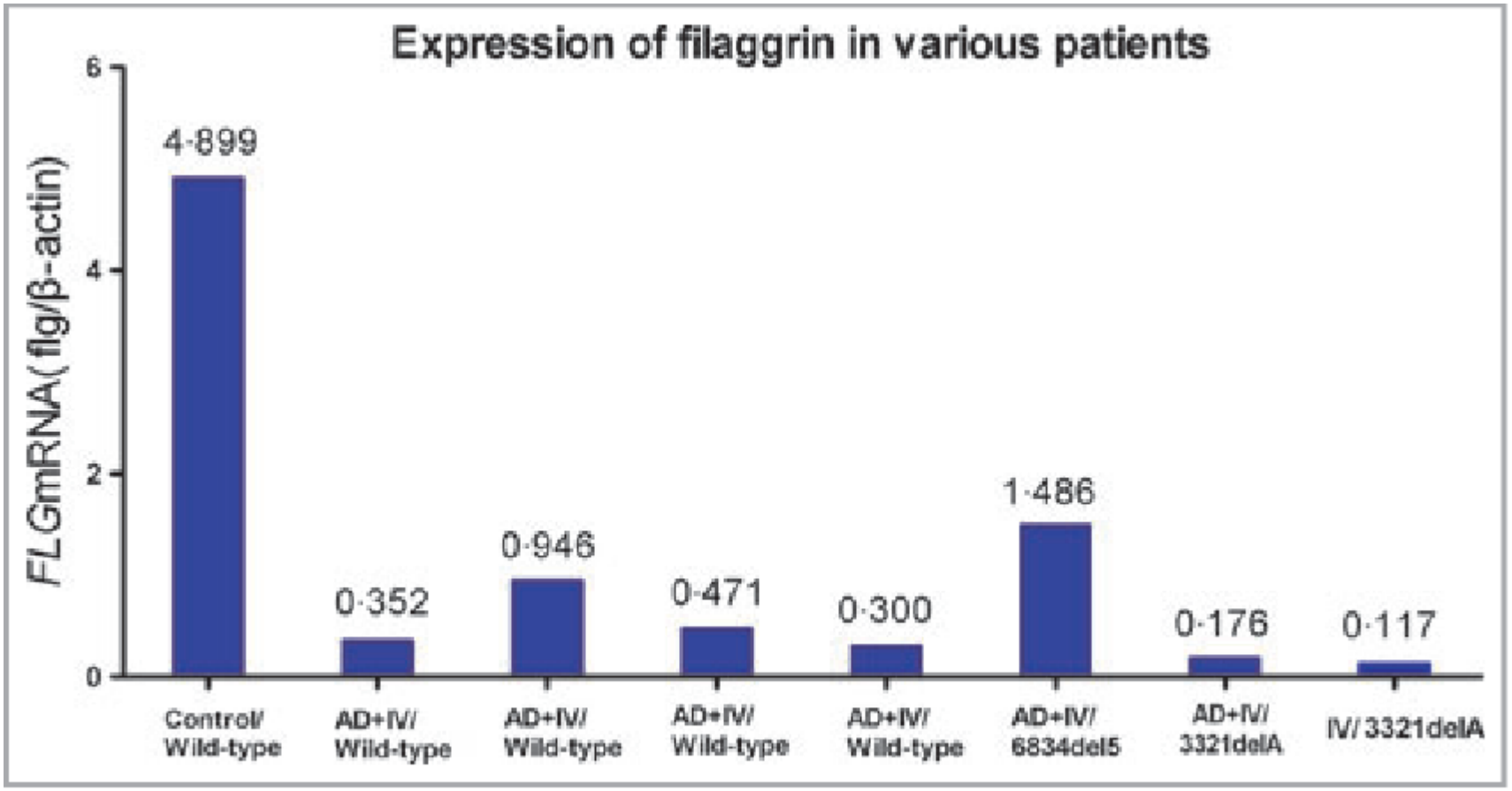
Atopic dermatitis may be **exacerbated by** food allergies (in approximately 40% of cases), as from eggs, wheat, peanuts, or cow's milk; environmental stimuli such as dust mites or animal dander; or emotional stress.



FILAGRRIN IN IV AND AD



FILAGRRIN


Expression of filaggrin in various patients
FLGmRNA(flg/β-actin)
6
4
2
0
4·899
0·352
0·946
0·471
0·300
1·486
0·176
0·117
Control/ Wild-type
AD+IV/ Wild-type
AD+IV/ Wild-type
AD+IV/ Wild-type
AD+IV/ Wild-type
AD+IV/ 6834del5
AD+IV/ 3321delA
IV/ 3321delA

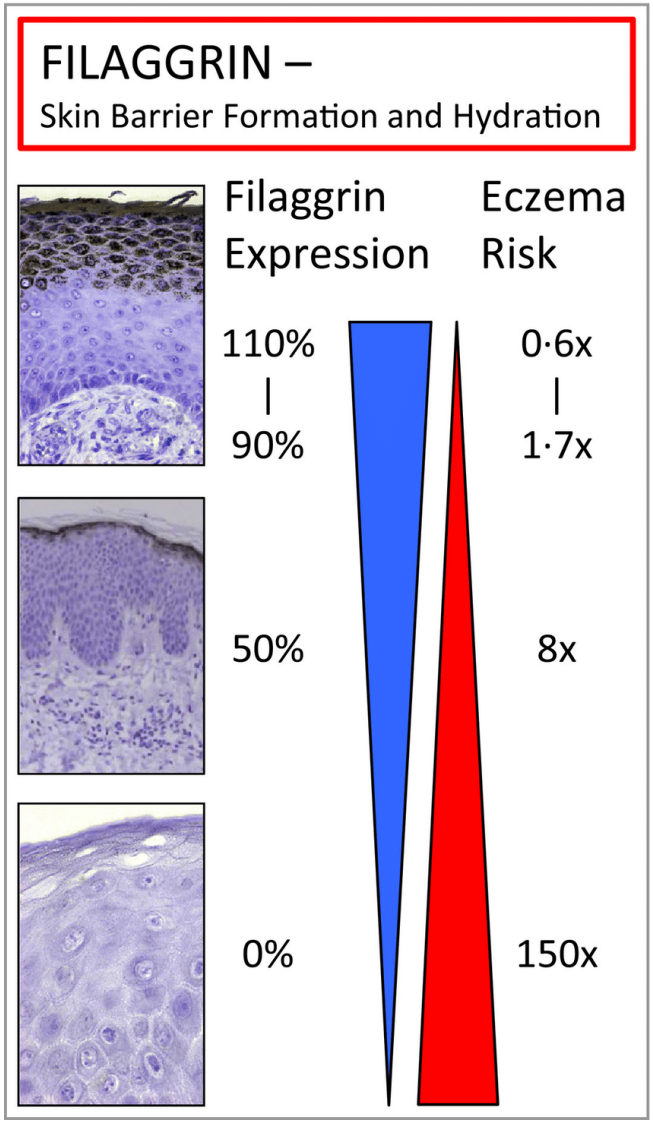
ICHYTHOSIS VULGARIS

Individual	Ancestry	Severity of phenotype	FLG genotype
Individual patients			
1	Austrian	++	R501X/wt
2	Austrian	++	R501X/2282del4
3	Austrian	++	R501X/2282del4
4	Austrian	++	2282del4/ 2282del4
5	Austrian	++	R501X/wt
6	Austrian	++	R501X/wt
7	Austrian	++*	wt/wt
8	Turkish	++*	wt/wt
9	Austrian	+	2282del4/wt
10	Austrian	+*	wt/wt
11	Austrian	+	wt/wt
12	Austrian	+*	wt/wt
13	Indian	+	wt/wt
Extended family patients			
14	Dutch	++*	R501X/wt
15	Dutch	++*	R501X/R501X
16	Dutch	++	R501X/wt
17	Dutch	+	R501X/wt
18	Dutch	+	R501X/wt
19	Dutch	+	R501X/wt
20	Dutch	+	R501X/wt
21	Dutch/ Australian	+	R501X/wt
Extended family healthy persons			
1	Dutch/ Australian	–	R501X/wt
2	Dutch	–	R501X/wt
3	Dutch/Swiss	–	wt/wt
4	Australian	–	wt/wt
5–16	Dutch	–	wt/wt

'+' denotes individuals with mild IV phenotype, that is, fine scaling primarily on the extensor surfaces of the extremities.
'++' denotes patients with severe IV phenotype, that is, generalized fine to coarse scaling and marked palmoplantar keratoderma. Individuals with concurrent atopic dermatitis, asthma and/or allergic rhinitis are marked with an asterisk.

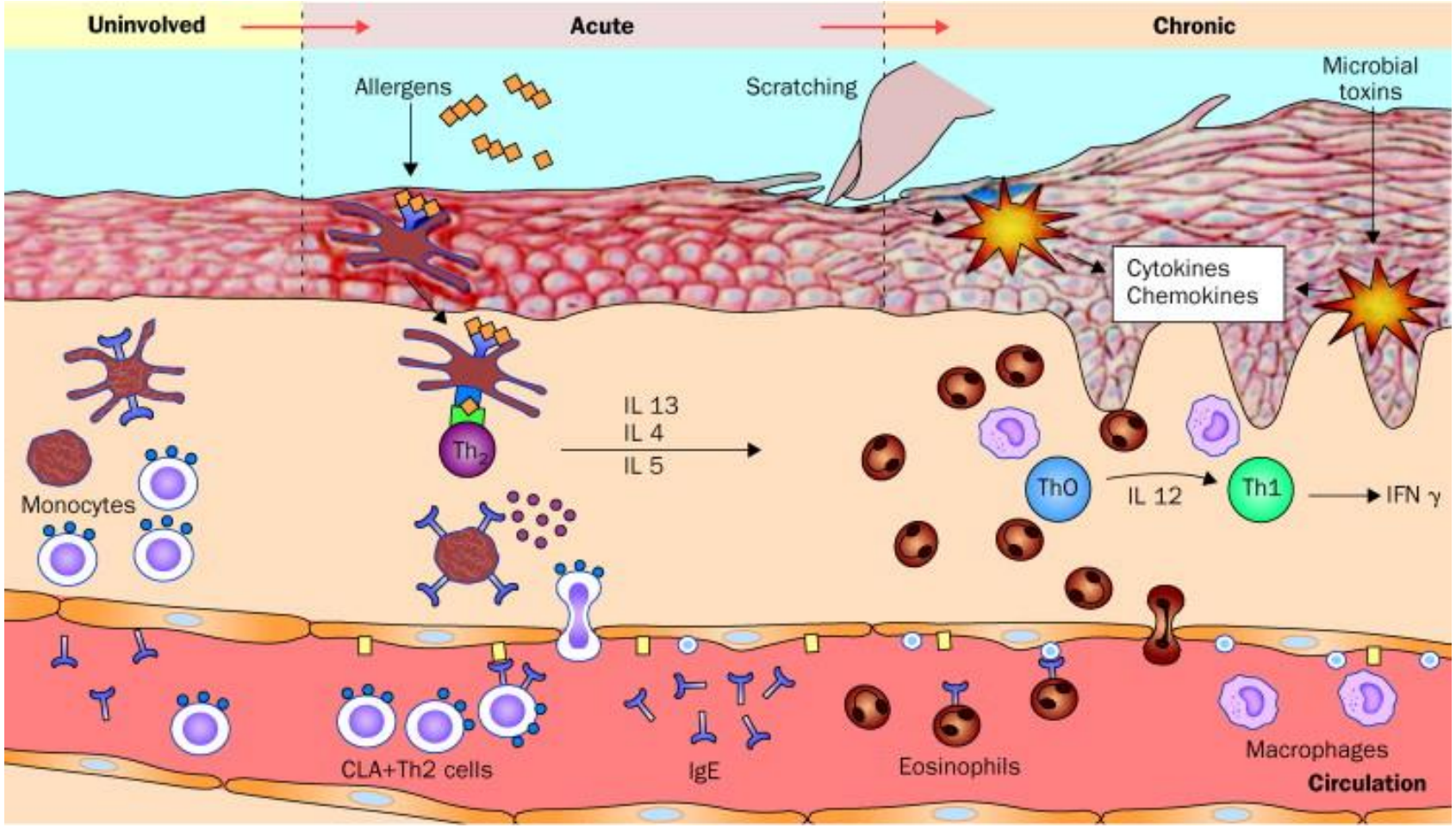
- FLG loss of function mutations are associated with IV
- Loss of function mutations
- R501X (c.1501C>T, p.Arg501Ter) - rs61816761
- 2282DEL4 rs558269137, also known as c.2284del4, c.2284delAGCT
- Individuals carrying two mutant copies of FLG are associated with 4-8 folds higher risk for developing IH

ECZEMA



- **Eczema** is a condition where patches of skin become inflamed, itchy, red, cracked, and rough. Blisters may sometimes occur. Different stages and types of **eczema** affect 31.6 percent of people in the United States.
- The word "**eczema**" is also used specifically to talk about atopic dermatitis, the most common type of **eczema**.

DERMATITIS


Uninvolved
Acute
Chronic
Allergens
Scratching
Microbial toxins
Cytokines
Chemokines
Monocytes
Th2
IL 13
IL 4
IL 5
Th0
IL 12
Th1
IFN γ
CLA+Th2 cells
IgE
Eosinophils
Macrophages
Circulation

DERMATITIS

- FLG loss of function mutations are associated with significant reductions in FLG protein levels and Atopic Dermatitis

	Blood of patients			
Tissue FLG	R501X Normal	R501X Mutant	2282del4 Normal	2282del4 Mutant
Lesional FLG (pg/mg)				
Mean ± SD	4.2 ± 2.1	3 ± 1.6	4 ± 2	3.1 ± 1.9
P-value	0.226		0.351	
Nonlesional FLG (pg/mg)				
Mean ± SD	8 ± 2	6.9 ± 2.5	7.7 ± 2.3	7.9 ± 2.3
P-value	0.311		0.604	
Control skin FLG (pg/mg)				
Mean ± SD	14.8 ± 3.2	15.3 ± 3.2	13.9 ± 2.2	16.8 ± 3.8
P-value	0.967		0.074	

Genotype	R501X		2282del4		R2447X		S3247X		Combined genotype	
	Co	AD	Co	AD	Co	AD	Co	AD	Co	AD
AA	392 (97.5)	432 (93.5)	388 (96.5)	394 (85.3)	396 (98.5)	448 (97.0)	401 (99.7)	454 (98.3)	371 (92.3)	356 (77.1)
Aa	10 (2.5)	29 (6.3)	14 (3.5)	63 (13.6)	6 (1.5)	14 (3.0)	1 (0.3)	8 (1.7)	31 (7.7)	86 (18.6)
aa	0 (0.0)	1 (0.2)	0 (0.0)	5 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	20 (4.3)
Total	402 (100.0)	462 (100.0)	402 (100.0)	462 (100.0)	402 (100.0)	462 (100.0)	402 (100.0)	462 (100.0)	402 (100.0)	462 (100.0)
P-value	0.007		< 0.001		0.142		0.066		< 0.0001	
OR	2.72		4.78		2.06		7.05		3.56	
CI	1.31–5.64		2.65–8.65		0.79–5.42		0.88–56.48		2.33–5.46	

Percentage of non-missing values are given in parentheses.

All ORs for the single mutations are given with respect to AA vs. Aa + aa.

AA refers to wild-type/wild-type genotype; Aa refers to heterozygous mutation carriers for either 2282del4, R501X, R2447X or S3247X; aa refers to homozygous mutation carriers.

WHAT DOES IT MEAN ?

- FLG loss of function mutations are associated with significant reductions in FLG protein levels
- Increased risk of Ichythosis vulgaris dependent on how many defective alleles are carried
- Increased risk of eczema, atopic dermatitis and dry skin
- Increased risk of asthma – allergens that drive dermatitis can further drive asthma development

- What to do if at risk?
- Avoidance of allergens
- Regular moisturizing of skin is absolutely needed

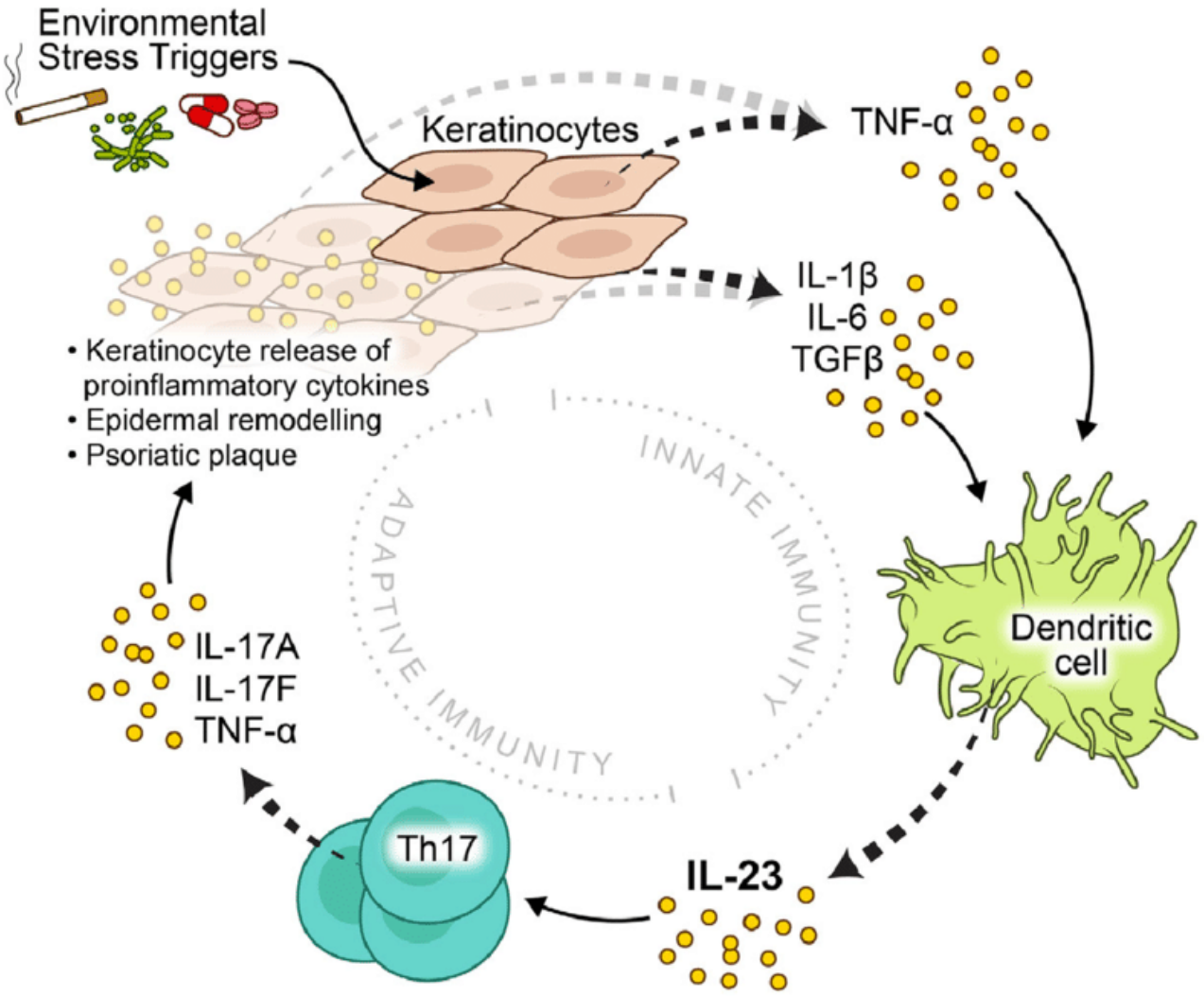
Psoriasis

- Chronic inflammatory skin disease
- Non- infectious, non-transmissible
- Genetic factors
- Environmental factors : aggressions, bacteria
- Skin immune system activation and increased skin proliferation and renewal
- Psoriatic arthritis (15 to 30%)

Psoriasis

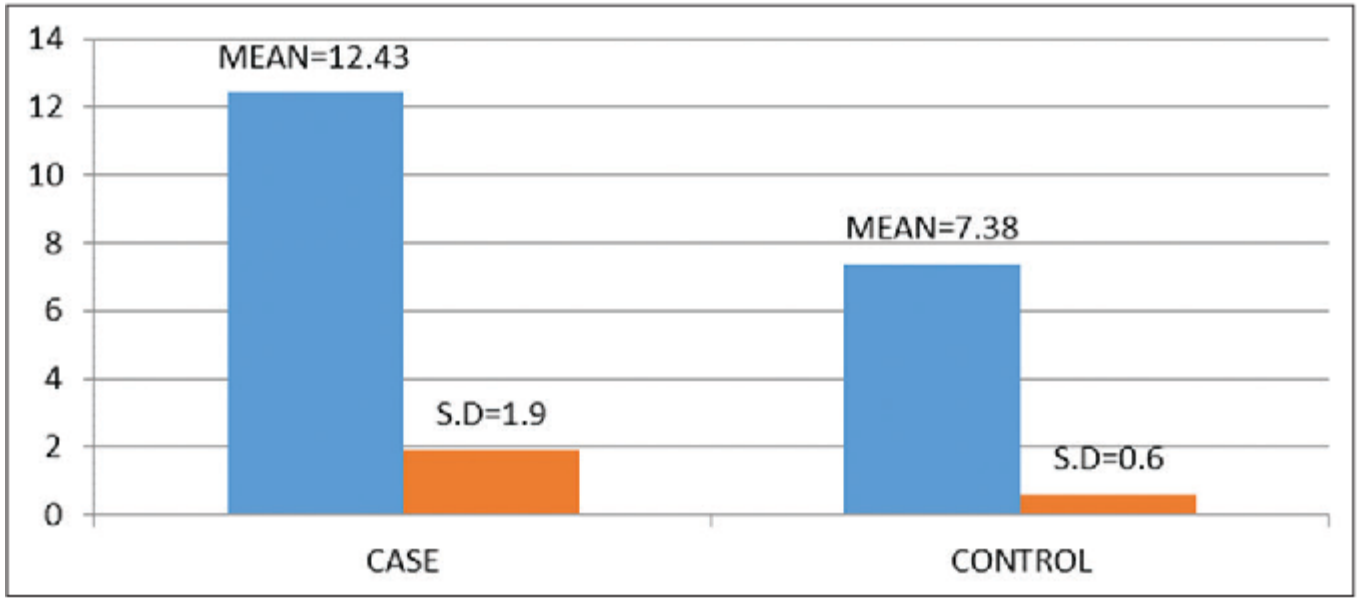
- Psoriasis is a common, chronic, relapsing, immune-mediated, inflammatory skin disease affeting 2-4% of the population.
- Psoriatic arthitis (appr. 42%)
- Frequent comorbidities: cardiovascular diseases, metabolic syndrome, depression, an increased risk for mortality and shorter life-span.

PSORIASIS PATHOPHYSIOLOGY



MTHFR AND PSORIASIS

- Enzyme MTHFR is involved in homocysteine and folic acid metabolism and it is responsible for the irreversible conversion to 5-methyl tetrahydrofolate
- Higher homocysteine levels in psoriasis patients
- Folate deficiency impacts keratinocytes proliferation – can induce DNA breakage, cellular imbalance which can drive inflammation



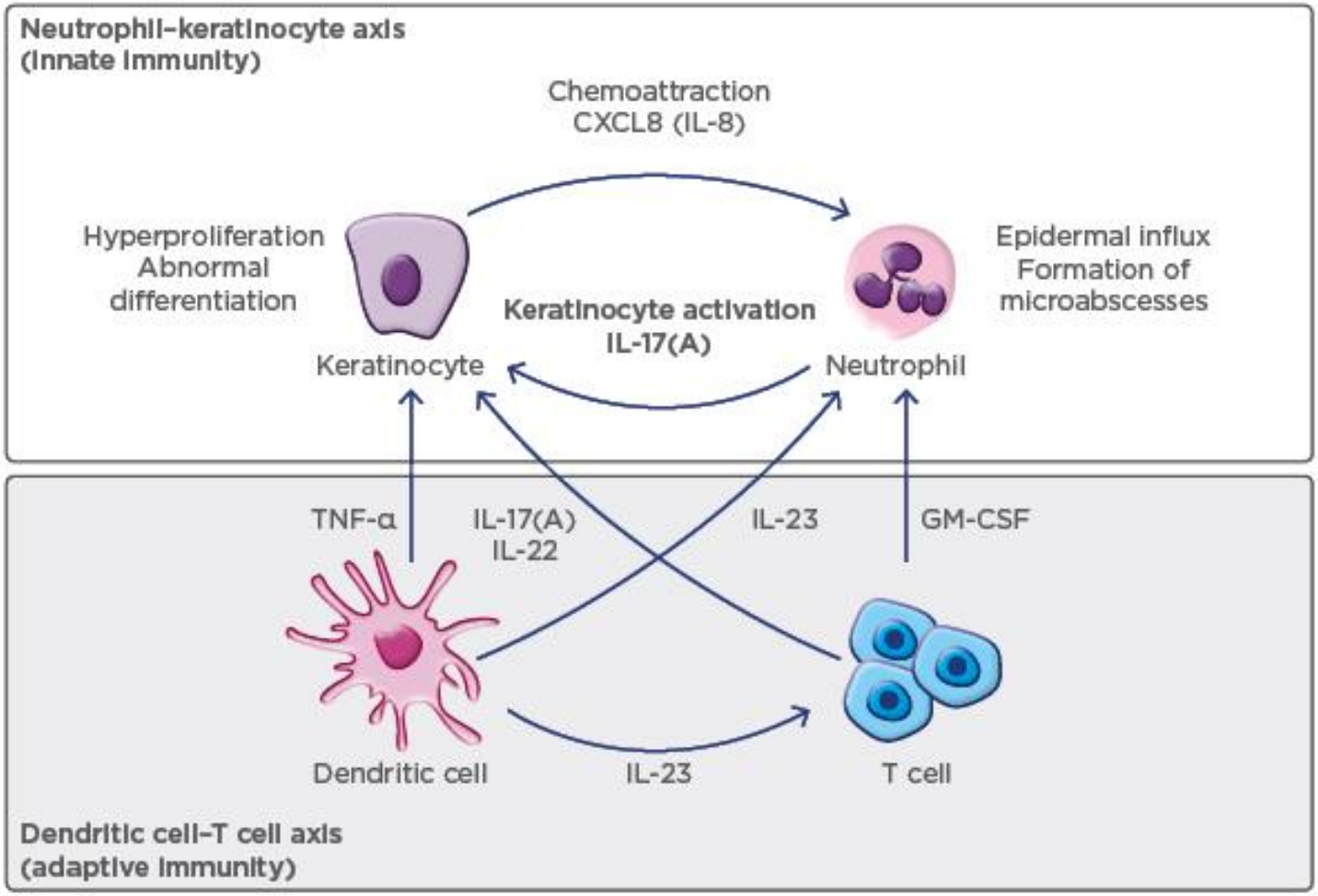
MTHFR AND PSORIASIS

- Significant differences in Hcy levels have also been reported in carriers of CC, CT, and TT genotypes of *MTHFR* polymorphism
- Mutations that impact folate metabolism impact homocysteine levels
- MTHFR mutations associated with psoriasis susceptibility along with disease severity

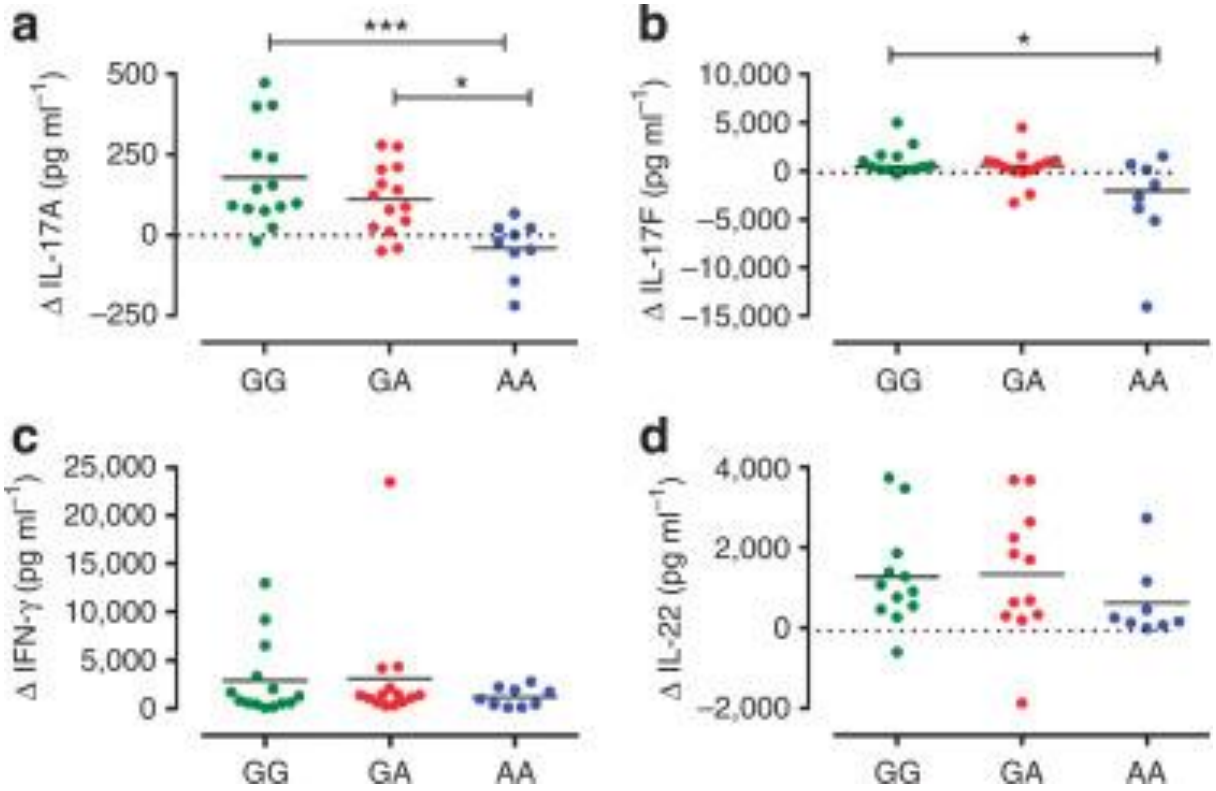
GENOTYPE/ ALLELE	MALE PATIENTS (N=64)		FEMALE PATIENTS (N=42)		*P*	CONTROLS (N=280)	
	N	FREQ. %	N	FREQ. %		N	FREQ. %
CC	35	55.17*	20	47.62*	.552	210	75.00
CT	26	41.38*	20	47.62*	.549	70	25.00
TT	3	3.45*	2	4.76*	1.00	0	0
C-allele	96	75*	60	72.43*	.633	490	87.50
T-allele	32	25*	24	28.57*	.633	70	12.50

Abbreviation: *MTHFR, methylenetetrahydrofolate reductase*.
*Statistically significant difference as compared with controls ($P < .01$).

IL-23 AND PSORIASIS



IL-23R GENETICS AND PSORIASIS



- (rs11209026G>A) of the IL-23 receptor gene (IL23R) protects against psoriasis
- G allele increases the risk
- IL-23 a central mediator of inflammation during psoriasis

HLA-C AND PSORIASIS

- HLA-C belongs to the MHC (human = HLA) class I heavy chain receptors.
- The C receptor is a heterodimer consisting of a HLA-C mature gene product and β2-microglobulin.
- Role in expressing self-proteins to cells
- Psoriasis – autoimmune, development of CD8+ T cells
- Autoimmune response to melanocyte antigens
- Mediated by specific alleles of HLA-c

HLA-C*06 AND PSORIASIS

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Table 2 HLA-C*06 allele distribution between psoriatic cases and controls

HLA-C*06	Patients with psoriasis (n = 355)	Controls (n = 360)	p value	OR (95 % CI)
HLA-C*06-positive heterozygous mutant (HT)	149	92	<0.0001	3.18 (2.26–4.49)
HLA-C*06-positive homozygous mutant (HM)	91	42	<0.0001	4.26 (2.77–6.54)
HLA-C*06 negative	115	226		

- HLA-C*06 allele associated with psoriasis along with psoriatic arthritis

Disease type	Number	HLA-C*06 allele positivity	OR	CI
Psoriasis	355	240	3.52	2.59–4.79
Early-onset psoriasis	217	160	4.72	3.27–6.87
Late-onset psoriasis	138	80	2.32	1.56–3.48
Sporadic psoriasis	298	198	3.33	2.42–4.61
Familial psoriasis	57	42	4.70	2.54–9.04
Psoriatic arthritis	138	98	4.12	2.70–6.35
Controls	360	134		

Reference group: controls

WHAT DOES IT MEAN ?

- MTHFR has a role in keratinocyte biology
- IL-23R and HLA-C alleles - autoimmunity

- What to do if at risk?
- Oral supplementation with omega 3 fatty acids, Vitamin D, Glucosamine, Chondroitin and Methylsulfonylmethane has shown clinical efficacy

Photoaging

Photoaging happens when the skin begins to show early signs of aging due to UV exposure.

Photoaging signs include:

- Wrinkles
- Frown lines
- Spider veins
- Freckles, age spots or uneven skin colour
- Stretched lips
- Skin that looks like leather
- Skin that sags

Photoaging

UV (ultraviolet) radiation

↓

affects gene expression in skin

(↑ collagenase ↓ collagen)

↓

acute collagen loss

↓

imperfect repair

↓

microscars

photoaging

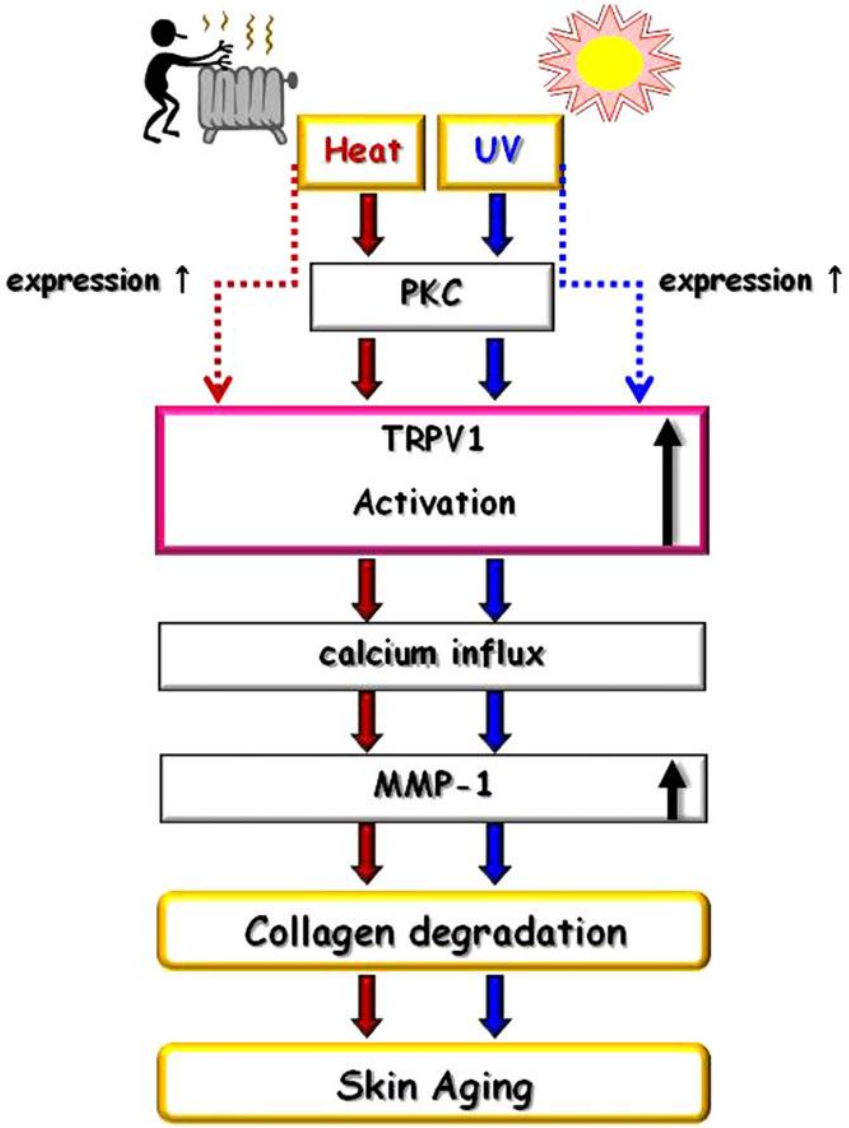
↓

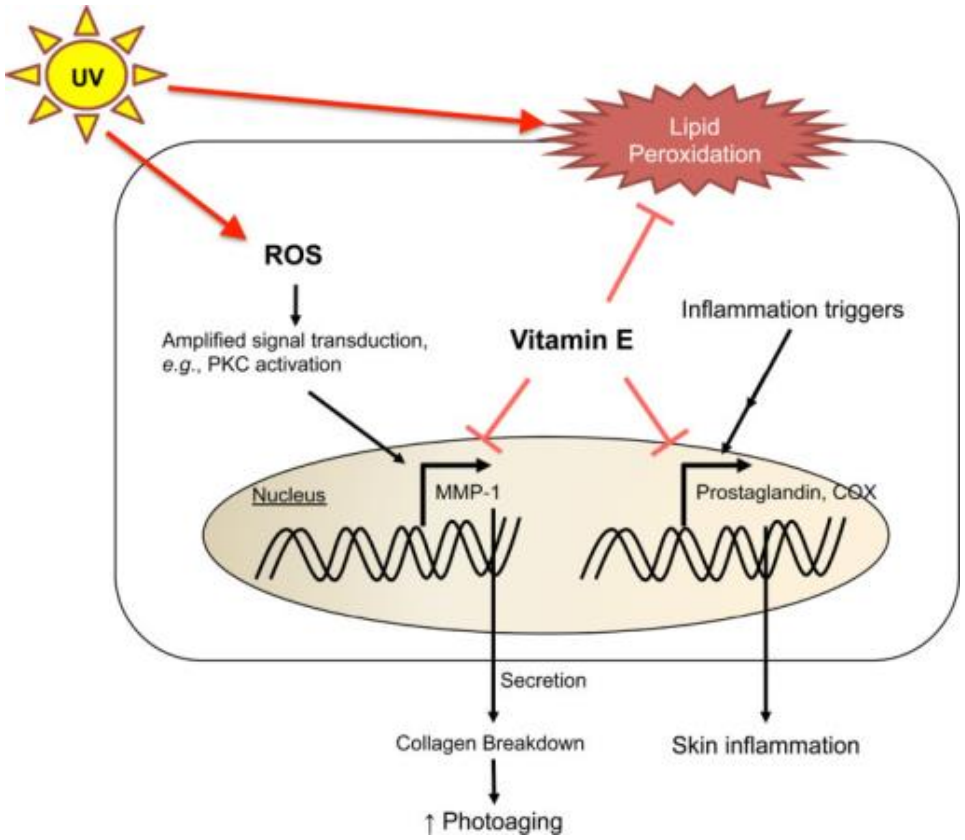
chronic collagen loss

MMP1 AND PHOTOAGING

- Matrix metalloproteinase-1 (MMP-1) also known as interstitial collagenase and fibroblast collagenase is an enzyme that in humans is encoded by the MMP1 gene.
- MMPs are involved in the breakdown of extracellular matrix in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis and metastasis.
- MMP can break down collagen
- specifically degrades a major component of the ECM, type I collagen, as well as other fibrillar collagens of types II, III, V, and IX

PHOTOAGING AND MMP-1





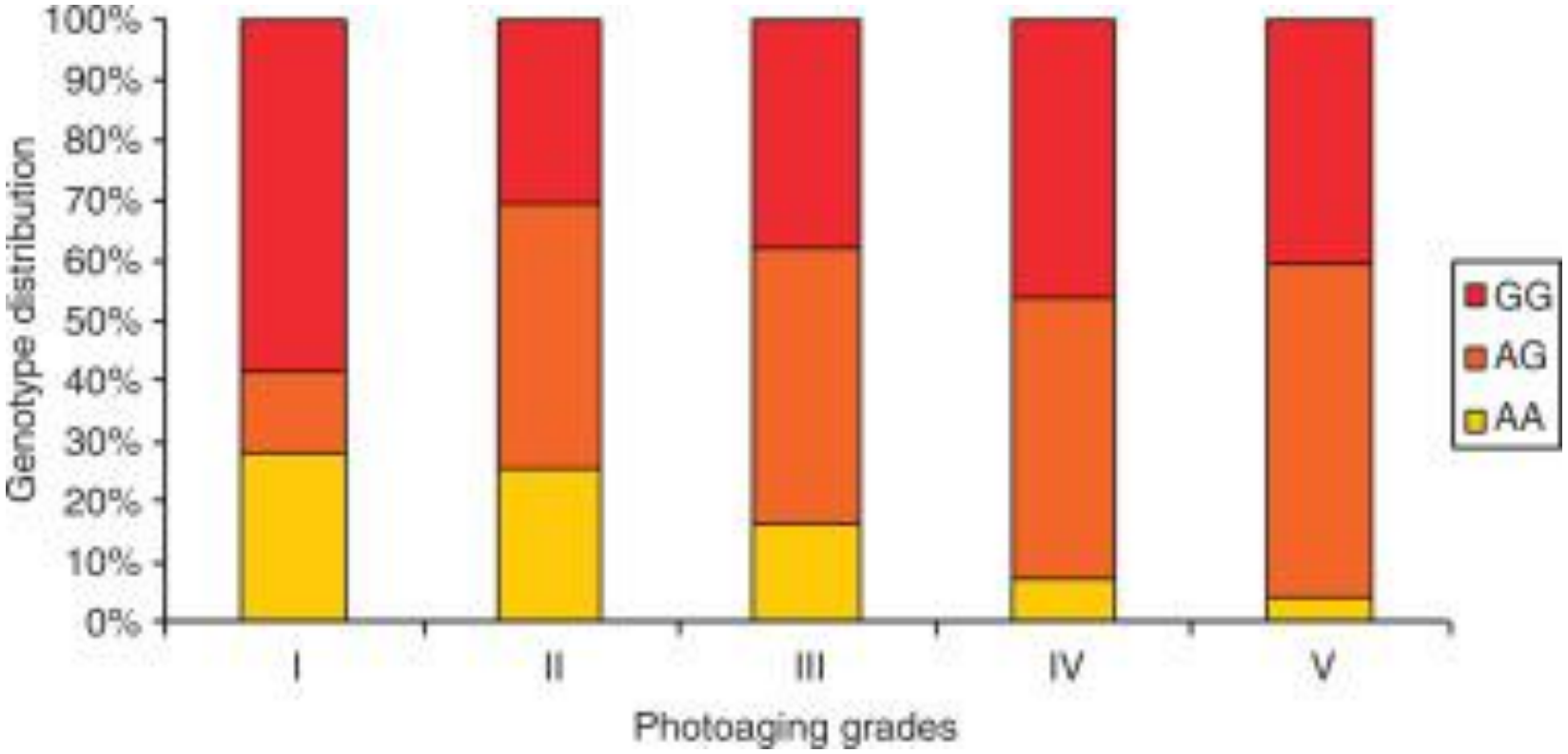
MMP1 POLYMORPHISMS AND WRINKLES

- MMP-1 2G allele associated with accelerated skin aging
- Rs1799750 – 2 G alleles (mutation in promoter region)
- Transcription impact
- Associated with increased expression of MMP1
- Increased susceptibility to wrinkles
- Increased photoaging susceptibility

STXBP5L AND WRINKLES

- Syntaxin-binding protein 5 is a protein that in humans is encoded by the STXBP5 gene.
- It is also known as tomosyn.
- Mainly expressed in brain and synaptic tissues
- Very low expression in skin
- Function not known
- Related proteins are involved in docking and fusion of synaptic vesicles with the presynaptic plasma membrane.

STXBP5L AND WRINKLES



- rs322458 variant associated with wrinkles
- G allele – increased photoaging

STXBP5L AND WRINKLES

outcome variables

	Age	Score of wrinkling	Score of sagging	Score of lentigines	Grade of photoaging
Age	1	0.61	0.61	0.27	0.56
Score of wrinkling		1	0.71	0.31	0.78
Score of sagging			1	0.26	0.66
Score of lentigines				1	0.31
Grade of photoaging					1

- rs322458 variant associated with wrinkles
- A allele – reduced photoaging

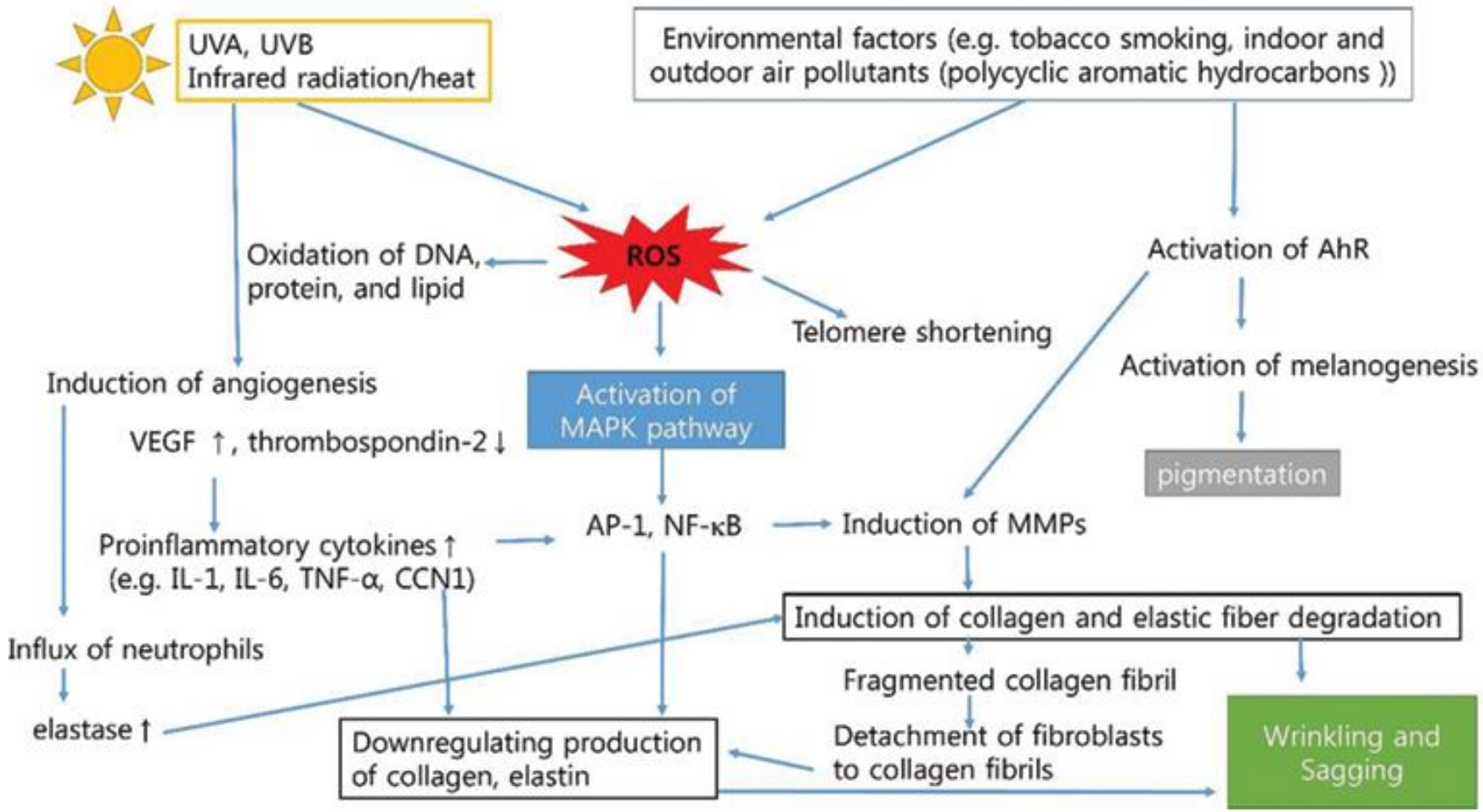
WHAT DOES IT MEAN?

- Increased MMP1 activity and G allele of STXBP5L associated with photoaging and wrinkles
- Topical application of creams containing glucosamine, coenzyme Q10, hyaluronan, isoflavones, lycopene, vitamins C, E , omega-3 fatty acids, Polypodium Leucotomos Extract and methylsulfonylmethane have shown efficacy in clinical trials.

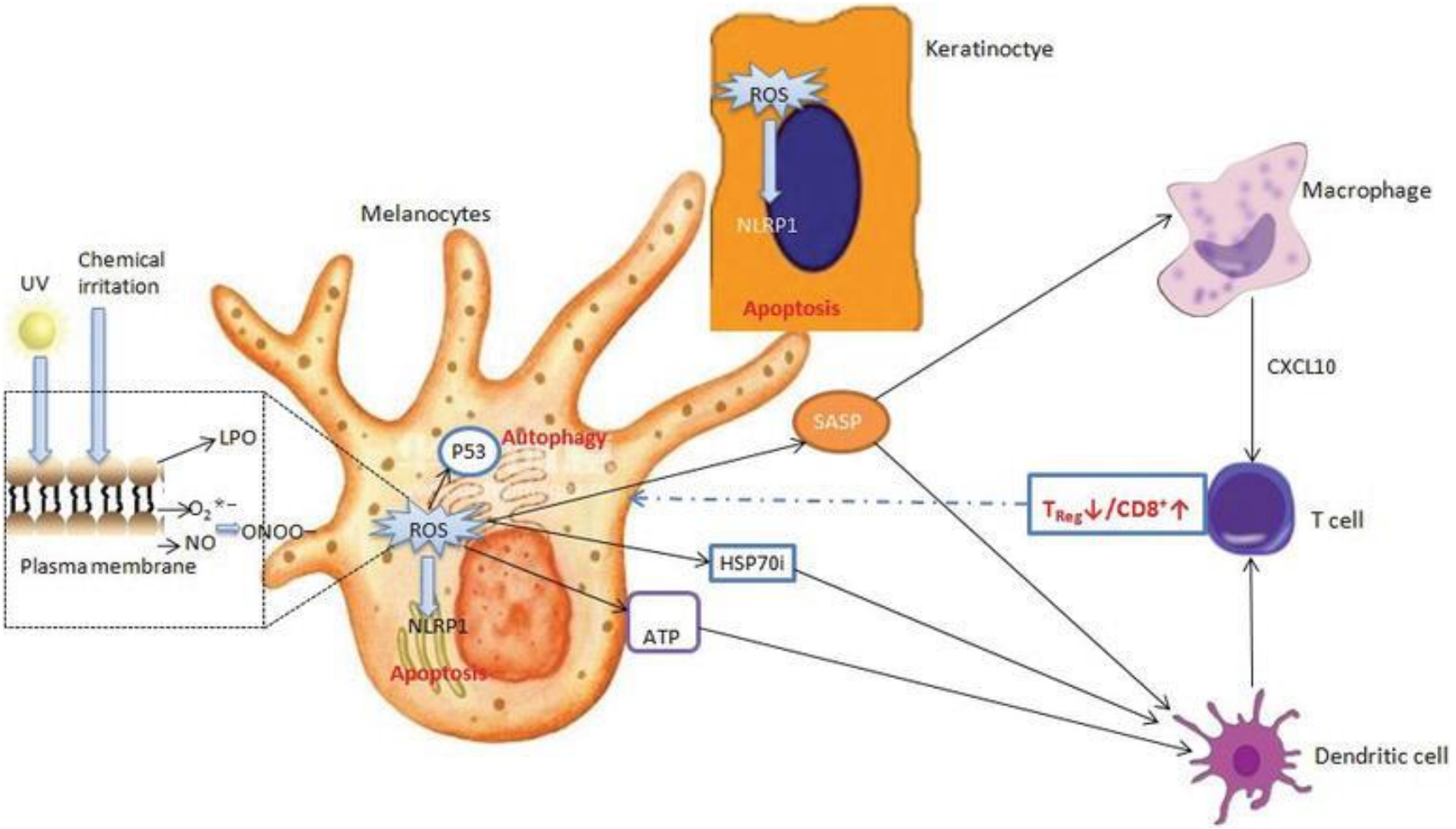
SKIN AGING AND OXIDATIVE DAMAGE

- As the heaviest, largest organ, with the most complex functions, the skin is very vulnerable to a variety of redox reactions, and the balance between oxidants and antioxidants must be maintained
- ROSs at low concentrations exert their physiological activity, but the increased levels of these molecules are involved in the pathological processes, including injuries, repair, tissue regeneration, aging, autophagy, apoptosis, and inflammation.
- ROSs are involved as the secondary messengers in the MAPK/AP1, NF-κB, and JAK/STAT-signaling pathways, which are activated early during the development of inflammatory disorders
- Genetics underlines susceptibility to increased production of ROS which can contribute to increase in skin aging

SKIN AGING AND OXIDATION

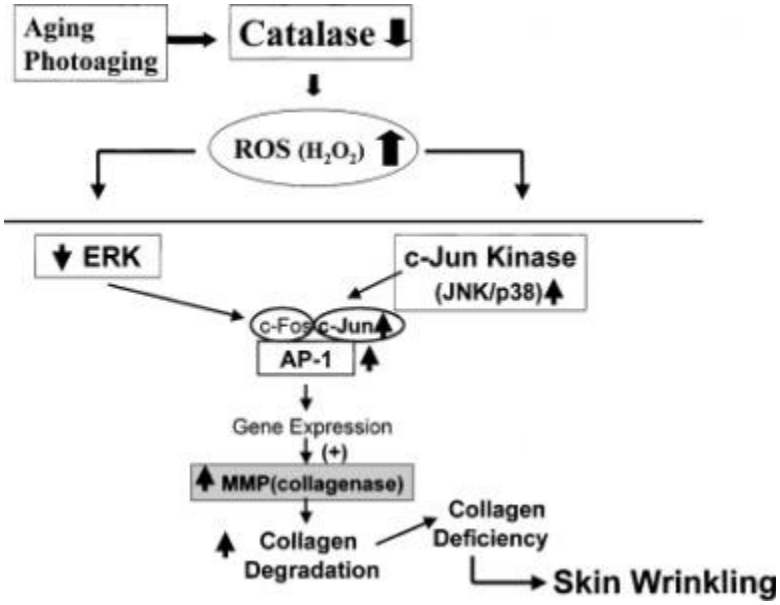


SKIN AGING AND OXIDATION



CAT AND OXIDATIVE DAMAGE

- The CAT gene provides instructions for making pieces (subunits) of an enzyme called catalase.
- Four identical subunits, each attached (bound) to an iron-containing molecule called a heme group, form the functional enzyme.
- Catalase is active in cells and tissues throughout the body, where it breaks down hydrogen peroxide (H2O2) molecules into oxygen (O2) and water (H2O).



CAT AND OXIDATIVE DAMAGE

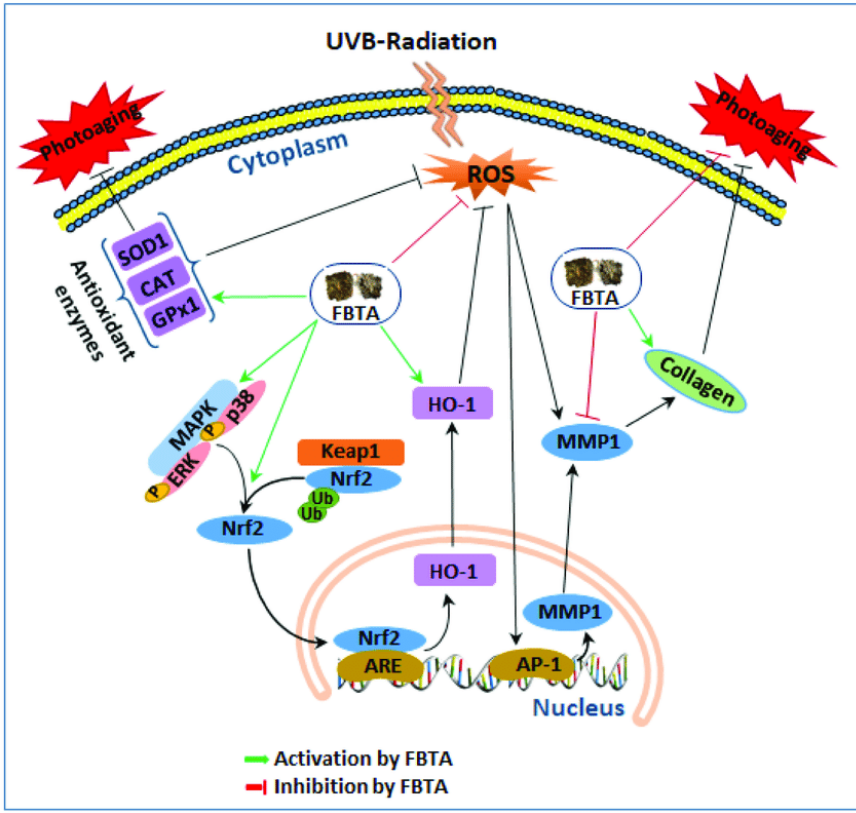
- T allele of the CAT C-262T gene polymorphism (rs1001179) has been associated with lower enzyme activity and hence increased levels of ROS
- T alleles associated with increased oxidative damage to skin and increased skin aging and melanoma

Genotype	Controls (%)	Patients (%)	OR	95 % CI	*p* value
C/C	65 (61.3 %)	58 (48.7 %)	Ref.	–	–
C/T	27 (25.5 %)	25 (21 %)	1.00	0.514–1.944	$1.00^{n.s}$
T/T	14 (13.2 %)	36 (30.3 %)	3.034	6.298–11.462	0.003

$^{n.s}$ Nonsignificant *p* value

GPX1 AND OXIDATIVE DAMAGE

- Glutathione peroxidase 1, also known as GPx1, is an enzyme that in humans is encoded by the GPX1 gene on chromosome 3
- This gene encodes a member of the glutathione peroxidase family.
- Glutathione peroxidase functions in the detoxification of hydrogen peroxide, and is one of the most important antioxidant enzymes in humans.
- Most important antioxidant defense in skin



GPX1 AND OXIDATIVE DAMAGE

- T allele of GPX-1 corresponding to a change of Proline to Leucine
- Reduced enzymatic activity
- Associated with increased oxidative stress including melanoma

Genotype	Controls	Melanoma			SCC			BCC		
	(%)	Cases (%)	Multivariate OR[b]	Multivariate OR[c]	Cases (%)	Multivariate OR[b]	Multivariate OR[c]	Cases (%)	Multivariate OR[b]	Multivariate OR[c]
GPX (rs1050450)										
Pro/Pro	419 (51.8)	94 (45.4)	1.00	1.00	128 (49.8)	1.00	1.00	141 (50.2)	1.00	1.00
Pro/Leu	327 (40.4)	86 (41.6)	1.18 (0.85 – 1.64)	1.18 (0.83 – 1.68)	107 (41.6)	1.07 (0.80 – 1.44)	1.08 (0.80 – 1.48)	124 (44.1)	1.12 (0.85 – 1.49)	1.20 (0.89 – 1.61)
Leu/Leu	63 (7.8)	27 (13.0)	1.93 (1.16 – 3.20)	2.14 (1.22 – 3.72)	22 (8.6)	1.14 (0.67 – 1.92)	1.15 (0.66 – 2.01)	16 (5.7)	0.76 (0.42 – 1.35)	0.85 (0.46 – 1.57)
p, trend			0.02	0.02		0.56	0.53		0.90	0.69
Pro/Pro	419 (51.8)	94 (45.4)	1.00	1.00	128 (49.8)	1.00	1.00	141 (50.2)	1.00	1.00
Leu carrier	390 (48.2)	113 (54.6)	1.30 (0.96 – 1.77)	1.32 (0.95 – 1.84)	129 (50.2)	1.08 (0.82 – 1.43)	1.09 (0.81 – 1.47)	140 (49.8)	1.06 (0.81 – 1.40)	1.14 (0.86 – 1.52)

NQO1 AND OXIDATIVE DAMAGE

- NAD(P)H dehydrogenase [quinone] 1 is an enzyme that in humans is encoded by the NQO1 gene
- Quinonoid compounds generate reactive oxygen species (ROS) via redox cycling mechanisms and arylating nucleophiles.
- NQO1 is employed in the removal of a quinone from biological systems
- This reaction ensures complete oxidation of the substrate without the formation of semiquinones and species with reactive oxygen radicals that are deleterious to cells.

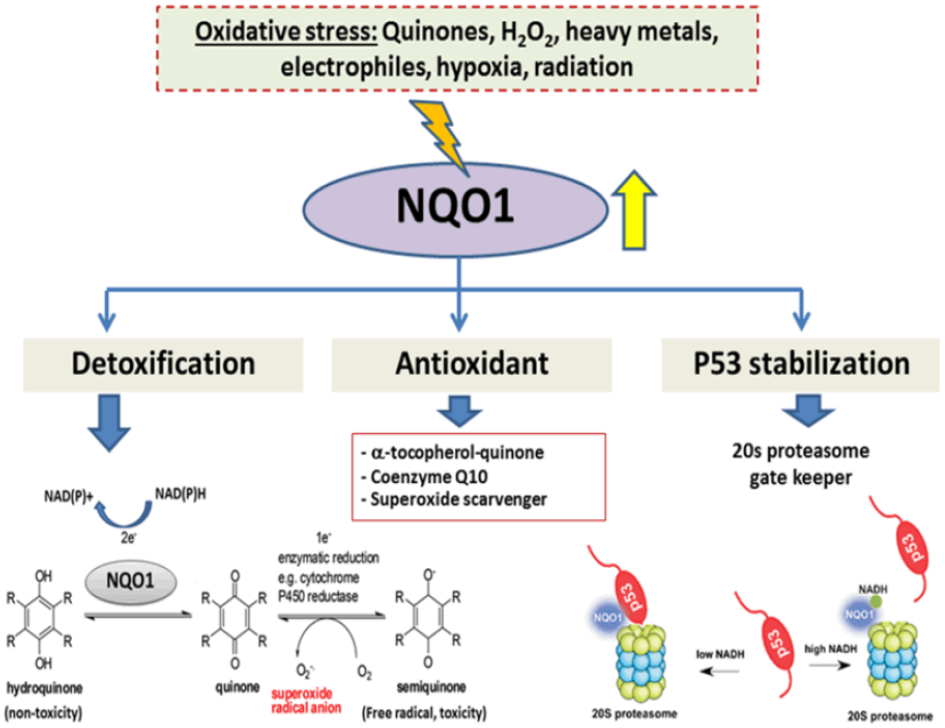


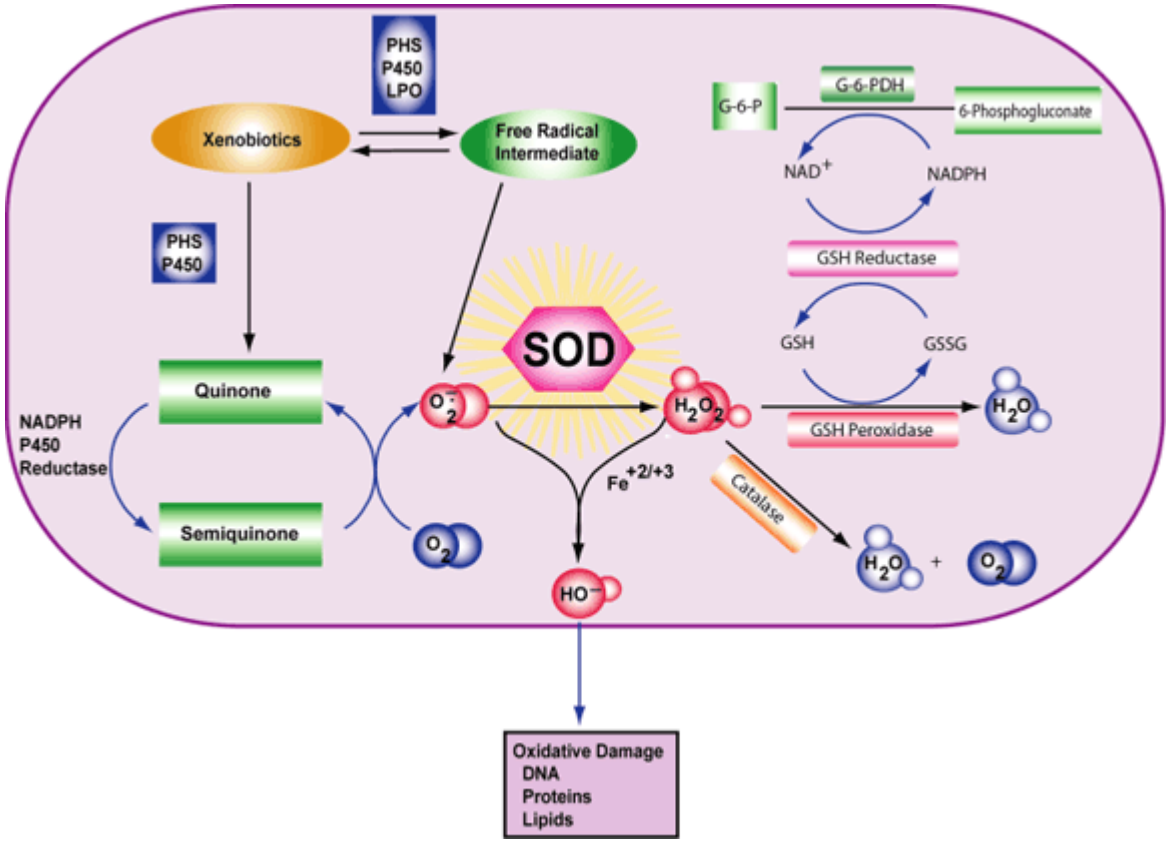
Figure 3: Schematic summarization of NAD(P)H-quinone oxidoreductase 1 (NQO1) functions.

NQO1 AND OXIDATIVE DAMAGE

- T allele of NQO1 rs1800566 associated with increased oxidative stress
- Reduced NQO1 protein expression (Proline -> Serine)
- Decreased NQO1 enzymatic activity is caused by increased polyubiquination and proteosomal degradation of the mutant NQO1 protein
- Associated with increased oxidative stress to skin
- Associated with increased progression of melanoma

Superoxide Dismutase

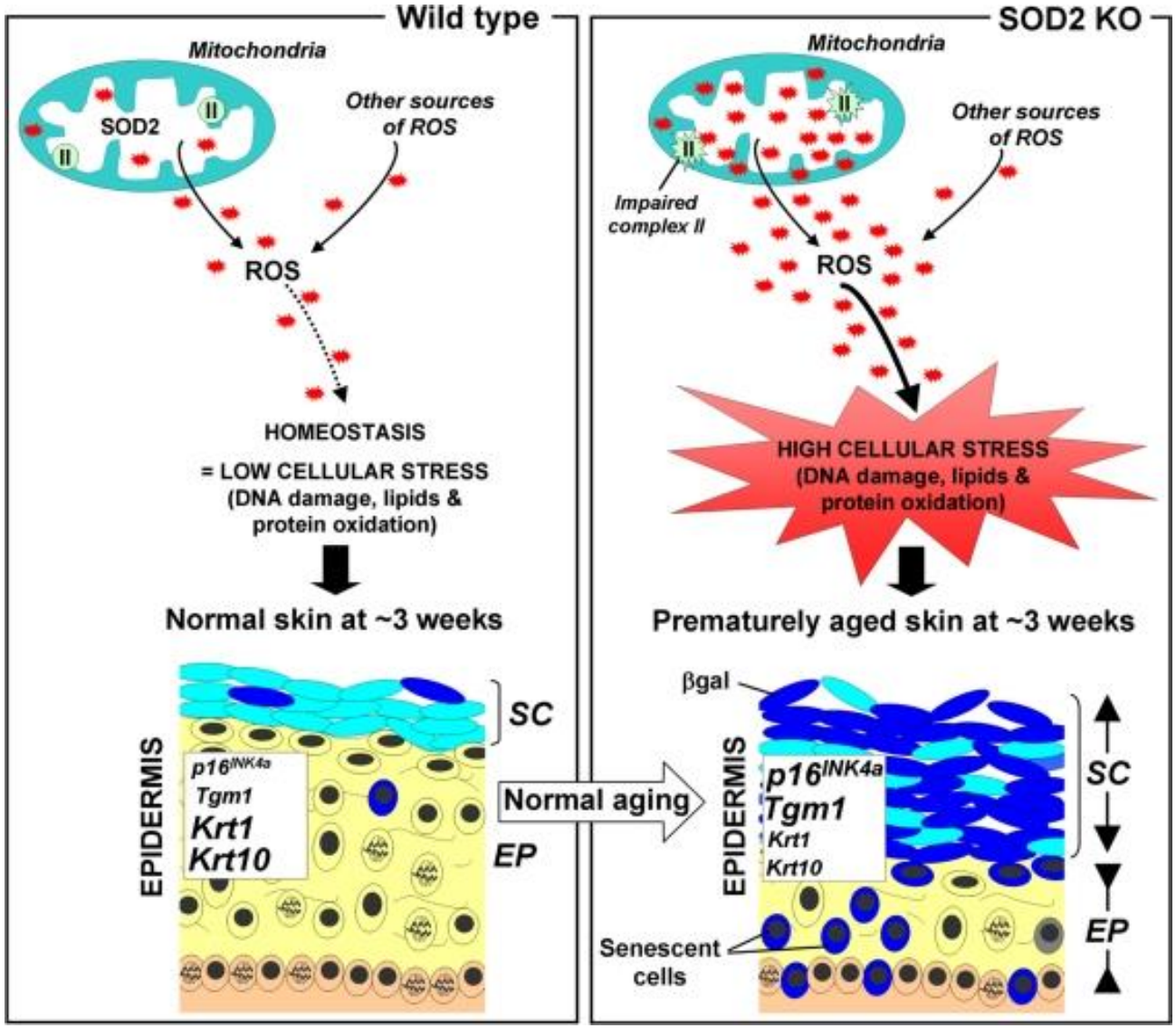
- Superoxide dismutase (SOD) is one of the primary antioxidant enzymes.
- SOD catalyzes the conversion of superoxide ($O_2^{\bullet -}$) to hydrogen peroxide (H_2O_2).



SOD AND OXIDATIVE STRESS

- Superoxides are a major causative agent for oxidative damage
- Reactive oxygen species
- Generated by immune cells as they kill infected cells
- Generated during mitochondrial respiration
- Generated by environmental toxins
- Associated with cancer, inflammation, aging and chronic diseases
- Superoxide dismutase is critical for elimination of superoxides

SOD2 AND PREMATURE SKIN AGING



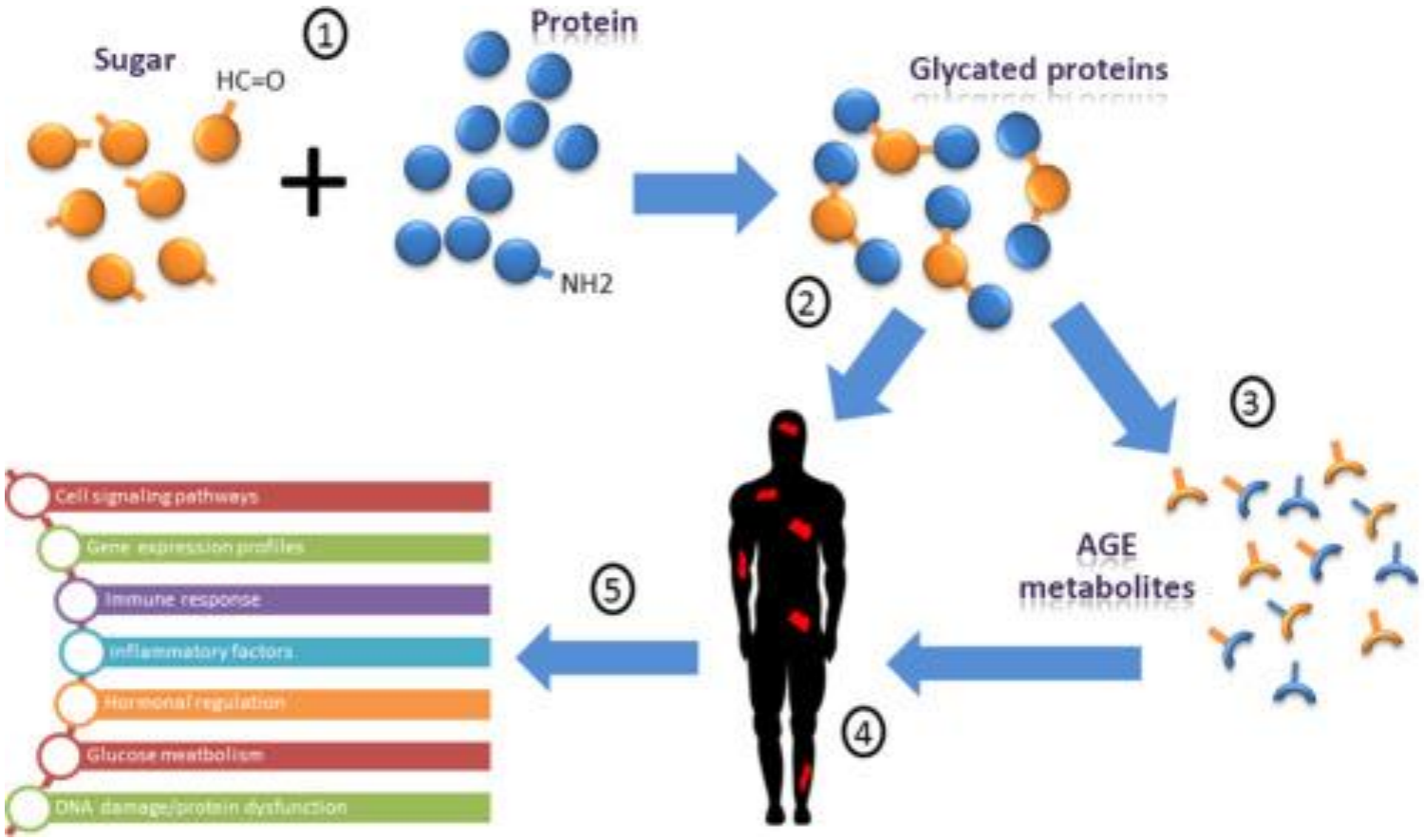
SOD2 AND OXIDATIVE DAMAGE

- Polymorphisms associated with reduced SOD activity
- Associated with reduced anti-oxidant activity
- Prone to oxidative damage
- Polymorphisms associated with premature skin aging, increased oxidative damage to skin and melanoma risk

WHAT DOES IT MEAN?

- Reduced CAT, GPX-1, NQO1 and SOD2 activity associated with increased production of ROS and increased oxidative stress to skin which can impact skin aging and melanoma risk
- Topical application of Ascorbic acid (Vitamin C), Vitamin E, resveratrol, zinc, coenzyme Q10 and tretinoin containing creams. Oral supplementation with lycopene, beta carotene along with green tea and cocoa.

AGE

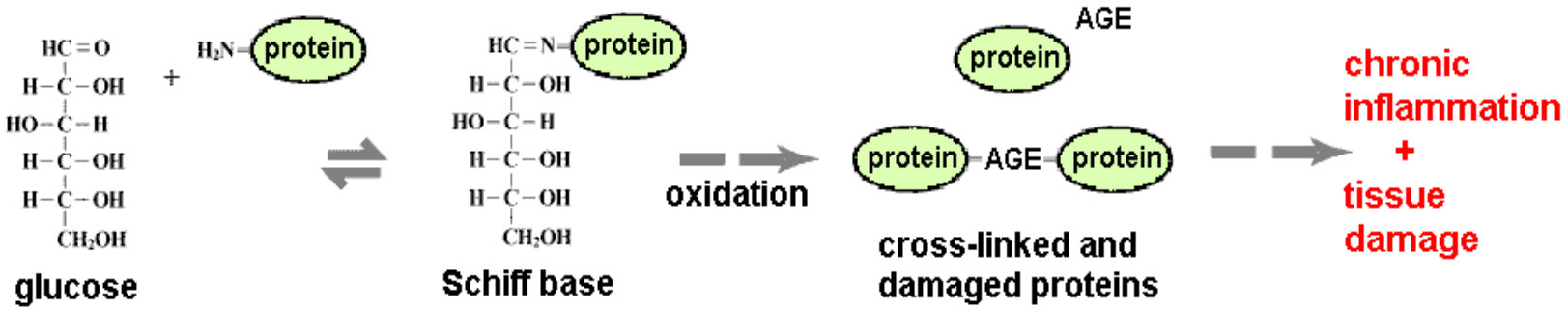

Sugar
HC=O
1
Protein
NH2
Glycated proteins
2
3
AGE
metabolites
4
5
Cell signaling pathways
Gene expression profiles
Immune response
Inflammatory factors
Hormonal regulation
Glucose metbolism
DNA damage/protein dysfunction

Formation of AGEs

Advanced glycation end products (AGEs for short) are complex, oxidant compounds created when simple sugars crosslink with proteins or lipids through non-enzymatic reaction.

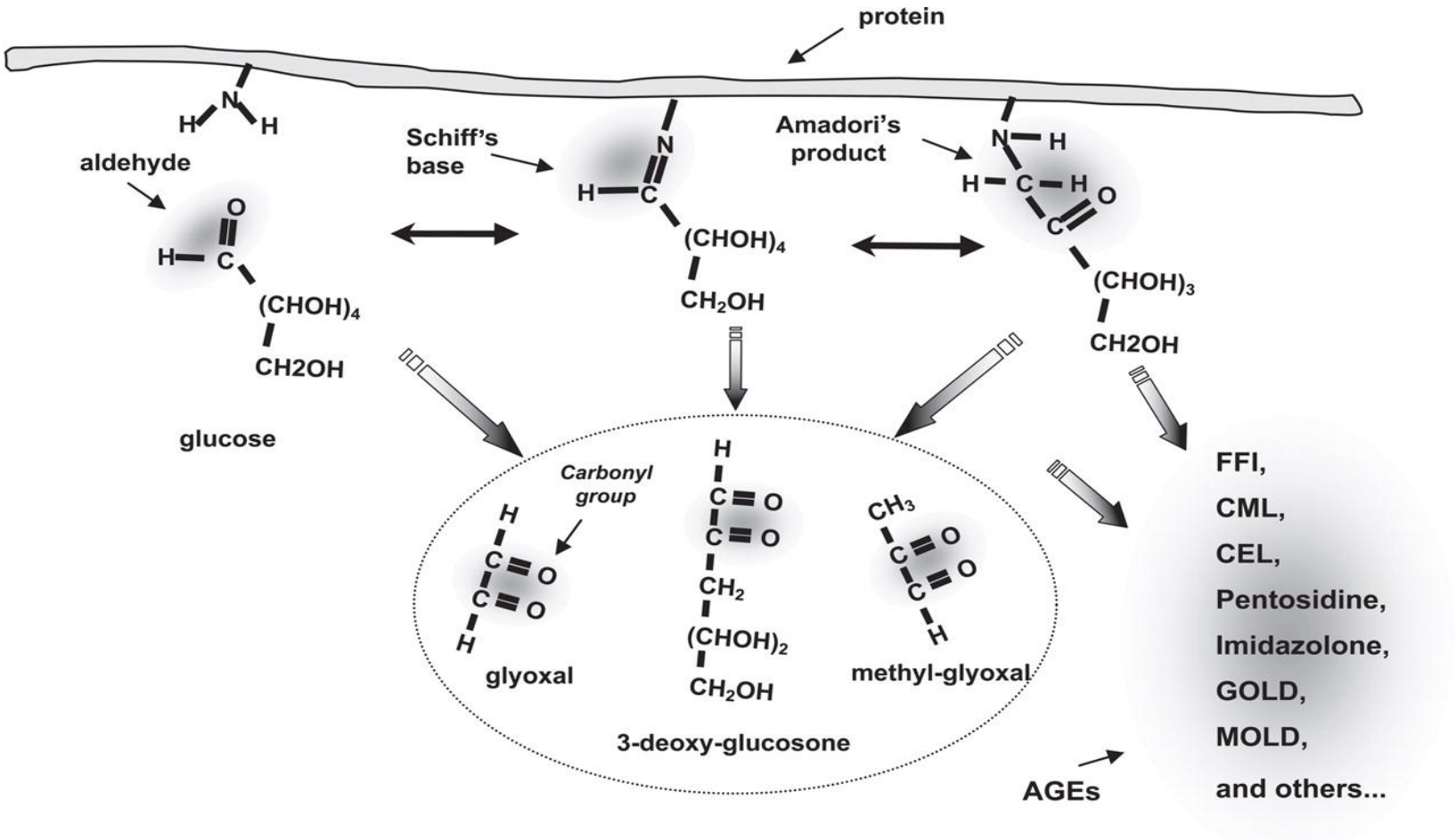
- Step 1: Non-enzymatic reaction between amine and reducing sugar makes Schiff's base
- Step 2: Schiff base converts to Amadori's product
- Step 3: Series slower chemical reactions occur to form irreversible products (AGEs)

Formation of AGEs



Glycation is the non-enzymatic condensation of the aldehyde and ketone groups in sugars with the amino groups in proteins to initially yield Schiff bases. These undergo further chemical reactions to produce AGEs.

Formation of AGEs



Basta et al. Advanced glycation end products and vascular inflammation: implications for accelerated atherosclerosis in diabetes. *Cardiovascular Research*. 2004; 63: 582-592.

SKIN AND AGE

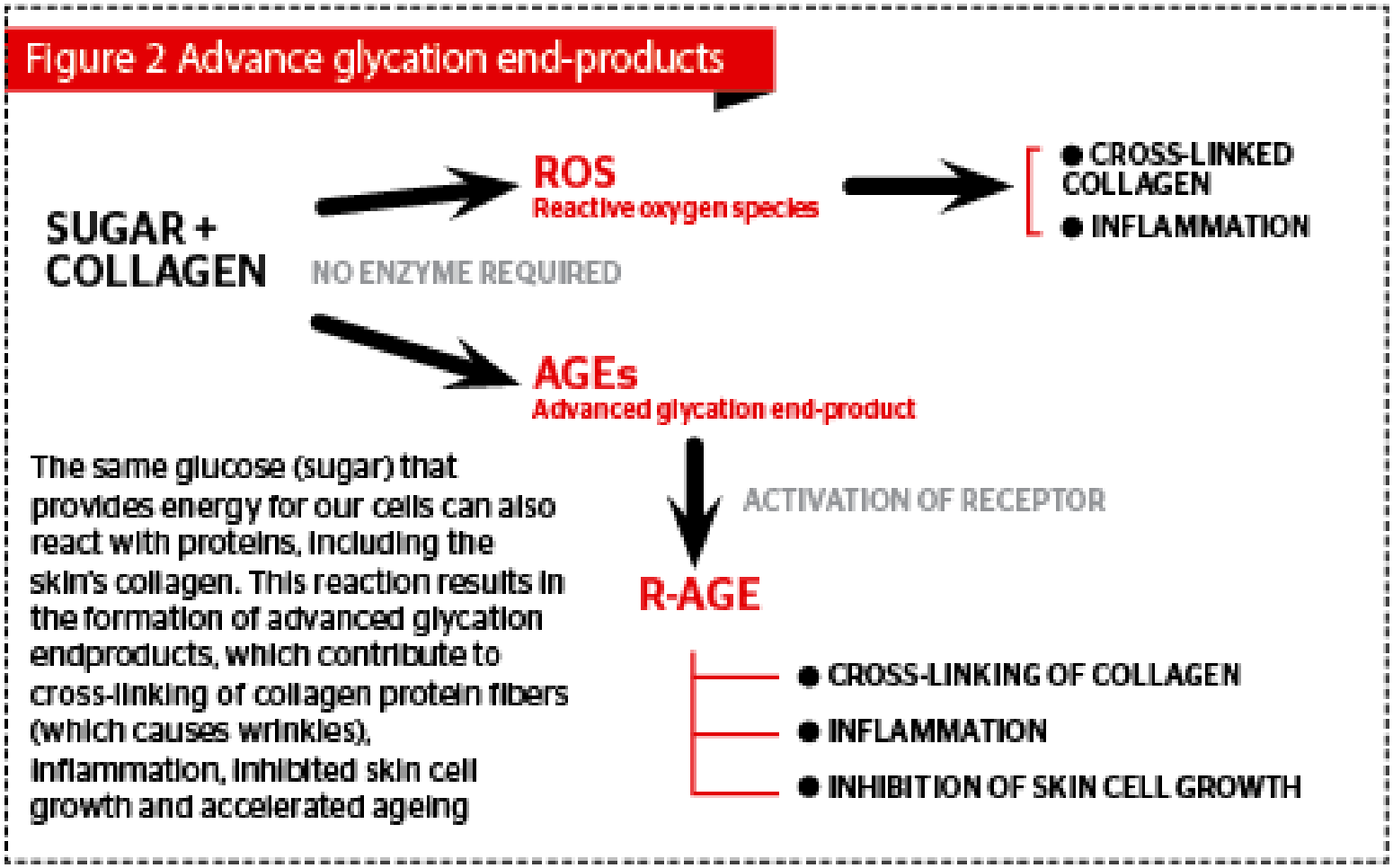


Figure 2 Advance glycation end-products
SUGAR + COLLAGEN
NO ENZYME REQUIRED
ROS
Reactive oxygen species
● CROSS-LINKED COLLAGEN
● INFLAMMATION
AGEs
Advanced glycation end-product
ACTIVATION OF RECEPTOR
R-AGE
● CROSS-LINKING OF COLLAGEN
● INFLAMMATION
● INHIBITION OF SKIN CELL GROWTH
The same glucose (sugar) that provides energy for our cells can also react with proteins, including the skin's collagen. This reaction results in the formation of advanced glycation endproducts, which contribute to cross-linking of collagen protein fibers (which causes wrinkles), inflammation, inhibited skin cell growth and accelerated ageing

AGE AND SKIN AGING

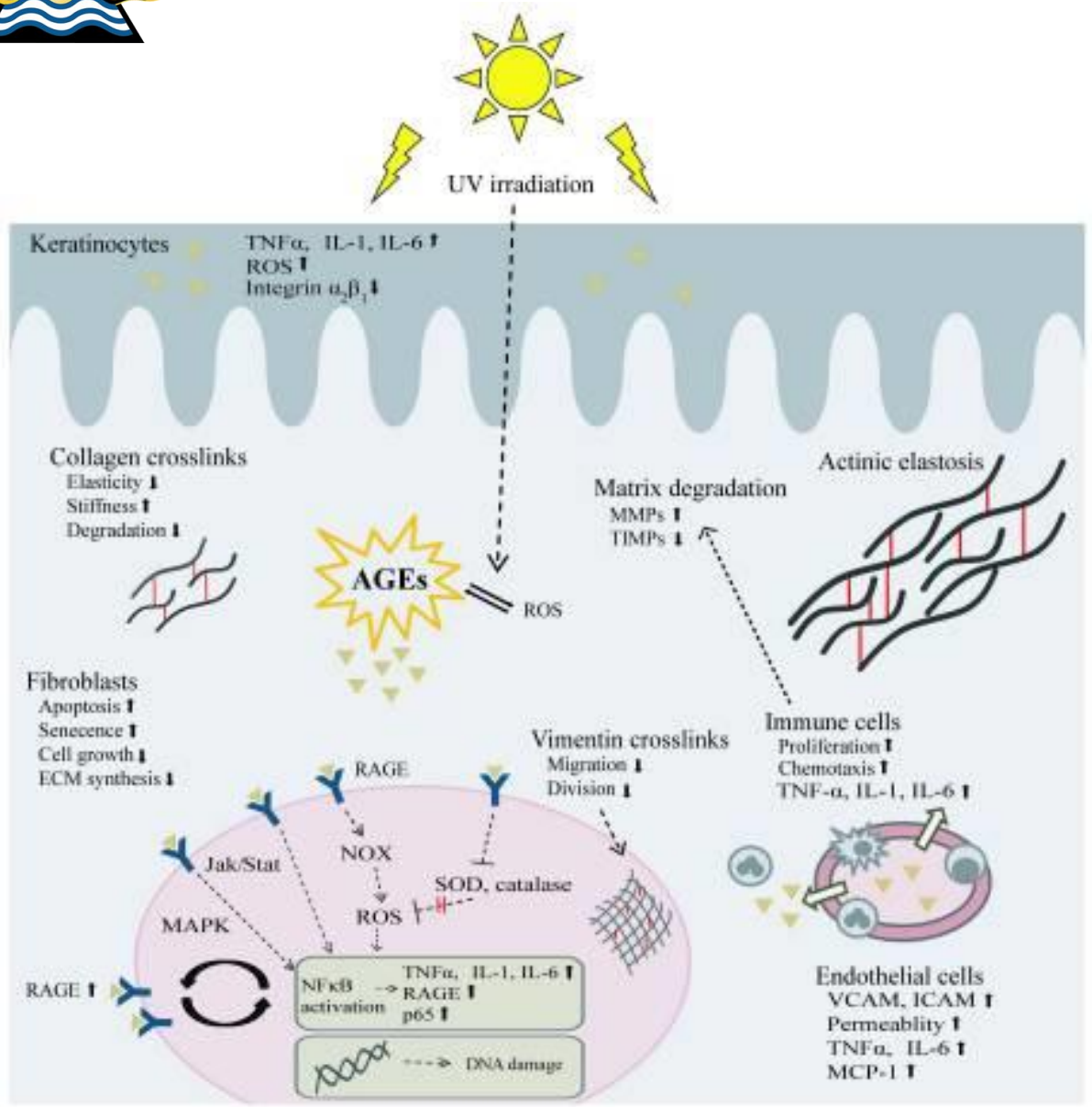
Table 1. Detected AGEs in skin*

CML	Epidermis[18] Aged and diabetic dermis[19-22] Photoaging-actinic elastosis[20,23]	Epidermis (SC -CK10, SS, SG)[18] Collagen[19-21] Vimentin[22] Elastin[20,23]	LC-ESI-TOF-MS, IF, IB[18] SIM/GC-MS[19,21] IHC[20,22,23] ELISA,[23] confocal microscopy[23]
Pentosidin	Aged and diabetic dermis[19,24,25]	Collagen[19,24,25]	Reversed-phase HPLC,[19,24] ELISA,[25] IB[25]
GO	Aged dermis[21]	Collagen[21]	LC/MS[21]
MGO	Aged dermis[21]	Collagen[21]	LC/MS[21]
Glucosepane	Aged dermis[21,26]	Collagen[21,26]	LC/MS[21,26]
Fructoselysine	Aged dermis[21]	Collagen[21]	LC/MS[21]
CEL	Aged dermis[21,27]	Collagen[21,27]	LC/MS[27] SIM/GC-MS[21]
GOLD	Aged dermis[28]	Collagen[28]	LC/MS[28]
MOLD	Aged dermis[28]	Collagen[28]	LC/MS[28]

RAGE AND SKIN AGING

- RAGE (receptor for advanced glycation end products), also called AGER
- RAGE binds to advanced glycation end products
- RAGE activation can directly induce oxidative stress by activating nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase (NOX), decreasing activity of superoxide dismutase (SOD), catalase and other pathways, and indirectly by reducing cellular antioxidant defenses, like GSH and ascorbic acid.
- The reduction of GSH leads furthermore to decreased activity of Glo I, the major cellular defense system against methylglyoxal, therefore supporting further production of AGEs.

RAGE AND SKIN AGING



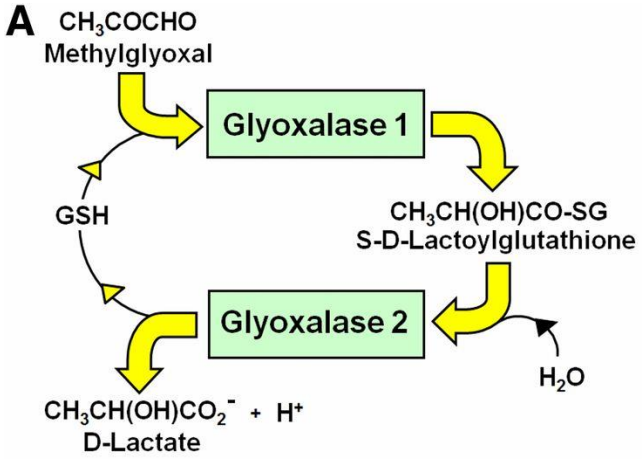
- Endogenous production of AGE
- AGE from diet

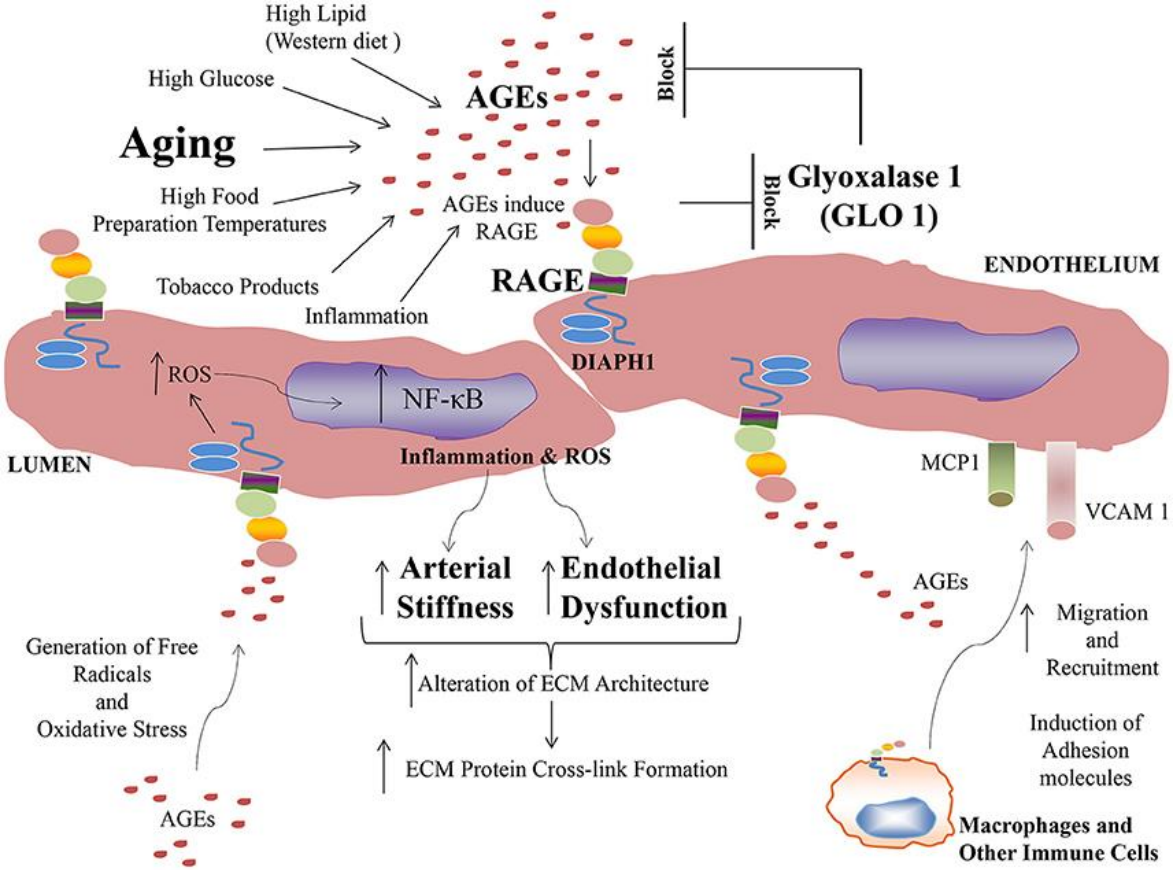
RAGE AND SKIN AGING

- One of the most frequently studied and relatively high prevalence variants is the Gly82Ser (or G82S) polymorphism
- It is at codon 82 (GGC→AGC) in exon 3 of RAGE and leads to a change from glycine to serine within the putative ligand-binding domain of the protein (rs2070600 – T allele)
- It has been proposed as a functional polymorphism and associated with enhanced RAGE signaling – associated with increased impact of AGE on skin and vital organs, also associated with increased cancer risk

GLO1 AND SKIN AGING

- Encodes for Glyoxalase I
- Breaks down AGE such as methylglyoxal





WHAT DOES IT MEAN?

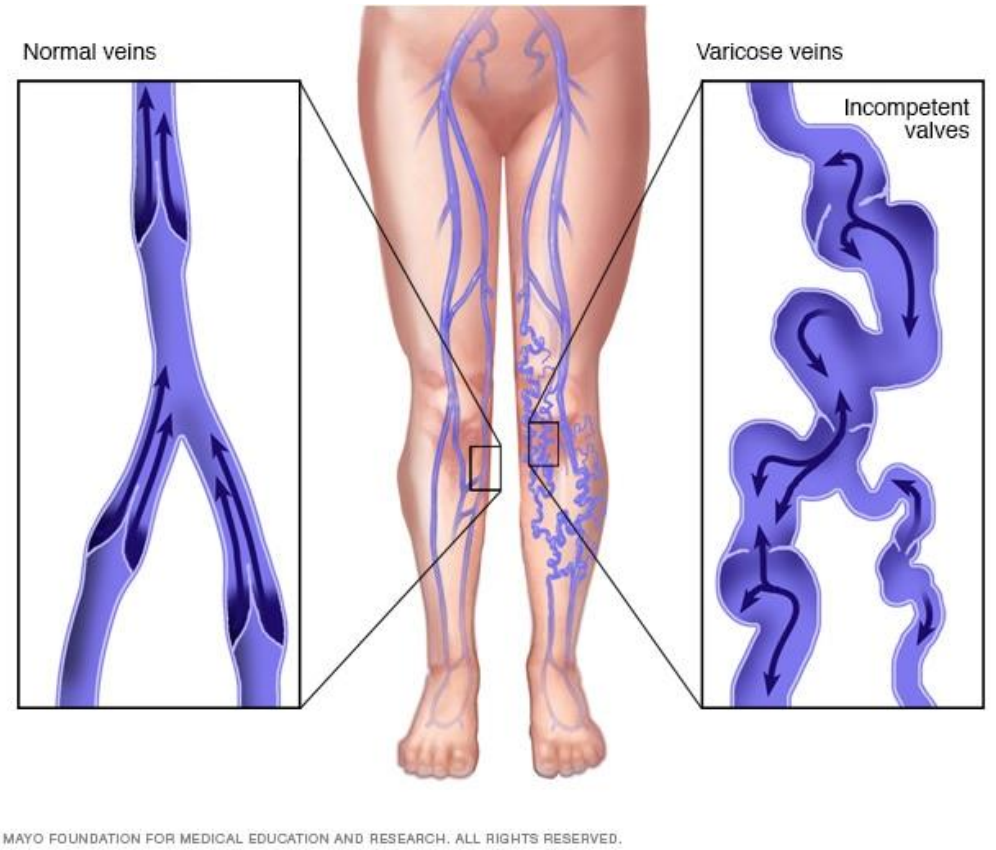
- Increased RAGE and reduced GLO1 activity associated with increased risk to glycation products which impacts skin health and promotes skin aging
- Limit intake of foods cooked at high temperature and use acidic liquids (lemon, vinegar etc.) with foods to reduce their AGE content. Incorporate consumption of green tea in your diet.

SKIN ELASTICITY

- Skin is one of the most elastic organs
- Skin aging associated with loss in skin elasticity
- Mutations associated with genes that play a role in maintaining skin architecture and elasticity associated with several disorders
- Varicose veins
- Cellulite
- Stretch marks

VARICOSE VEINS

- Varicose veins are superficial veins that have become enlarged and twisted. Typically they occur just under the skin in the legs.
- Usually they result in few symptoms but some may experience fullness or pain in the area.
- Spider veins – minor varicose



MTHFR AND VARICOSE VEINS

- MTHFR is an enzyme that is important in homocysteine metabolism.
- Therefore, alterations in the enzyme function (as seen in gene polymorphic variants) could lead to elevated levels of homocysteine, free radical formation, and endothelial damage.
- This could potentially lead to oxidative stress and dysfunctional endothelium.
- Impact on the valve in the veins -> Varicose veins

MTHFR AND VARICOSE VEINS

c.1298A>C combined genotypes.

677 \ 1298	AA	AC	CC
CC	unclear, most likely trunk type	perforator type, increasing risk of CEAP C3–6	perforator type, highest risk of CEAP C3–6,
CT	trunk type	trunk and perforator type, increasing risk of CEAP C3–6	
TT	trunk type		

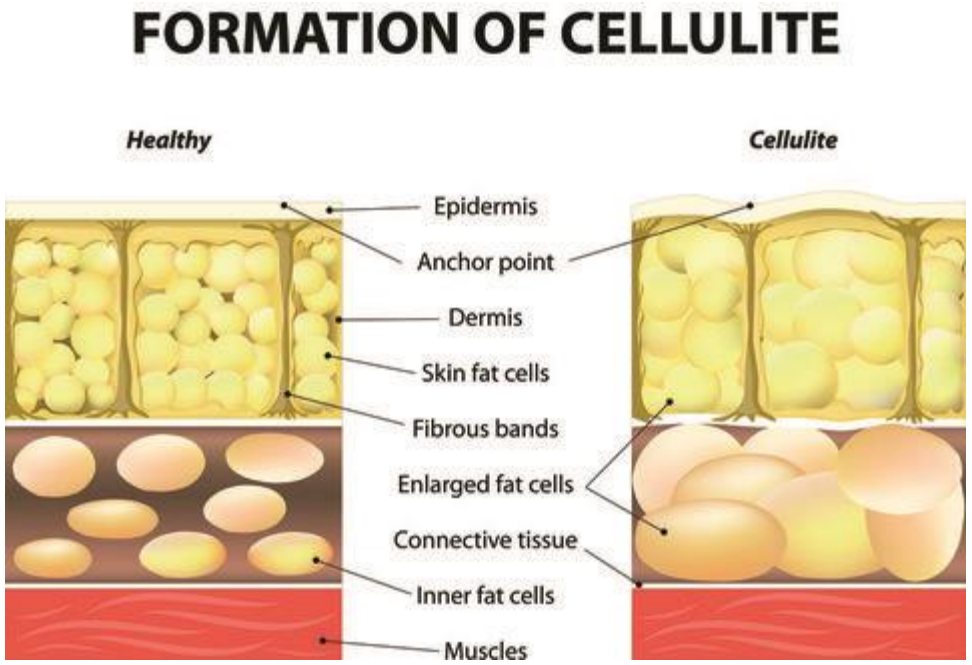
trunk varicose veins – these are near to the surface of the skin and are thick and knobbly; they're often long and can look unpleasant.

Perforator – deeper impact

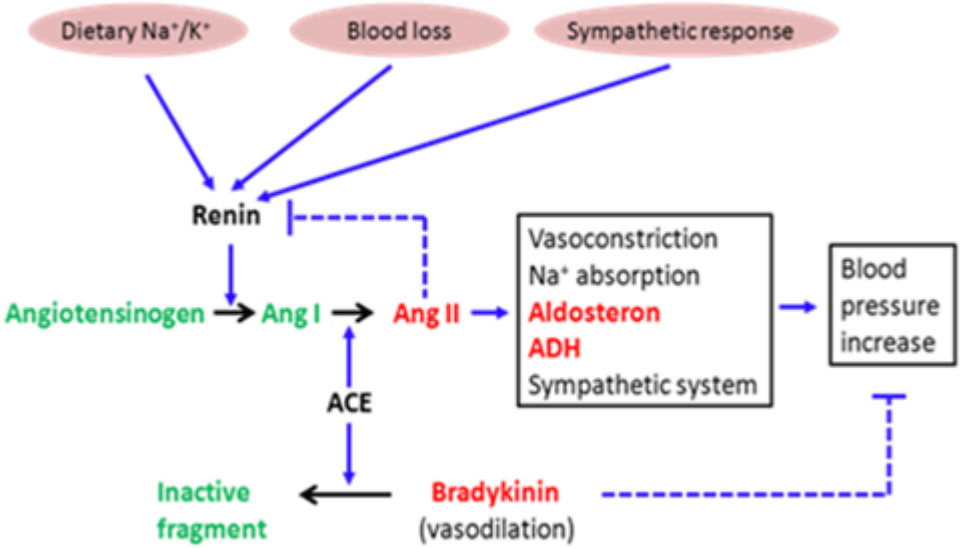
If at risk - Maintain a healthy lifestyle (with diet and exercise) to prevent weight gain and 5-methylfolate supplementation

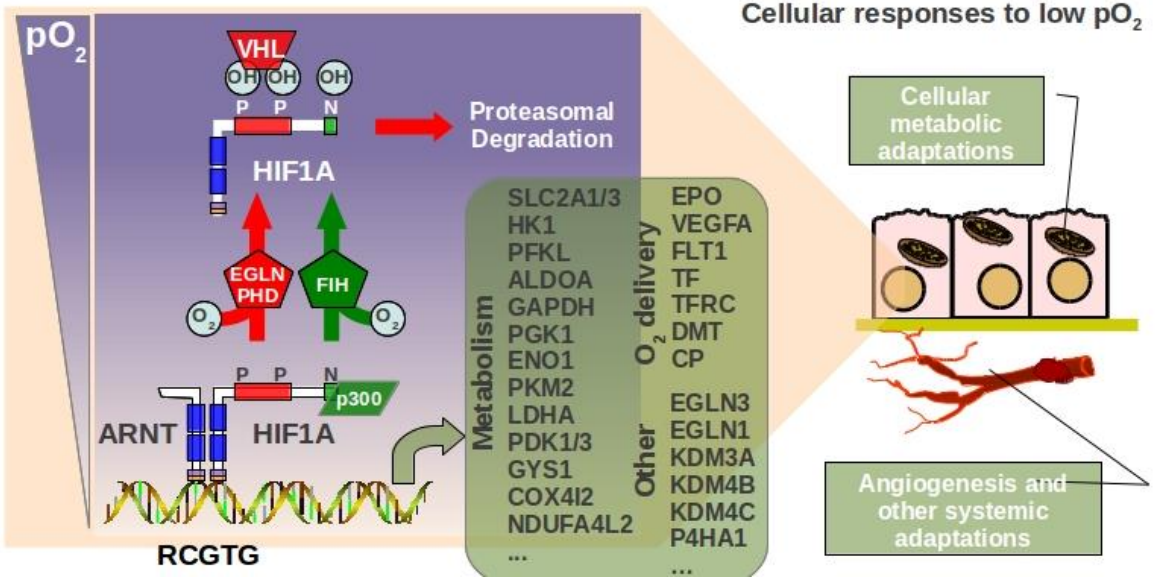
CELLULITE

- Cellulite is a condition in which the skin has a dimpled, lumpy appearance.
- It usually affects the buttocks and thighs but can also occur in other areas.
- Cellulite occurs when fat deposits push through the connective tissue beneath the skin.

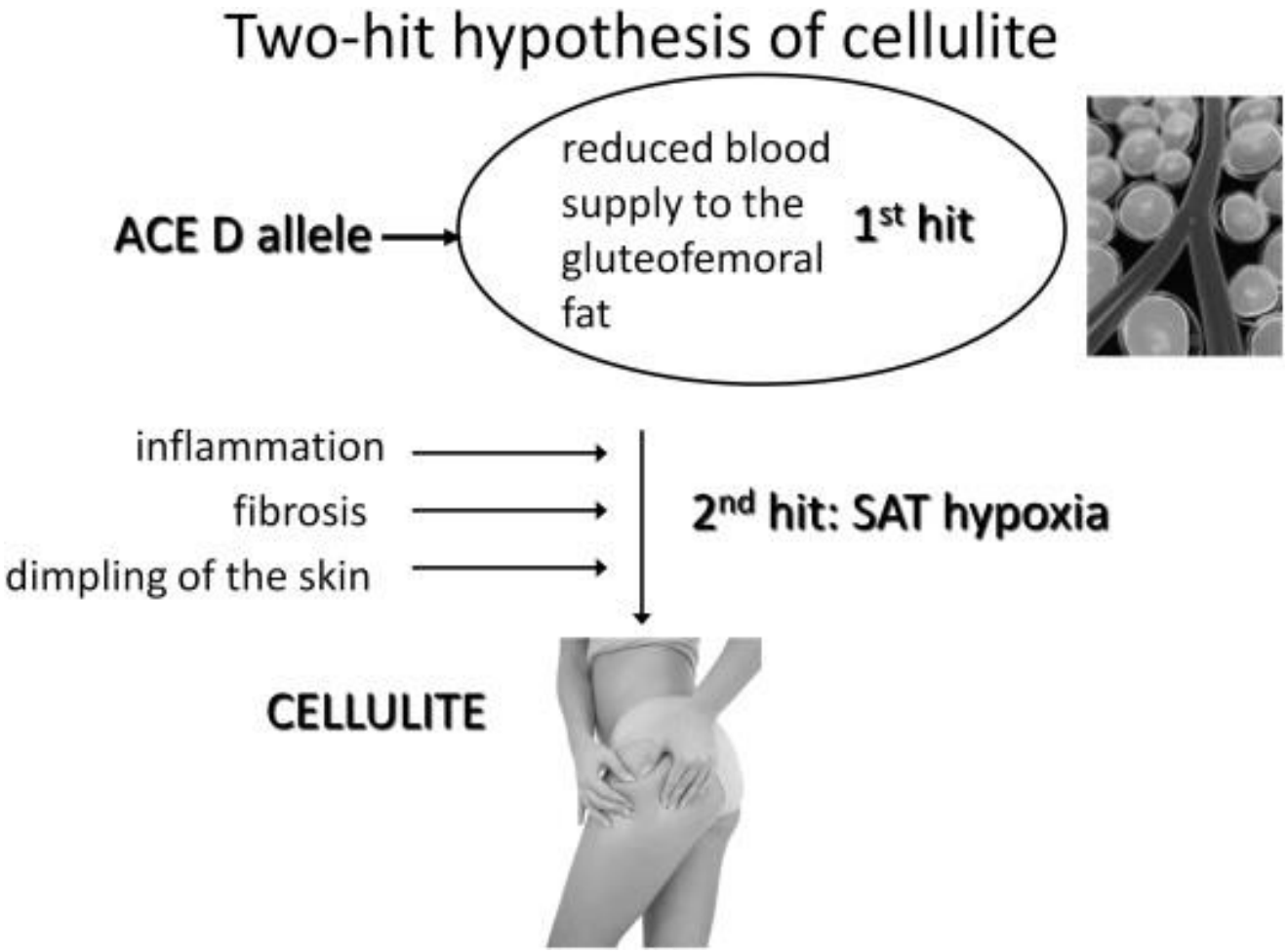


CELLULITE – ACE AND HIF1A





CELLULITE – ACE AND HIF1A



CELLULITE – ACE AND HIF1A

out cellulite

ACE rs1799752		Lean women with cellulite (n = 200), n (%)	Lean women without cellulite (n = 200), n (%)	P
Genotype	Allele			
ACE II		32 (16.0%)	52 (26.0%)	<0.01
ACE ID		87 (43.5%)	93 (46.5%)	
ACE DD		81 (40.5%)	55 (27.5%)	
	ACE D	249 (62.3%)	203 (50.8%)	<0.01
HIF1A rs11549465				
Genotype				
HIF1A CC		170 (85.0%)	145 (72.5%)	<0.01
HIF1A CT		25 (12.5%)	42 (21.0%)	
HIF1A TT		5 (2.5%)	13 (6.5%)	
	HIF1A T	35 (8.7%)	68 (17.0%)	

WHAT DOES IT MEAN?

- ACE and HIF1A polymorphisms contribute to development of cellulite
- Oral consumption of bioactive collagen peptides has shown efficacy in reducing cellulite. Topical application of creams containing caffeine and retinol has shown efficacy in combating cellulite risk

STRETCH MARKS

- Stretch marks, the medical term for which is striae (striae distensae; striae atrophicus), are common skin findings which typically develop in the first half of life. They are usually benign but may be a source of cosmetic concern to patients.
- Clinically striae appear initially as asymmetric, raised, red linear streaks (striae rubrae) that tend to flatten and lighten over time.
- They are typically found on the hips, thighs, abdomen and buttocks in patients who are adolescents, overweight, pregnant women or anyone whom experiences a phase of rapid development or weight gain.

STRETCH MARKS GENETICS

- ELN gene encodes for Elastin which is a major protein that provides strength and flexibility to connective tissues including skin. Genetic variants that impact ELN are associated with predisposition to stretch marks.
- HMCN1 encodes for a protein which is involved in attachment of mechanosensory neurons to the epidermal layer of the skin. Genetic variants in HMCN1 have been associated with stretch mark development.
- Although the exact function of SRPX is not understood, mutations in SRPX are associated with development of stretch marks.
- TMEM18 encodes for transmembrane protein 18 which plays a role in obesity and related traits. Certain genetic variants of TMEM18 are associated with development of stretch marks.

STRETCH MARKS

AnantLife

Table 1. Index SNPs for regions associated with striae distensae at a significance level of $P<1e{-}6$

						Discovery		Pregnancy	
SNP	Chr (pos)[1]	Gene[2]	All[3]	MAF[4]	r^2 [5]	P[6]	OR (CI)[7]	P[6]	β (CI)[8]
rs7787362*	7 (73392603)	*ELN* (u)	C/T	0.467	0.992	1.8E − 23	0.84 (0.81–0.87)	7e − 5	0.072 (0.053–0.091)
rs35318931	X (38009121)	*SRPX* (i)	G/A	0.079	0.964	1.1E − 13	0.82 (0.77–0.86)	0.026	0.067 (0.033–0.102)
rs10798036	1 (186052962)	*HMCN1* (i)	C/C	0.485	0.989	6.9E − 10	1.11 (1.08–1.15)	0.06	− 0.029 (− 0.048 to − 0.010)
rs7594220	2 (643320)	*TMEM18* (d)	A/G	0.194	0.946	9.8E − 09	0.88 (0.84–0.92)	0.70	− 0.067 (− 0.192 to 0058)
chr6:36311047	6 (36311047)	*PNPLA1* (d)	C/T	0.007	0.988	9.7E − 08	1.80 (1.45–2.23)		
rs3910516	2 (216303053)	*FN1* (u)	G/A	0.262	0.909	2.7E − 07	1.11 (1.07–1.16)		
rs62034322	16 (28535834)	*NPIPL2* (i)	G/A	0.359	0.946	4.7E − 07	1.10 (1.06–1.14)		

[1]Chromosome (chr) and position (pos) are with respect to build 37.

[2]Gene is gene that is the most likely candidate for the association or the association or the closest gene. Whether the single-nucleotide polymorphism (SNP) is upstream (u), downstream (d), or within (i) the gene is indicated in parentheses.

[3]Alleles are major/minor in the context of European ancestry.

[4]MAF is minor allele frequency in the entire 23andMe European research cohort (over 120,000 individuals).

[5]r^2 is the estimated imputation accuracy.

[6]Associations with a P-value $<5e-8$ are genome-wide significant, and those with P-values between $1e-6$ and $5e-8$ are defined as suggestive.

[7]For the discovery set (which included both men and women), the odds ratio (OR) plus confidence interval (CI) is with respect to the minor allele and represents the risk of developing stretch marks.

[8]For the pregnancy set (which included only women), the β plus CI is with respect to the major allele, with positive numbers representing an increase in the severity of stretch marks. These tests were run only for SNPs reaching genome-wide significance in the discovery set. SNPs marked with an asterisk are typed by our genotyping array.

WHAT TO DO?

- If at risk identified
- Topical application of cream containing all of Centella asiatica extract, vitamin E, and collagen hydrolysates has shown efficacy in reducing incidence of stretch marks

SKIN PIGMENTATION

- Melanin is the key component responsible for skin pigmentation.
- Dermal melanin is produced by melanocytes, which are found in the stratum basale of the epidermis.
- Although human beings generally possess a similar concentration of melanocytes in their skin, the melanocytes in some individuals and races more frequently or less frequently express the melanin-producing genes, thereby conferring a greater or lesser concentration of skin melanin.
- In response to sunlight, UV radiation triggers melanogenesis which leads to production of melanin, not only leading to tanning but also acting as dissipater of most of the UV radiation, thereby playing a protective role in prevention of melanoma.
- Genetic variants that regulate melanogenesis play a key role in determining our response to sun exposure.
- CANCER RISK

Skin Cancer

- Most common cancer in US
- Fastest increasing cancer in US
- 1,000,000 people had some form of skin cancer in 2003

Skin Cancer

- Three main types
  - basal-cell
  - squamous-cell
  - melanoma

The main difference between melanomas and other skin cancers is that melanoma can metastasize (spread) to distant body sites including the lungs, liver or brain.

Melanoma

*Seventh most common cancer in the United States.

*One out of every 105 Americans born in 1991 will develop malignant melanoma (compared to 1 out of 1,500 in 1935).

*The number of new cases of melanoma has more than doubled since 1973.

Melanoma (cont.)

- Most common cancer in young adults age 25-29
- Among women age 30-35, incidence is exceeded only by breast cancer
- Incidence increasing 4% annually, higher than any other cancer
- On average, one melanoma death in the U.S. per hour

Melanoma (cont.)

- Increase is the result of recreational sun exposure, thinning of the ozone layer, and better detection.
- In 2001, an estimated 48,000 new cases of melanoma occurred.
- In 2003, 54,000 new cases occurred
- In 2000, skin cancer claimed the lives of 9,600 people.

Risk factors- Malignant Mel

- Fair skin, red hair, and blue eyes
- Intermittent sun exposure
  - Sunburns
  - Tanning beds
- Freckles and melanocytic nevi
- Family history of melanoma

Ultraviolet (UV) Radiation
UVA – UVB - UVC

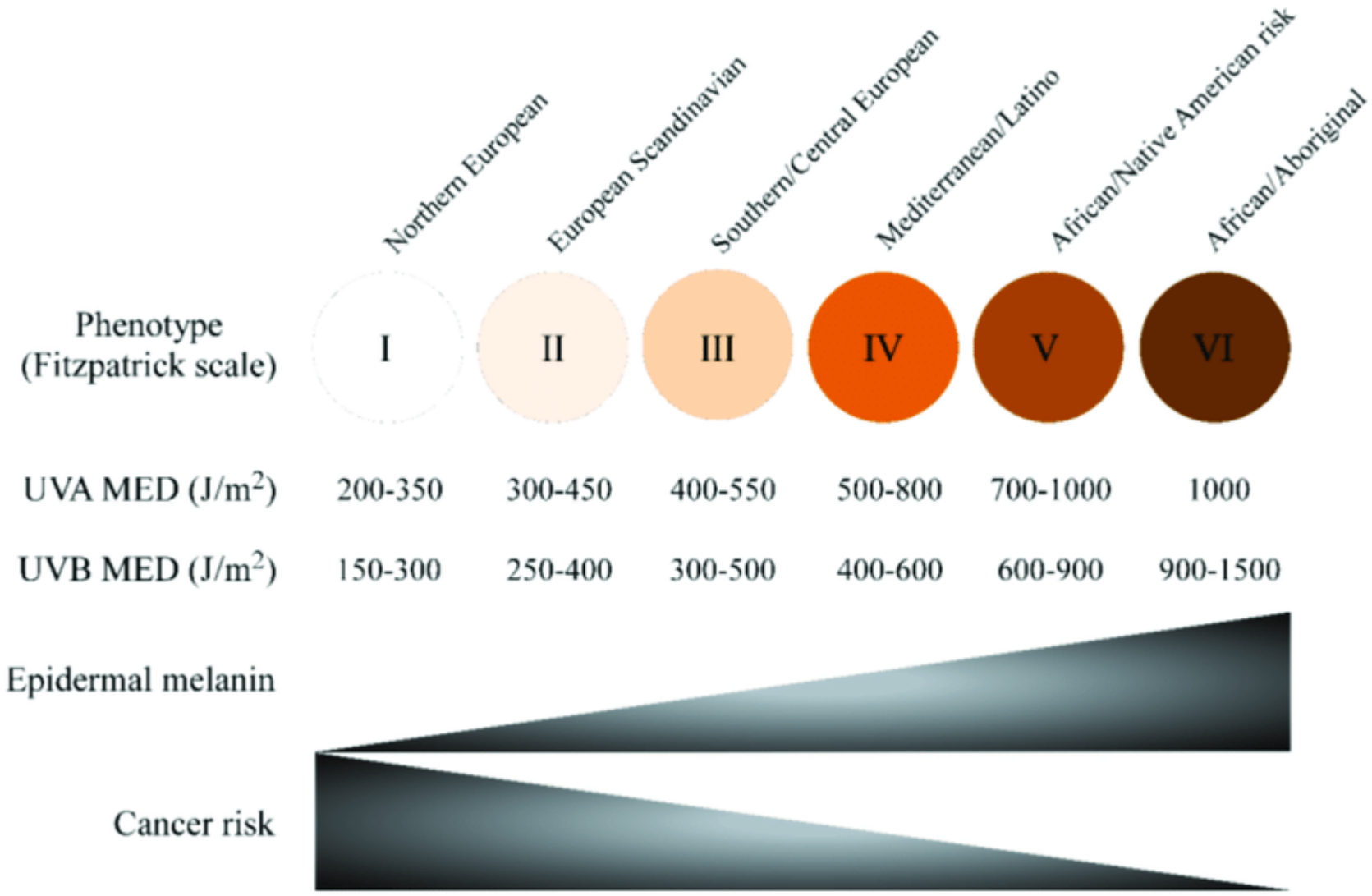
The sun radiates energy over a broad spectrum of wavelengths. UV radiation, which has a shorter wavelength than visible blue or violet light, is responsible for sunburns and other health effects:

- Skin cancer
- Cataracts
- Suppression of the immune system
- Premature aging of the skin

SKIN PIGMENTATION AND CANCER

Extrinsic Risk Factors		Intrinsic Risk Factors	
Ultraviolet Radiation	UV exposure, especially blistering sunburns in childhood, correlates with melanoma risk.	**History of Skin Cancer**	A family and personal history of melanoma and non-melanoma skin cancer increases risk of melanoma
	Countries located closer to the equator with increased sun exposure have a higher melanoma incidence rate	**Nevi**	A large number of congenital nevi, nevi with large diameter, and dysplastic nevi are all associated with an increased risk
	Indoor tanning bed use increases incidence and mortality rate of melanoma	**Medical History**	Immunosuppressive states and a past medical history of non-cutaneous skin cancer increase the risk of melanoma
Medication	Psoralen, UVA light therapy and neonatal blue light phototherapy are associated with an increased risk of melanoma	**Defective DNA Repair**	Individuals diagnosed with xeroderma pigmentosum cannot repair UV induced DNA damage
Environmental Exposure	Polyvinyl chloride, heavy metals and pesticides are associated with an increased risk of melanoma	**Skin Complexion**	Fair skin, inability to tan, and increased susceptibility to UV induced sunburn increase risk for melanoma

SKIN PIGMENTATION AND CANCER



SKIN PIGMENTATION-EVOLUTION

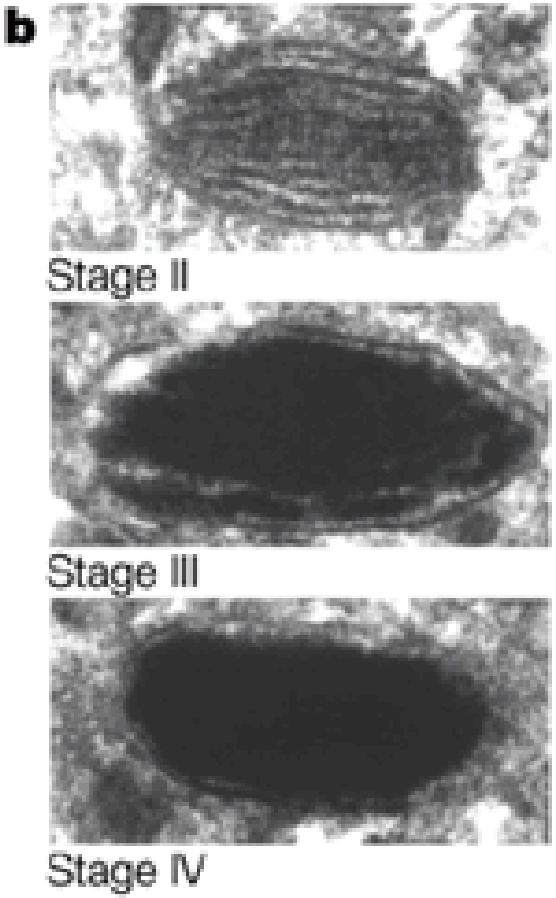
- The evolution of dark skin at low latitudes has been mainly accredited to the requirement of photo-protection against UVR which causes sunburn and skin cancer, whereas the evolution of light skin has been most commonly associated with vitamin D deficiency
- It has been proposed that as humans started to colonize higher latitudes, where UVR levels were lower, dark skin could not absorb sufficient UVR for efficient vitamin D synthesis, hence natural selection favored the evolution of light skin
- This is indirectly supported by the observation that candidate pigmentation genes are collectively enriched by high-FST single-nucleotide polymorphisms (SNP)

Where the action is: Melanosomes

- Melanosomes are membrane bound structures found in the epidermal cells, melanocytes and keratinocytes. They are the basic unit of skin pigmentation.
- The number, distribution, level of packing and size of melanosomes determine the degree of skin pigmentation. The pigment made is one of two kinds, eumelanin or phaomelanin.

Maturing Melanosomes

- Melanosomes accumulate more pigment as they mature and move to the periphery of the melanocyte.
- Stage II is a “young” melanocyte and Stage IV is a mature melanocyte.
- The internal environment of the melanosome dictates how much pigment is made along the way.

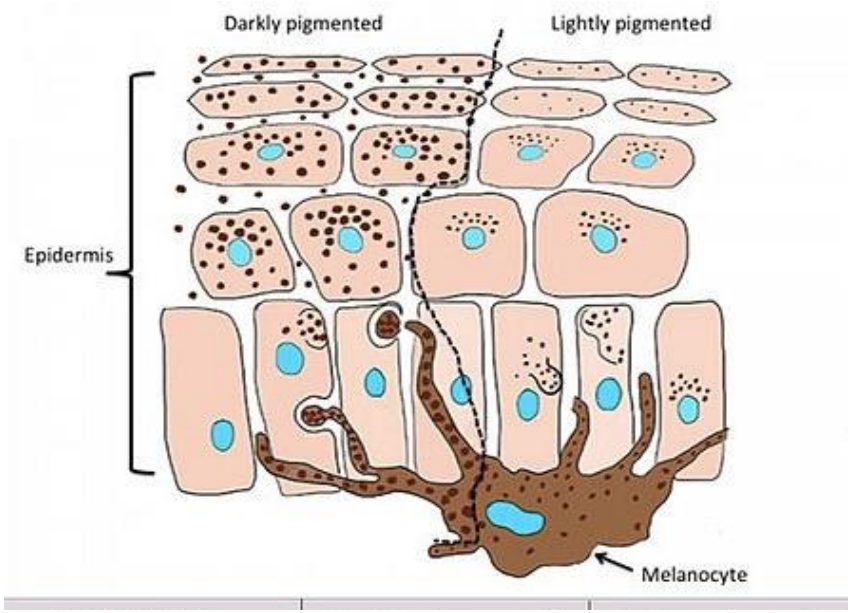


EM photo of three melanosome stages

What's happening in melanosomes?

Genes are expressed in melanocytes for three processes fundamental to skin pigmentation:

- Melanin (pigment) biosynthesis
- Regulation of melanin biosynthesis
- Melanosome transport



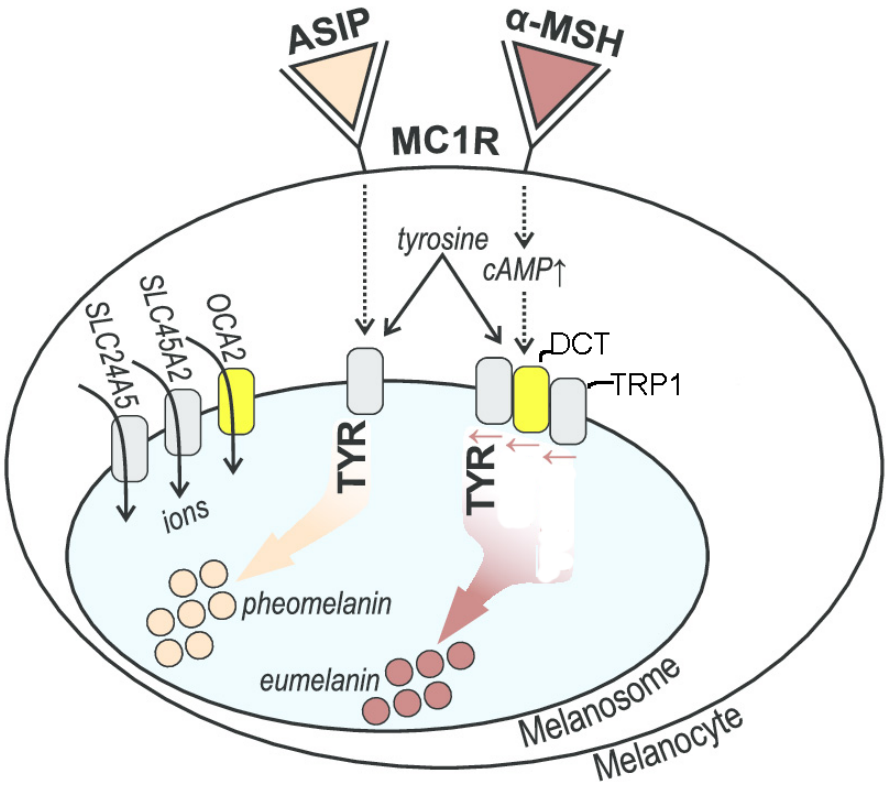
Key Genes and Their Products

The genes and proteins required for the third process, melanosome transport, vary little. Therefore, a small sample of those related to melanin synthesis and its regulation will be discussed based on:

- How **extensively each has been studied** and characterized;
- Their **relevance** (as far as we know) **to variability in human skin pigmentation**; and
- Their **distribution and expression** (as far as we know) **in different human populations**

Melanin Biosynthesis

- This diagram illustrates the pathway for producing either eumelanin or pheomelanin in human skin.
- Initiation of synthesis occurs in the melanocyte cell membrane.
- Synthesis is in the melanosome.
- The genes and their expressed proteins: MC1R, ASIP, TYR,TRP1 and DCT (TRP2).



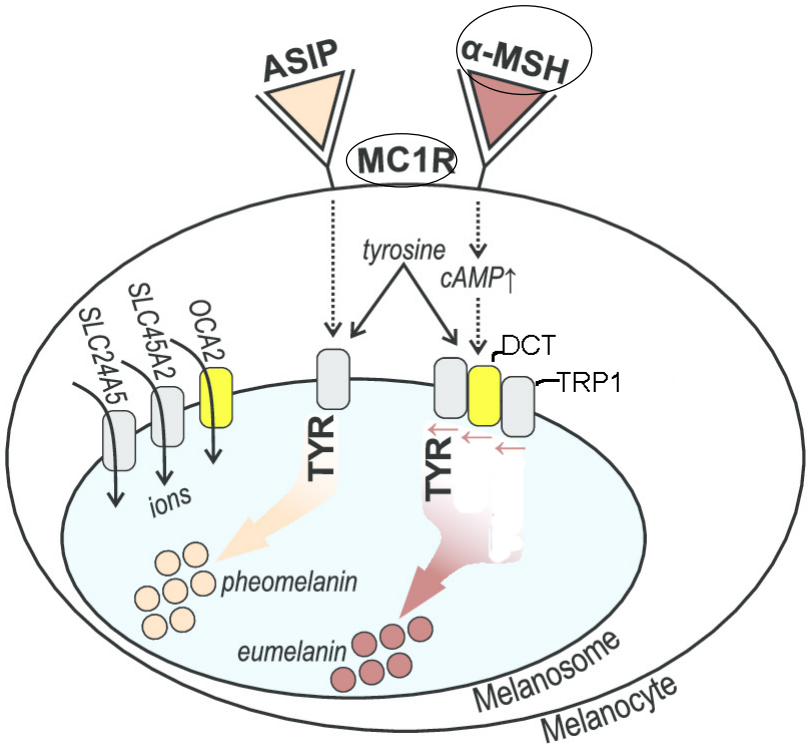
Melanin Biosynthesis Short and Sweet

The hormone alpha melanocyte stimulating hormone (alpha-MSH) interacts with the melanocortin 1 receptor, MC1R, on the outside membrane of melanocytes. cAMP levels increase. Usually, a cascade of reactions converts the amino acid tyrosine to the pigment eumelanin.

People with dark skin have lots of eumelanin.

People with light skin have little or no eumelanin.

Red hair and skin pheomelanin.



Melanin Biosynthesis Some Alternatives

However, changes in DNA, mutations, produce alternative forms of genes (alleles) connected to the synthesis of melanin. These mutations can result in changes in pigmentation. These alterations are related to:

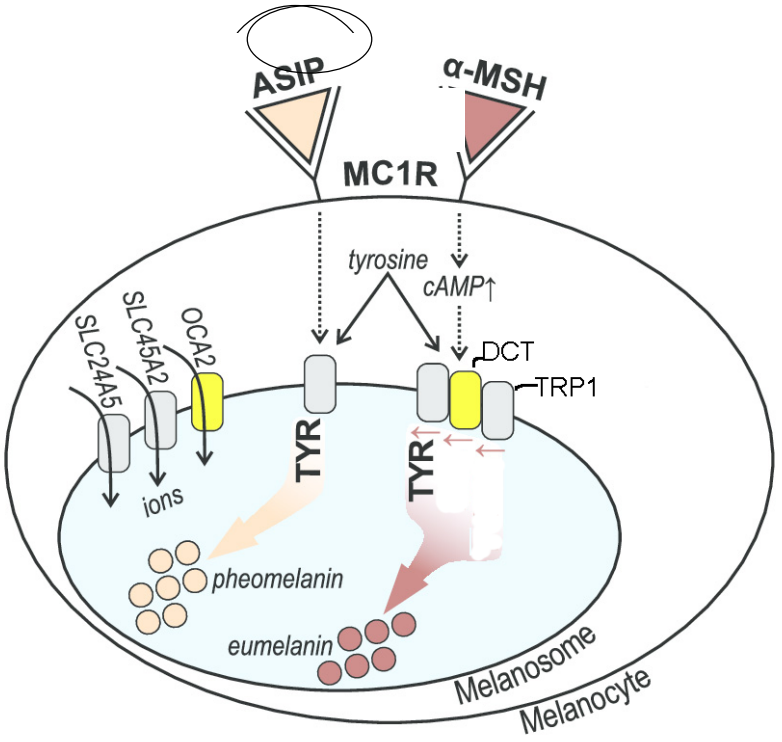
- MC1R receptor and its activation
- The pathway that makes pigment

Melanin Biosynthesis
melanocortin 1 receptor (MC1R)

- MC1R is coded by the *MC1R* gene. One common allele in humans is stable in indigenous African populations, favoring dark skin.
- A single change in an amino acid lowers MC1R's affinity for alpha-MSH. The result is the synthesis of the pigment pheomelanin instead of eumelanin and lighter skin.
- There are many alleles (polymorphisms) of the *MC1R* gene. These variably affect the production of pheomelanin in melanosomes. These differences are associated with populations having lighter skin and living at higher latitudes.

Melanin Biosynthesis
Agouti Signaling Protein

Agouti Signaling Protein (ASIP, coded by the *ASIP* gene) is an antagonist to MC1R, shutting down the pathway of eumelanin synthesis. Thus, the production of pheomelanin is favored. Variations of this gene, alleles, are found in people with lighter skin.



MC1R: Activated or Not

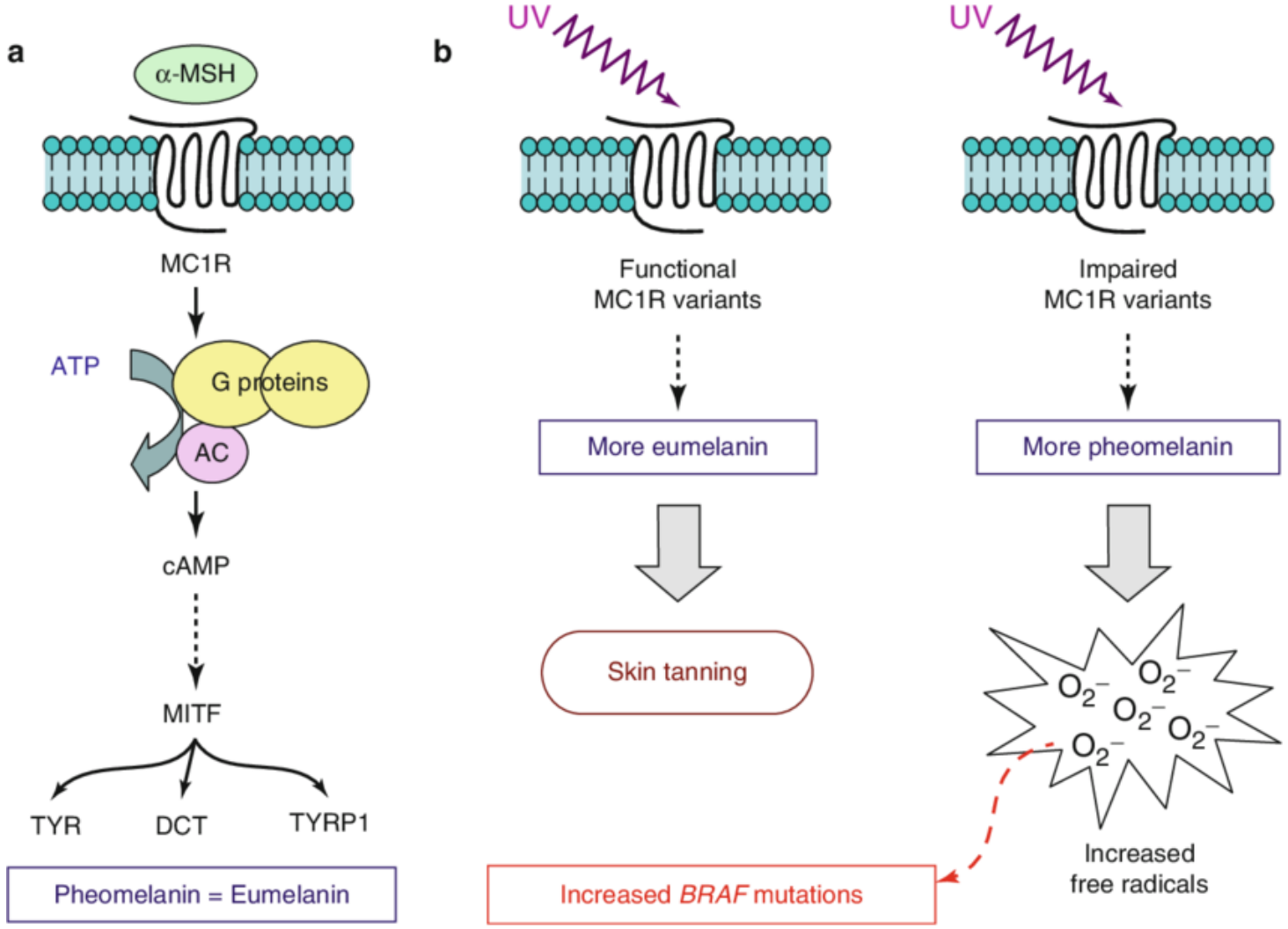
Activation of the MC1R protein by alpha-MSH leads to a series of chemical reactions that stimulates the production of eumelanin, associated with darker skin. The eumelanin pathway is engaged.

However, interference with MC1R by ASIP leads to a different result: gears don't mesh.

MC1R genetics

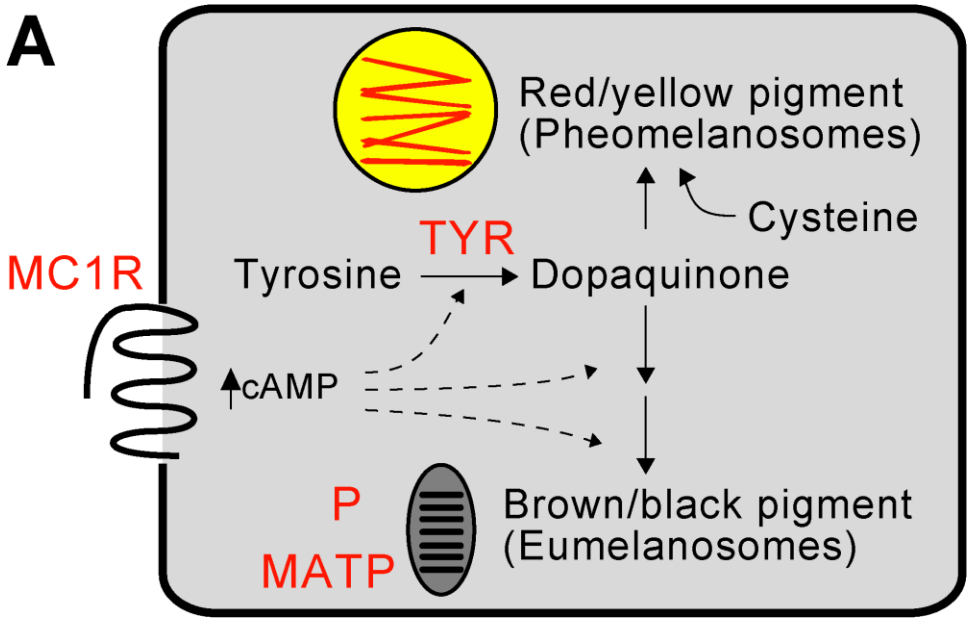
- MC1R encodes for melanocortin 1 receptor, which plays a role in skin pigmentation.
- Mutations in MC1R that reduce melanin production are associated with low response to tanning.
- Low pigmentation -> increased response to UV radiation
- Tendency to have increased sun exposure due to lower tanning response
- Elevated risk of melanoma with sun exposure
- Avoidance of sun exposure and need for sunscreen

MC1R and Melanoma



Melanin Biosynthesis Tyrosinase (TYR)

Tyrosinase, coded by the *TYR* gene) is the primary enzyme involved in the conversion of tyrosine to melanin, although other proteins are involved. TYR is a copper-containing oxygenase and is rate-limiting for the melanin synthesis pathway.



TYR Polymorphisms

Nucleotide differences in the *TYR* gene correlate with skin pigmentation variation in humans.

For example, the *TYR* variant, rs2733832, is associated with lighter skin pigmentation in human populations, particularly in those founded in current day Europe.

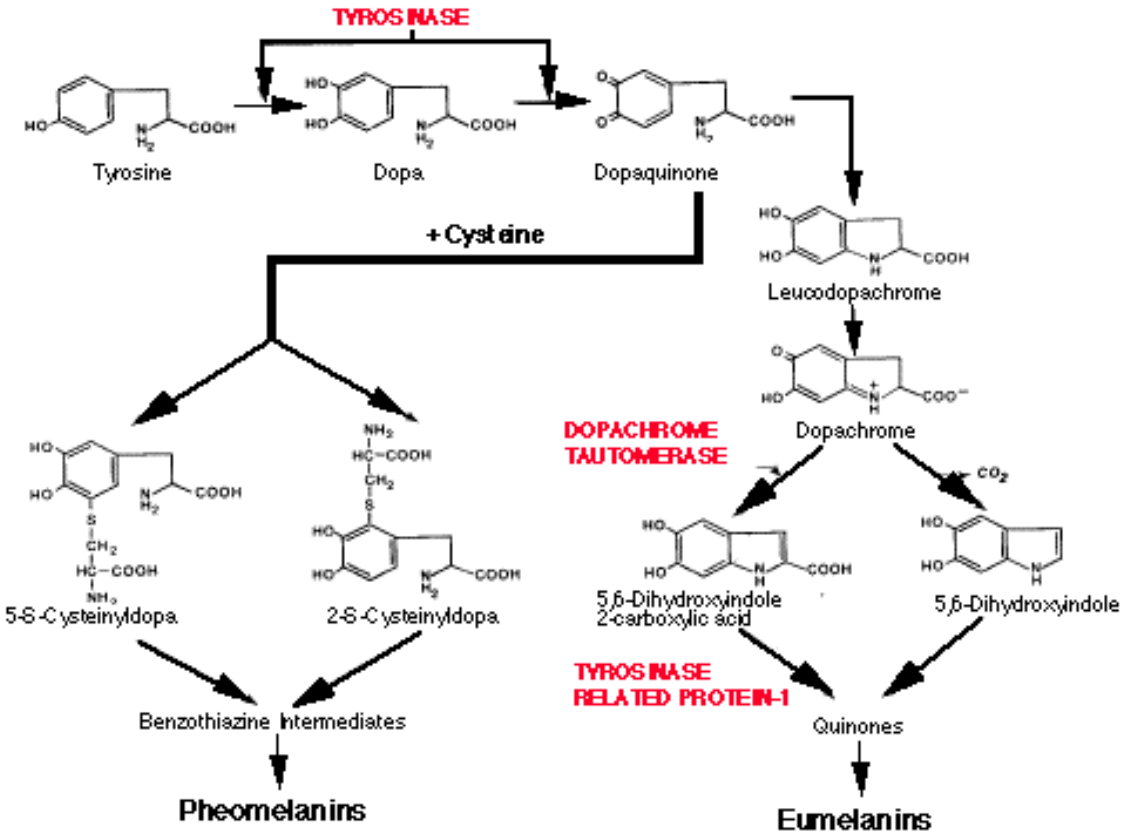
Types of OCA	Gene	Affected protein	Phenotype
OCA1A (OMIM 203100)	TYR	Tyrosinase absent/inactive	White hair, pinkish skin, red pupils
OCA1B (OMIM 606952)	TYR	Tyrosinase partially active	Yellow pigment in hair, eyes and skin

TYR Polymorphisms and Cancer

The variant in TYR encoding the R402Q amino acid substitution, previously shown to affect eye color and tanning response, conferred risk of CM (OR = 1.21, P = 2.8 x 10(-7)) and BCC (OR = 1.14, P = 6.1 x 10(-4)).

TYR variants -> reduce skin pigmentation -> Increased skin cancer risk

The Tyrosinase Related Protein
The TRPs



There are two tyrosine related proteins that work with tryrosinase to produce melanins. One is TRP1; the other is dopachrome tautomerase , DCT, which is also known as TRP2.

The TRPs

The exact function of TRP1 (the gene is *TRP1*) in human skin coloration is unclear. However, particular versions of the gene are associated with light skin. It is thought to:

- stabilize tyrosinase.
- influence the shape of melanosomes.
- regulate or influence the type of melanin synthesized.

In some way, DCT (the gene is DCT or TRP2) regulates the levels of eumelanin and pheomelanin in human skin cells.

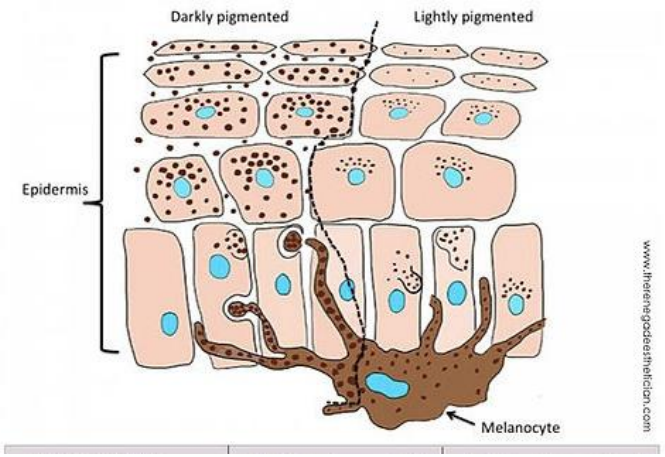
There are 9 different transcripts and thus 9 different gene products. The differential function of these proteins is not clear.

TRPs and skin pigmentation

- Premature death of melanocytes in Vitiligo is related to an increased sensitivity to oxidative stress caused by changes in TRP-1.
- Mutations in TRP-1, present in Oculocutaneous Albinism type 3, result in skin and hair hypopigmentation
- TRP-2 acts as a dopacrome tautomerase and, similarly to tyrosinase, requires a metal ion for its activity, zinc instead of copper
- Mutations impact skin pigmentation

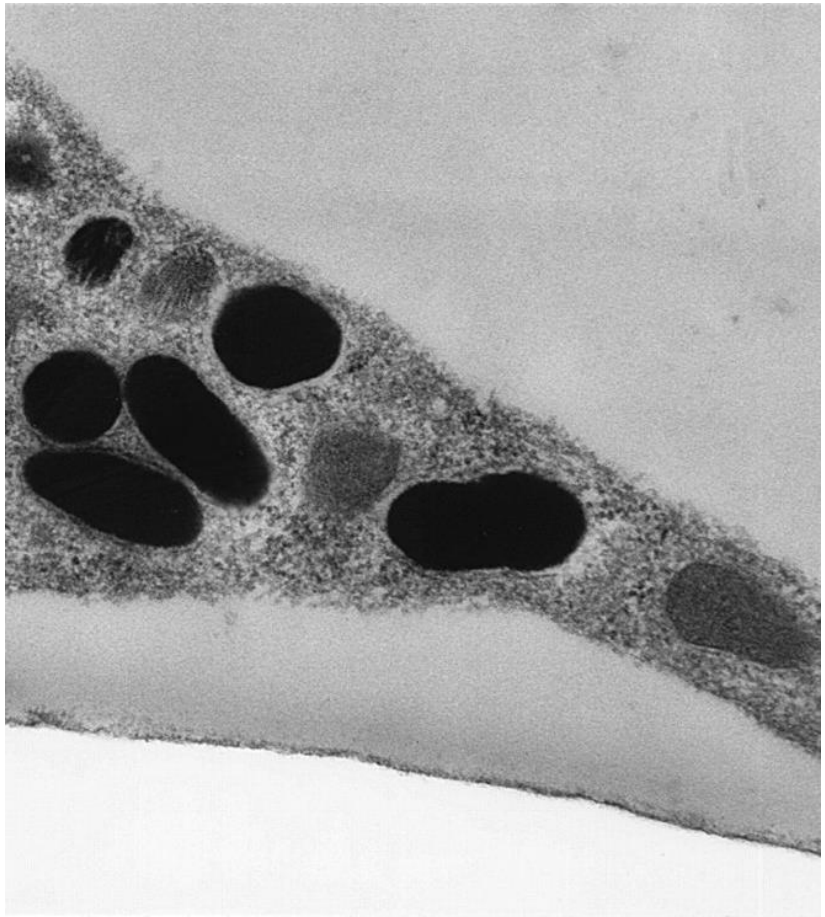
Other genes

Genes are expressed in melanocytes for three processes fundamental to skin pigmentation: melanin (pigment) biosynthesis, regulation of pigment biosynthesis and melanosome transport. We will now consider the expression of genes that regulate the melanin synthesis pathway.



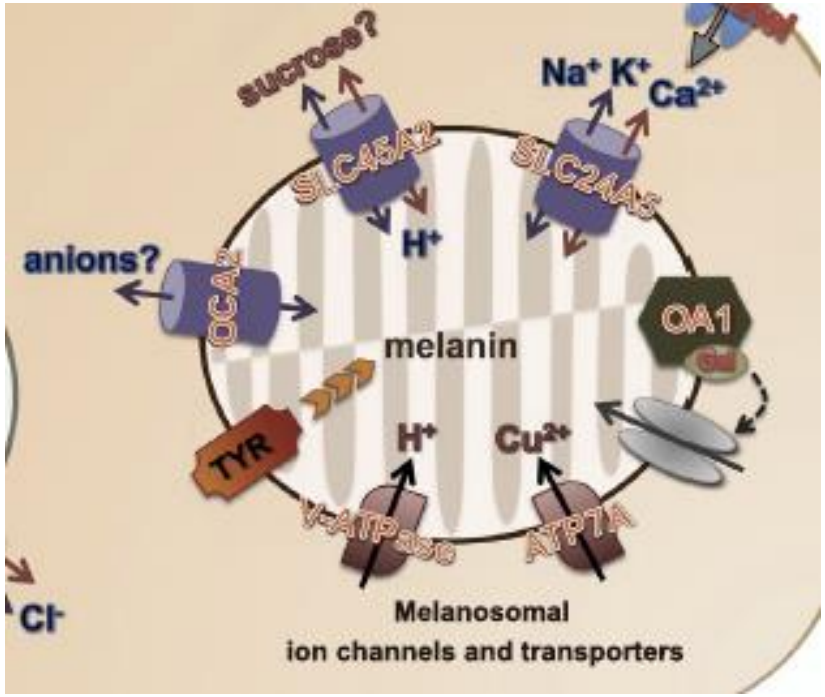
Regulation of pigment biosynthesis

- This electron micrograph shows melanosomes that are fully pigmented and others that are not.
- Many genes regulate the amount of melanin packed into a melanosome.



Regulation of pigment biosynthesis
The internal environment

The pH and ionic concentration of the internal melanosomal environment is critically important for determining the amount of pigment made. This environment depends on transmembrane carriers (passive movement) and transporters (active transport).



Regulation of pigment biosynthesis The internal environment

- The internal environment of the melanosome is really important. First, it is a determinant of whether or not tyrosine can enter a melanosome.
- It also influences the activity of the synthetic pathway for making pigment.
- Thus, membrane carriers and transporters regulate melanin synthesis.

Regulation of pigment biosynthesis Genes and Proteins

- Several genes and proteins are critical for regulation of melanin synthesis. There are known polymorphisms in some of these genes in populations that are related to skin color.

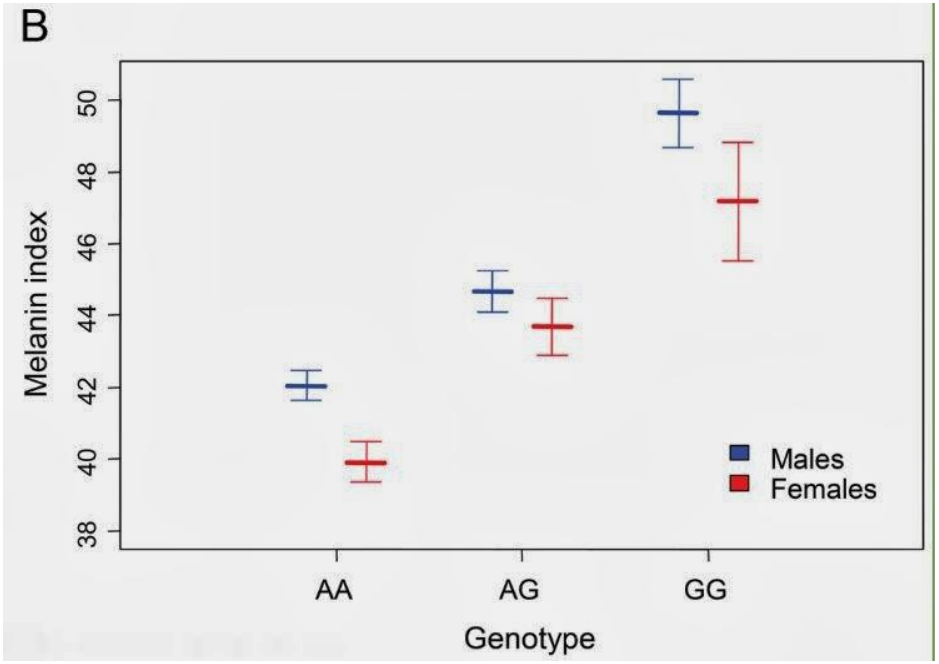
- *OCA_2* – p protein
- *$SLC_{24}A_5$* – a solute carrier; transporter
- *$SLC_{45}A_2$ (=MATP)* – a solute carrier; transporter

Regulating Melanin Synthesis $SLC_{24}A_5$

- The *$SLC_{24}A_5$* gene codes for a potassium dependent (K+) sodium/calcium (Na+/Ca++) exchange Calcium serves as a signal for melanin formation.
- Bottom line: this transporter is thought to regulate the amount of calcium entering the melanosome, which affects tyrosine entering the melanosome, which determines the amount of melanin made.
- A specific allele of this gene is common in light skin populations (Western Europe)

$SLC_{24}A_5$ and genetics

- It has been suggested that a single nucleotide difference in SLC24A5 accounts for 25–38% European-African pigmentation differences and correlates with lighter skin
- Rs1426654 – G allele African and Asian population (more active)
- A allele – European population



Regulating Melanin Synthesis MATP/$SLC_{45}A_2$

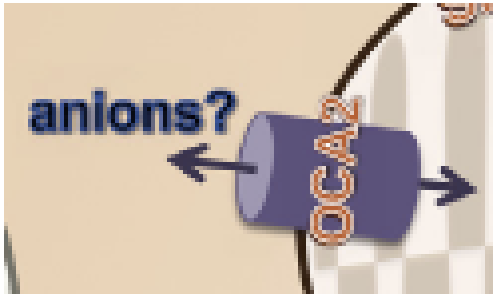
- Membrane-Associated Transporter Protein - MATP or $SLC_{45}A_2$ (corresponding gene is *$SLC_{45}A_2$)* regulates the melanosomal pH.
- Knocking down MATP lowers pH. When that happens, tyrosinase activity goes down, affecting eumelanin and pheomelanin synthesis.
- There are many variations (alleles) in the gene coding for MATP.

SLC45A2 and genetics

- rs26722(T) allele – increased pigmentation
- c.1122C>G, p.Phe374Leu (NCBI dbSNP rs16891982) in SLC45A2 – associated with protection from malignant melanoma

Regulating Melanin Synthesis
OCA_2 or p-protein

- OCA_2, coded by the gene *OCA_2*, resembles anion transporters in bacteria.
- It helps to regulate pH level in melanosomes and thus entry of the amino acid, tyrosine, into melanosomes.
- OCA_2 is thought to serve as a control point at which skin color variation is determined.



Summary of Function of Key Proteins

- Activation of the MC1R receptor begins the process.
- Conversion of tyrosine to either eumelanin, typical of dark skin, or pheomelanin, associated with some populations having light skin, depends on interacting proteins (TYR, TRP1, DCT).
- The amount of either pigment made is determined by the internal environment regulated by transporters (p-protein, MATP, $SLC_{24}A_5$)

EXOC2 AND TANNING

- Exocyst complex component 2 is a protein that in humans is encoded by the EXOC2 gene
- The protein encoded by this gene is a component of the exocyst complex, a multiple protein complex essential for targeting exocytic vesicles to specific docking sites on the plasma membrane.
- Polymorphisms associated with skin and hair pigmentation

HERC2

- This gene belongs to the HERC gene family that encodes a group of unusually large proteins, which contain multiple structural domains.
- All members have at least 1 copy of an N-terminal region showing homology to the cell cycle regulator RCC1 and a C-terminal HECT (homologous to E6-AP C terminus) domain found in a number of E3 ubiquitin protein ligases.
- Genetic variations in this gene are associated with skin/hair/eye pigmentation variability.
- rs12913832-T (brown eye) homozygotes compared to rs12913832-C (blue eye). correlations with skin, eye, and hair color variation.
- Polymorphisms associated with skin pigmentation by modulation of OCA2 activity

PIGMENTATION GENETICS

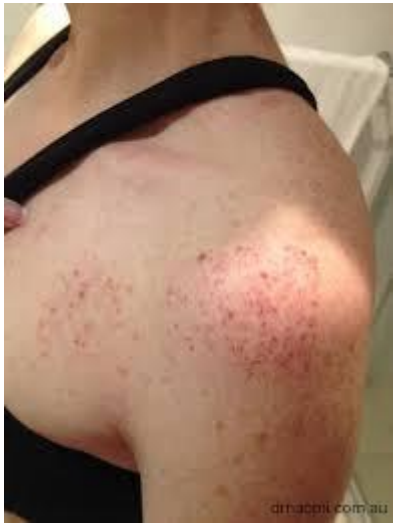
- If at risk -> reduced tanning response
- Sunscreen (SPF30) should be used to avoid UV exposure. Prevent excessive exposure to the sun to reduce melanoma risk.

- Oral supplementation with Vitamin C together with Vitamin E, Vitamin D as well as catechins found in green tea has shown efficacy in reducing inflammatory responses induced by tanning.

- Topical ointments containing Epigallocatechin Gallate (comes from green tea extract), blackberry extract have also shown efficacy in reducing inflammatory responses following sun exposure.

FRECKLES

A small patch of light brown colour on the skin, often becoming more pronounced through exposure to the sun.



- Freckles are predominantly found on the face, although they may appear on any skin exposed to the sun, such as arms or shoulders.

FRECKLES

- **Freckles**, or ephelides are clusters of concentrated melaninized cells which are most easily visible on people with a fair complexion.
- No increased number of melanocytes,
- But overproduction of melanin granules (melanosomes) changing the coloration of the outer skin cells called (keratinocytes).

FRECKLES

- Freckles, also known as ephelides, first develop at about 2-3 years of age.
- Freckles sometimes fade with age, and can darken or lighten depending on sun exposure.
- The formation of freckles is triggered by exposure to sunlight.
- The exposure to UV-B radiation activates melanocytes to increase melanin production, which can cause freckles to become darker and more visible.

FRECKLES

- Freckles are rare on infants, and more commonly found on children before puberty.
- Upon exposure to the sun, freckles will reappear if they have been altered with creams or lasers and not protected from the sun, but do fade with age in some cases.
- Freckles are not a skin disorder, but people with freckles generally have a lower concentration of photo-protective melanin, and are therefore more susceptible to the harmful effects of UV radiation.
- It is suggested that people whose skin tends to freckle should avoid overexposure to sun and use sunscreen

FRECKLES

- Freckles are thought to develop as a result of a combination of
- genetic tendency (inheritance) –MC1R and IRF4
- and sun exposure.
- Two people receiving the same sun exposure may not have an equal chance of developing freckles.
- People with blond or red hair, light-colored eyes, and fair skin are especially susceptible to the damaging effect of UV rays.

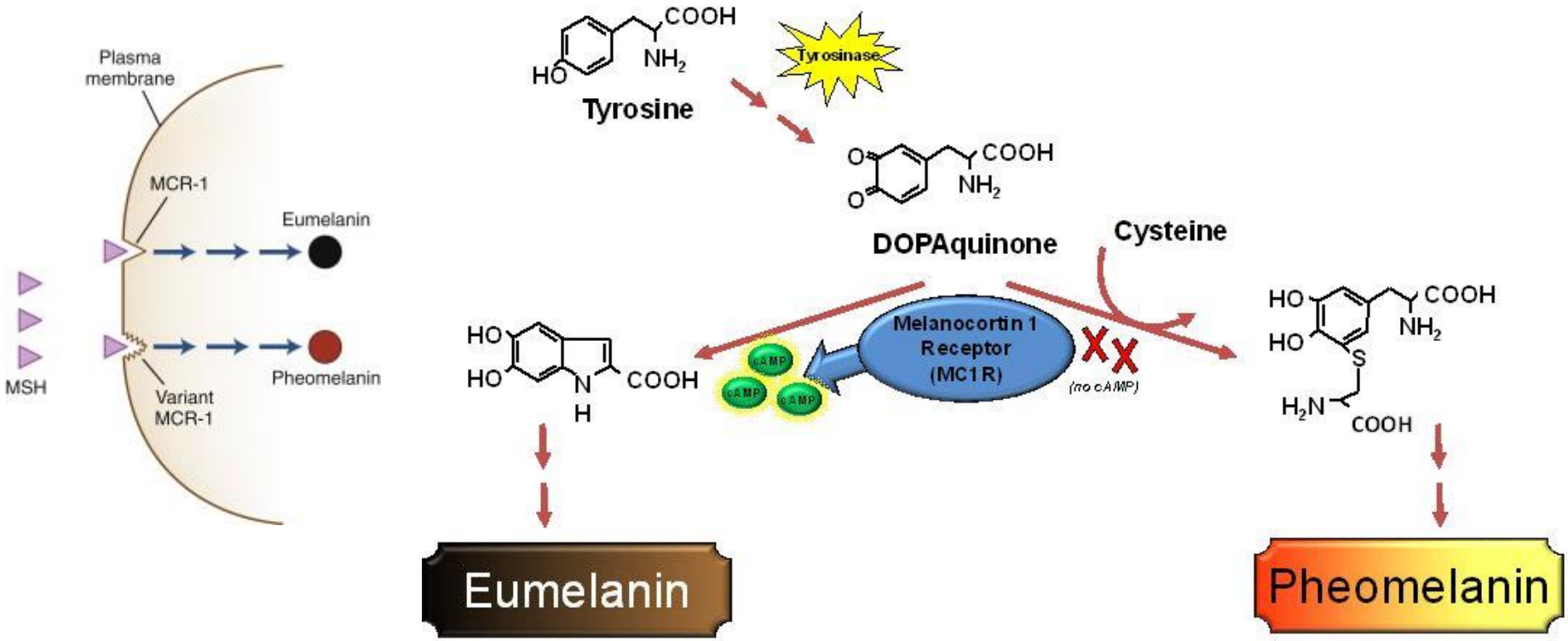
FRECKLES GENETICS – MC1R

- MC1R polymorphisms are associated with predisposition to freckles
- Variants associated with reduced MC1R activity – loss of function alleles
- These MC1R polymorphisms reduce the ability of the melanocortin 1 receptor to stimulate eumelanin production, causing melanocytes to make mostly pheomelanin.

Gene	Protein	SNP[1]	Codon/position/ haplotype	Amino acid/ isoform	European[2] allele frequency, %	Skin[3]	Eye[3]	Hair[3]	Naevi[3]	Frecking[3]
MC1R	G-protein coupled receptor	rs1805005*G/T rs1805006*C/A rs2228479*G/A rs11547464*G/A rs1805007*C/T rs1110400*T/C rs1805008*C/T rs885479*G/A rs1805009*G/C	Coding, nonsynonymous *WT, r, R*	Val60Leu (r) Asp84Glu (R) Val92Met (r) Arg142His (R) Arg151Cys (R) Ile155Thr (r) Arg160Trp (R) Arg163Gln (r) Asp294His (R) WT	12.79 0.88 7.86 0.73 6.98 0.84 8.07 5.30 1.38 ~50	++	–	+++		+++
ASIP	MC1R antagonist	rs4911442*T/C	Extended haplotype on chromosome 20	–	87.88/12.12[4]	+	–	+		++

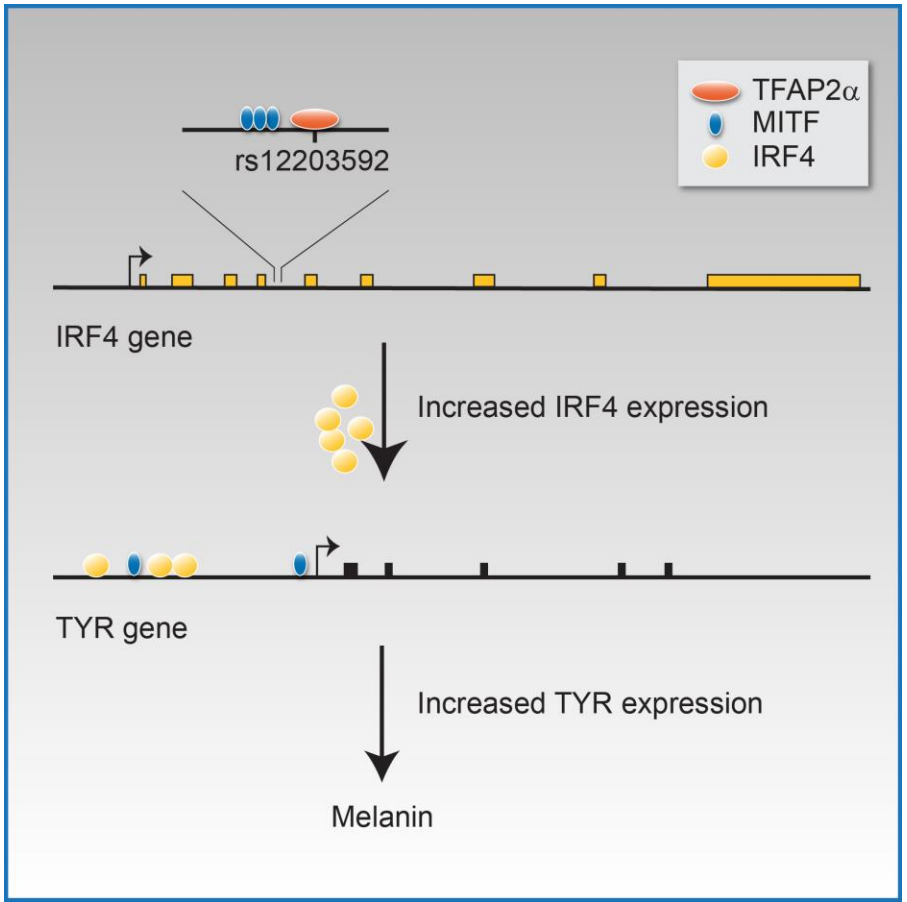
FRECKLES GENETICS – MC1R

- These MC1R polymorphisms reduce the ability of the melanocortin 1 receptor to stimulate eumelanin production, causing melanocytes to make mostly pheomelanin.
- Pheomelanin – Red color



FRECKLES GENETICS – IRF4

- IRF4 – Interferon regulatory factor -4
- Rs122033592 – T allele associated with freckles and light skin coloration ie greater pheomelanin production



WHAT TO DO IF AT RISK?

- At risk implies increased pheomelanin and risk of freckles
- Sunscreen (SPF30) should be used to avoid UV exposure and limit excessive exposure to the sun.
- Topical application of ointments containing Caragana sinica, Transexamic acid, azelaic acid, kojic acid, retinoids, glycolic acid, mequinol, and arbutin have shown efficacy.

SUNSPOTS

- Lentigines/sunspots are distinguished from freckles based on the :
- 1-proliferation of melanocytes.
- 2-Freckles have a relatively normal number of melanocytes but an increased *amount* of melanin.
- 3-Freckles will increase in number and darkness with sunlight exposure, whereas lentigines will stay stable in their color regardless of sunlight exposure.
- Polymorphisms in MC1R and IRF4 associated with increased genetic risk of sunspots

SUNSPOTS – IF AT RISK

- To prevent solar lentigines:
- avoid exposure to sunlight in midday (10 AM to 3 PM),
- wear sun-protective clothing (tightly woven clothes and hats),
- and apply sunscreen (SPF 30 UVA and UVB block).

NUTRITION AND SKIN HEALTH

- Maintenance of skin health requires supplementation with appropriate vitamin and minerals which can not only maintain health skin but also suppress visible signs of skin aging.
- Nutritional deficiencies have been linked to detrimental effects of skin health and genetics plays a role in determining one's predisposition to nutritional deficiencies.
- Understanding one's predisposition to nutritional deficiencies is the key to determining which nutrients are preferentially needed to maintain healthy skin.

VITAMIN A AND SKIN HEALTH

- Human skin is highly enriched in beta carotene
- Role in photoprotection
- β-carotene is the most prominent member of the group of carotenoids, natural colorants that can be found in the human diet
- Compared with other carotenoids, the primary role of β-carotene is its provitamin-A activity
- β-carotene can be cleaved by BCMO1 enzyme into 2 molecules of all-trans-retinal.
- Furthermore, β-carotene can also act as a lipid radical scavenger and as a singlet oxygen quencher, as demonstrated in vitro.
- Based on the distribution of BCMO1 in human tissues it seems that β-carotene metabolism takes place in a wide variety of organs, including the skin

VITAMIN A AND SKIN HEALTH

- Upon dietary supplementation, β-carotene can be further enriched in skin, in which it is already a major carotenoid
- β-carotene is an endogenous photoprotector, and its efficacy to prevent UV-induced erythema formation has been demonstrated in various studies
- In healthy volunteers, a 12-week oral administration of β-carotene may result in a reduction of UV-induced erythema.
- In studies documenting protection against UV-induced erythema, supplementation with carotenoids lasted for at least 7 weeks, with doses > 12 mg/d of carotenoids
- β-carotene supplementation can significantly reduce the rate of mitochondrial mutation in human dermal fibroblasts after UV irradiation

VITAMIN A AND SKIN HEALTH

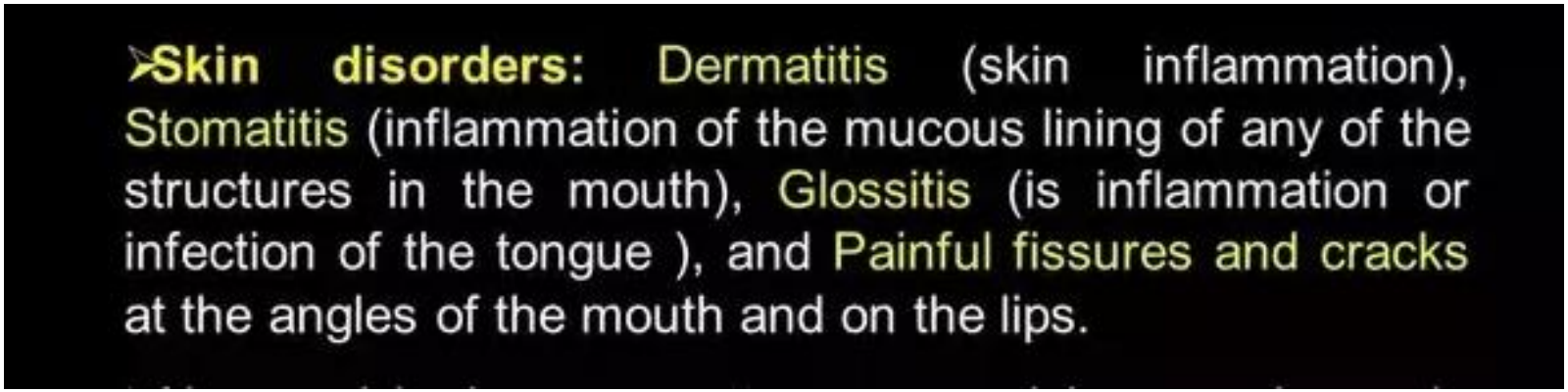
- Lack of vitamin A causes the skin to become keratinized and scaly, and mucus secretion is suppressed
- Rough, dry skin is a common sign of vitamin A deficiency, which often first appears as rough, raised bumps on the back of the arms
- BMCO1 mutations associated with Vitamin A deficiency
- Increase consumption of Vitamin A rich foods (sweet potato, pumpkin, carrots, cantaloupe, animal liver).
- Vitamin A containing creams (particularly with Retinol) have shown efficacy in improving skin health

VITAMIN B6 AND SKIN HEALTH

- Vitamin B6 has been believed to be essential for skin development and maintenance.
- Vitamin B6 deficiency has been known to be associated with dermatitis
- For skin cancer, a recent study has underlined that dietary supplemental vitamin B6 to a low vitamin B6 diet enhanced UV-irradiated skin tumorigenesis in mice.
- Potential role in preventing skin cancer?
- Topical application of vitamin B6 has been reported to exaggerate UV-irradiated skin phototoxicity.
- The toxic properties of irradiated vitamin B6 compounds have been also demonstrated for human fibroblasts.

VITAMIN B6 AND SKIN HEALTH

- Excessive dose or abuse of vitamin B6 might cause adverse effect on skin health under certain conditions such as strong sunlight despite its essential roles for skin maintenance.



- Neuroblastoma Breakpoint Member 3 (NBPF3) gene is associated with the synthesis of NBPF3, a hormone found to be associated with the clearance of vitamin B6 from the body.
- C allele – Vitamin B 6 deficiency

VITAMIN C AND SKIN HEALTH

- Vitamin C is a cofactor for lysyl and prolyl hydroxylase, which stabilize the triple helical structure of collagen.
- It also plays a role in cholesterol synthesis, iron absorption and increases the bioavailability of selenium.
- The most commonly described cutaneous manifestations accompanying vitamin C deficiency are attributed to the impaired collagen synthesis.
- Enlargement and keratosis of hair follicles mainly of the upper arms and curled hairs, the so-called ‘corkscrew hairs’, are usually described.
- The follicles become hemorrhagic with time and they sometimes mimic the palpable purpura of leucocytoclastic vasculitis.

VITAMIN C AND SKIN HEALTH

- SLC23A1 Vitamin C transporter
- rs33972313 is known to lie in exon 8 of SLC23A1 and to yield a missense change delivering a methionine (Meth/ATG) form in the presence of the rare A allele
- Results in by-product of a conformational change or protein failure which impairs active transport.

- If at risk – photoaging – reduced stabilization of collagen in the skin
- Increase consumption of Vitamin C rich foods (guava, peppers, citrus fruits).
- Vitamin C containing creams have shown efficacy in boosting collagen synthesis

VITAMIN D AND SKIN HEALTH

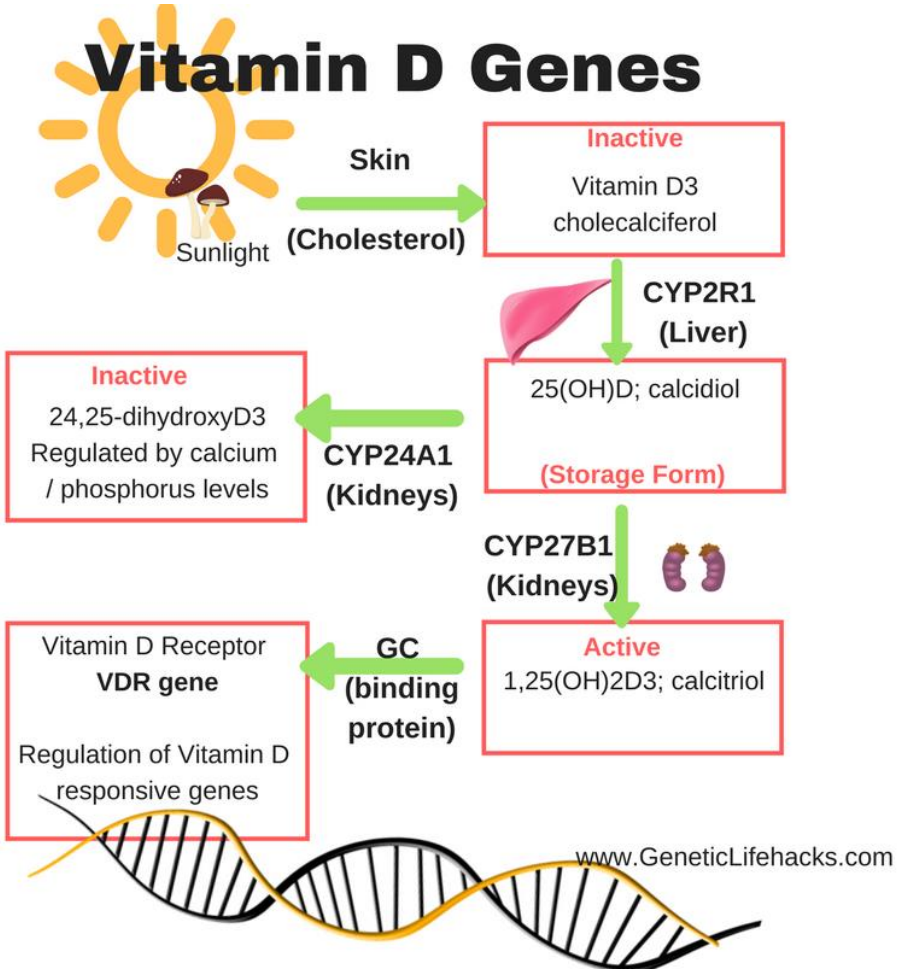
- The skin is one of the key tissues of the human body vitamin D endocrine system.
- Skin is the major site for UV-B mediated vitamin D3, and 1,25-dihydroxy vitamin D3 synthesis.
- Besides its role in calcium homeostasis and bone integrity 1,25-dihydroxy vitamin D3 [1,25(OH)2D3] is also essential for numerous physiologic functions including immune response, release of inflammatory cytokines and regulation of growth and differentiation in normal and malignant tissues such as breast, lung and colon.

VITAMIN D AND SKIN HEALTH

- 1,25(OH)2D3 protects human skin cells from UV-induced cell death and apoptosis
- inhibits the activation of stress-activated protein kinases,58 such as the c-Jun NH2-terminal kinase and p38, and suppresses IL-6 production
- Several in vitro and in vivo studies have documented the protective effect of 1,25(OH)2D3 against UVB-induced skin damage and carcinogenesis.
- Furthermore, 1,25(OH)2D3 induces the expression of antimicrobial peptide genes in human skin and plays a significant role in preventing opportunistic infections.
- With increasing age the capacity of the skin to produce vitamin D3 declines and consequently the protective effects of the vitamin.

VITAMIN D AND SKIN HEALTH

- In skin, the concentration of 7-dehydrocholesterol—a vitamin D3 precursor—showed an approximately 50% decline from age 20 y to age 80
- The total amount of pre-vitamin D3 in the skin of young subjects was at least two times greater than when compared with that of the elderly subjects.
- CYP2R1 and GC mutations associated with Vitamin D deficiency

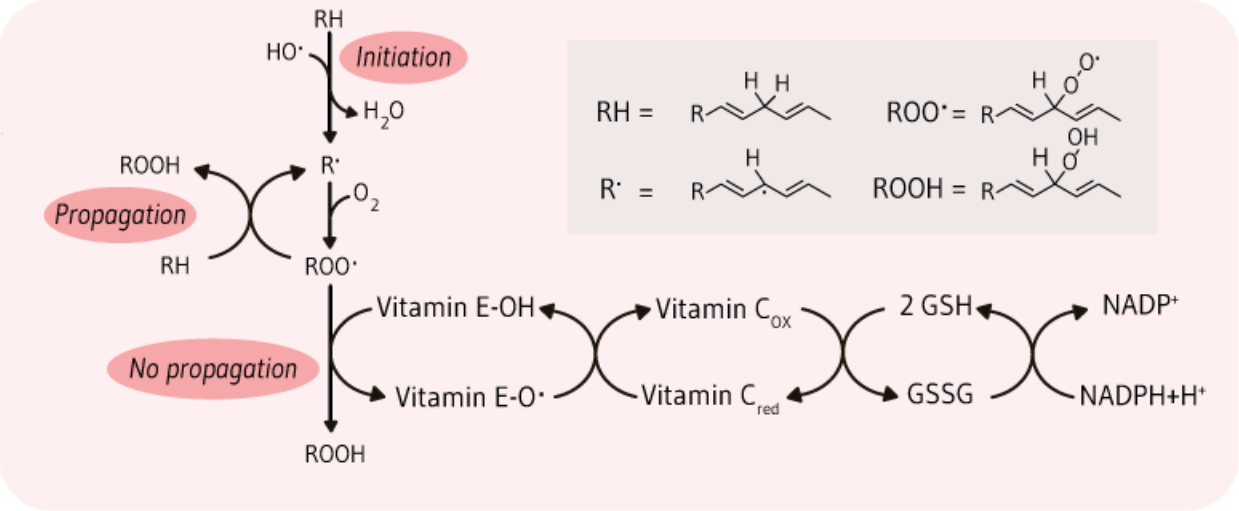


VITAMIN E AND SKIN HEALTH

- The vitamin E complex is a group of 8 compounds called tocopherols.
- Tocopherol is a fat-soluble membrane bound antioxidant and consequently a free-radical scavenger especially of highly reactive singlet oxygen.
- Tocopherol is like vitamin C a naturally occurring endogenous non-enzymatic antioxidant.

VITAMIN E AND SKIN HEALTH

- Vitamin C and vitamin E act synergistically.
- When UV-activated molecules oxidize cellular components, a chain reaction of lipid peroxidation in membranes rich in polyunsaturated fatty acids is induced.
- The antioxidant d-α-tocopherol is oxidized to the tocopheroxyl radical in this process and it is regenerated by ascorbic acid to d-α-tocopherol
- D-α-tocopherol is involved in stabilizing the cell membrane by inhibiting oxidation of polyunsaturated fatty acids, such as arachidonic acid of membrane phospholipids.



VITAMIN E AND SKIN HEALTH

- Scavenger receptor class B type I (SR-BI) mutations – Vit E deficiency
- Involved in transport of vitamin E across enterocytes (epithelial cells in intestine – intestinal absorption
- Mutations that increase CYP4F2 activity associated with reduced Vitamin E levels
- If predisposed to Vitamin E deficiency – Lowered potential of skin to fight oxidative damage -> photoaging
- Dietary and topical

FOLIC ACID AND SKIN HEALTH

- Folate may have a role in melanogenesis by regulating the production and stabilisation of tetrahydrobiopterin
- Tetrahydrobiopterin is a required cofactor for tyrosine hydroxylase, which converts tyrosine into dopa in the production of melanin pigments
- folate and melanin compounds are synergistic; melanin, on the one hand, protects folate from UVR-related degradation, which in turn supports the influence of folate in melanogenesis.
- Folate may also play a part in skin immune responses, although this role is not well understood.
- Notably, a high folate status correlates with increases in the expression of proteins involved in the activation and regulation of the complement system, an important non-specific skin defense mechanism