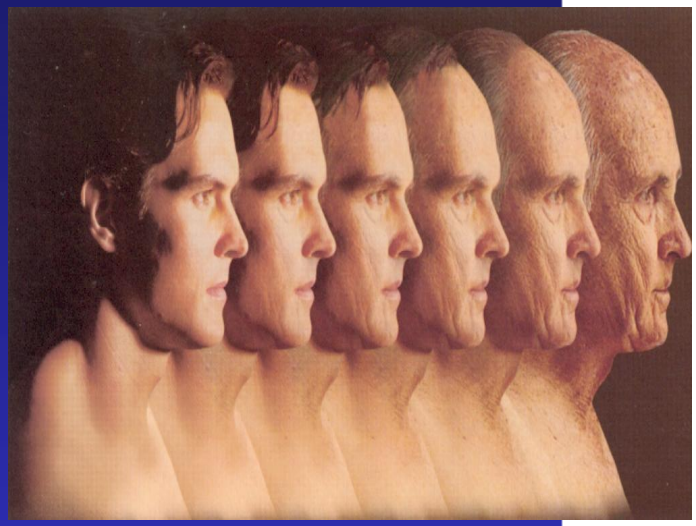
Beauty and Skin Care
Pathological Aspects of Skin Aging

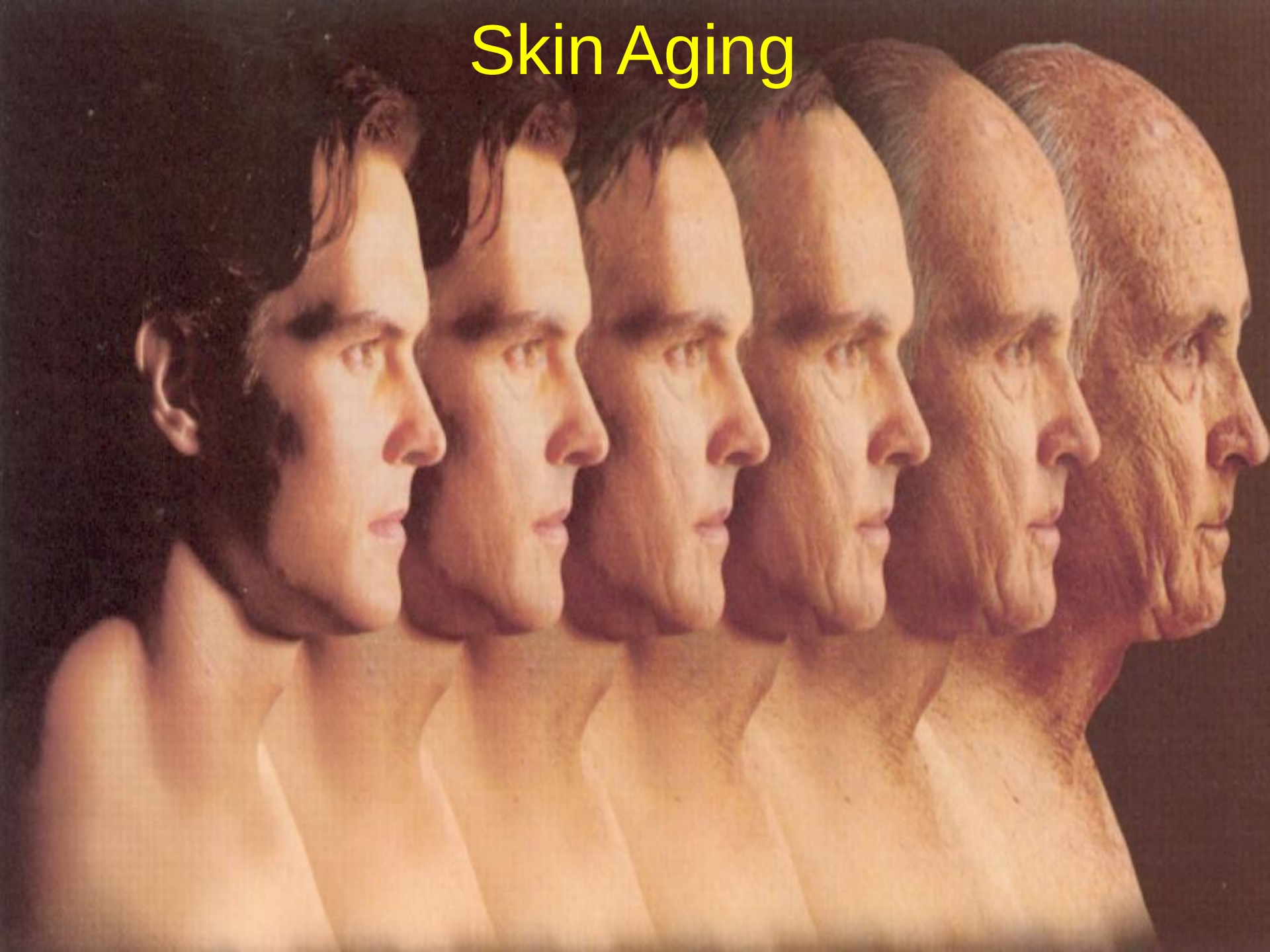


Mohamad Al Homssi, MD, FCAP

Diplomat of American Board of Pathology

Fellow of College of American Pathologists

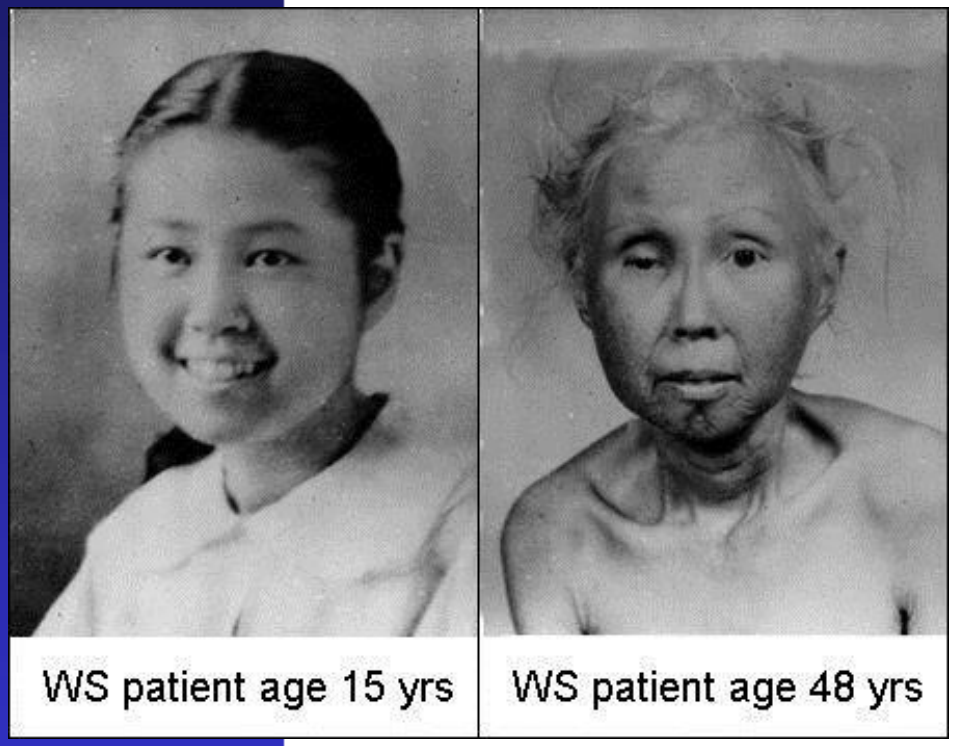
Skin Aging



Skin Aging



Progeria
10-year-old girl



Werner's syndrome
Helicase gene mutation→ slow down replication and reduced life span of cells

Skin Aging

Programmed vs. Error Theories

Programmed Theories

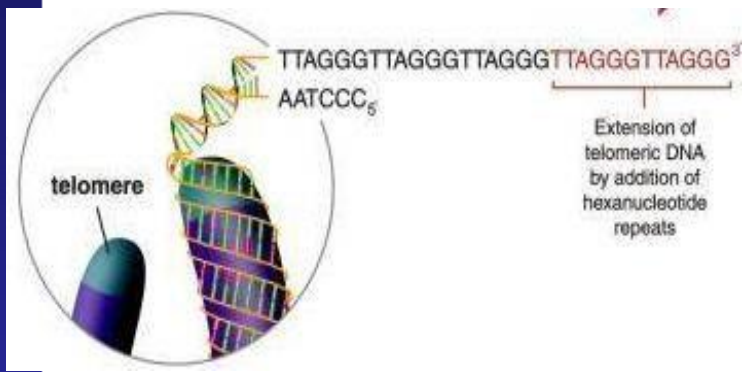
- Programmed Senescence Theory
- Endocrine Theory
- Immunology Theory

Error Theories

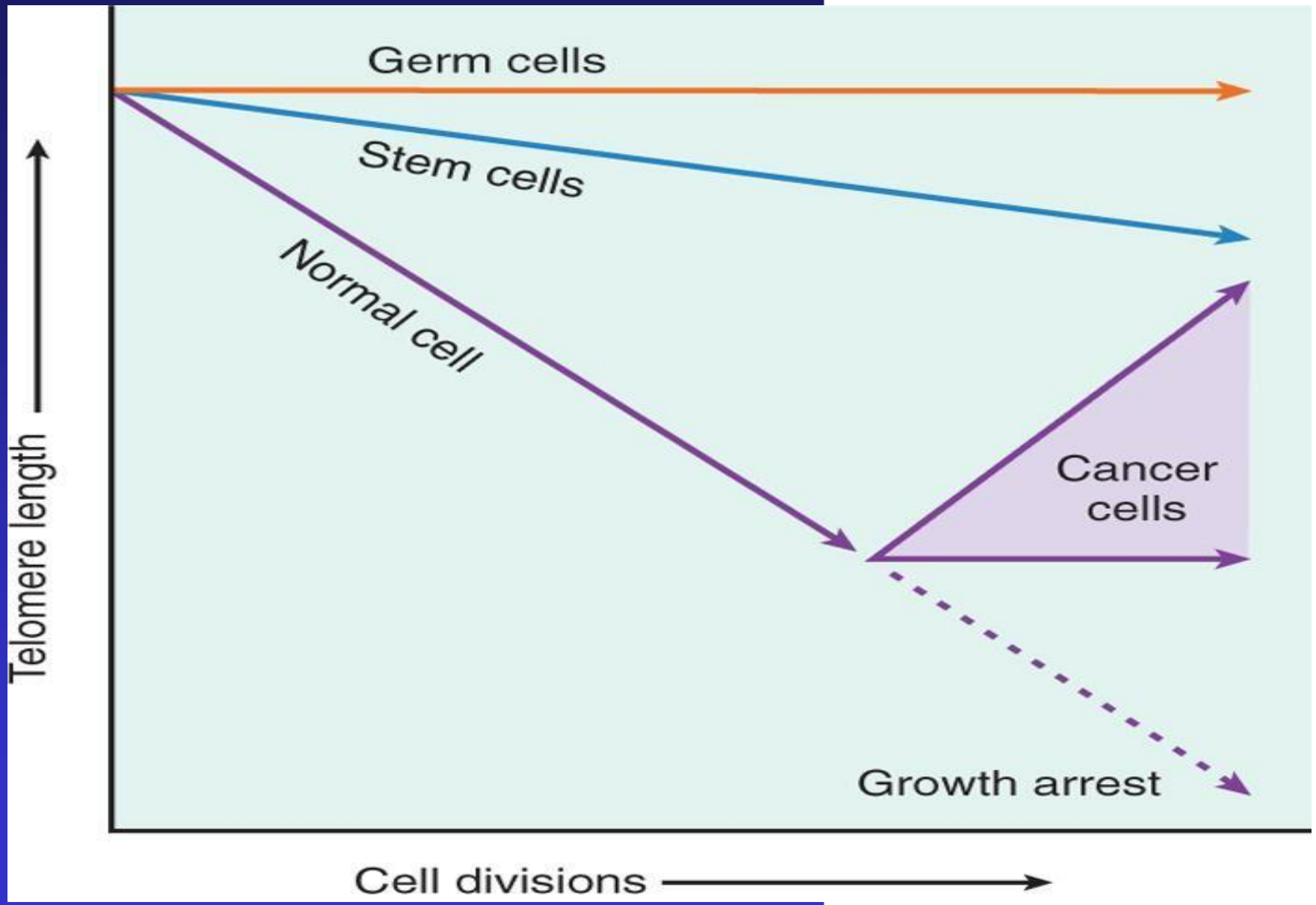
- Free Radical Theory
- Error Catastrophe Theory
- Somatic Mutation Theory
- Wear and Tear Theory
- Rate-of-Living Theory
- Cross-linking Theory

Skin Aging

- Telomeres
  - made of DNA
  - repeated sequence of DNA
  - contain no genetic information
  - cap and seal ends of chromosomes
  - protect chromosomes from damage
  - progressive shortening with each cell division



Skin Aging

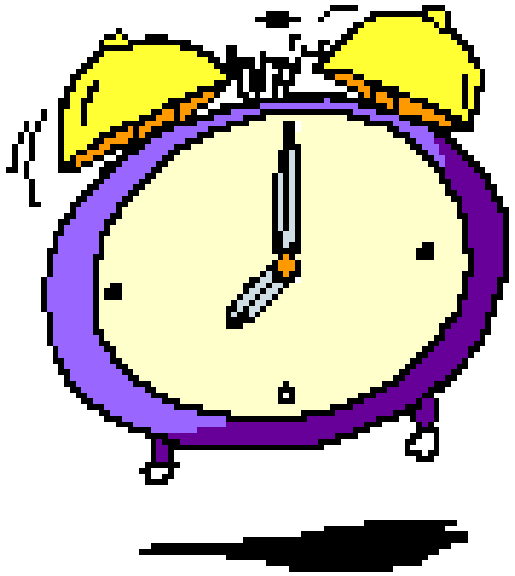

Germ cells
Stem cells
Normal cell
Cancer cells
Growth arrest
Telomere length
Cell divisions

Skin Aging

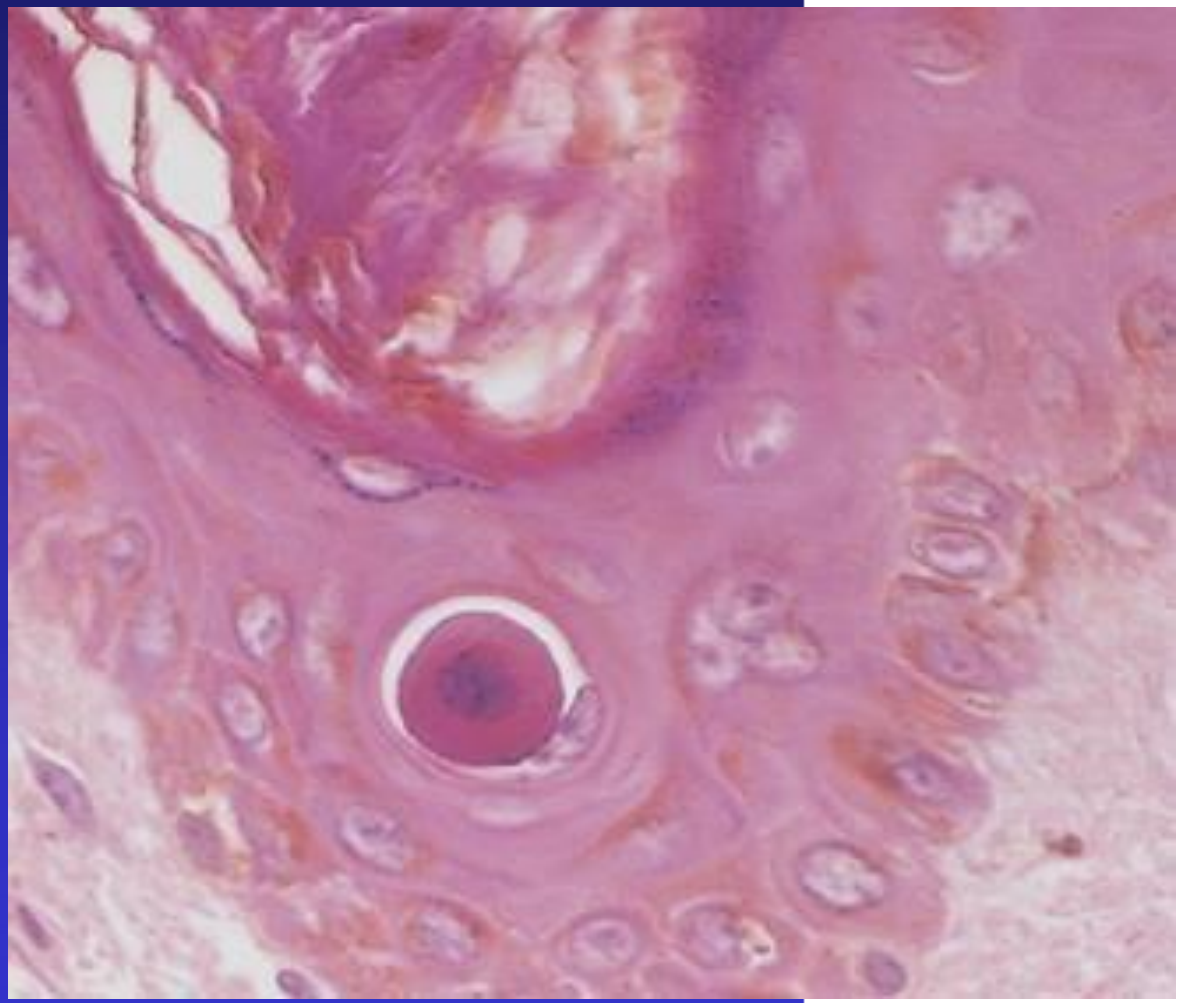
Telomere could be the clock that determine loss of proliferative activity of the cell

When the clock rings, it's time for

APOPTOSIS

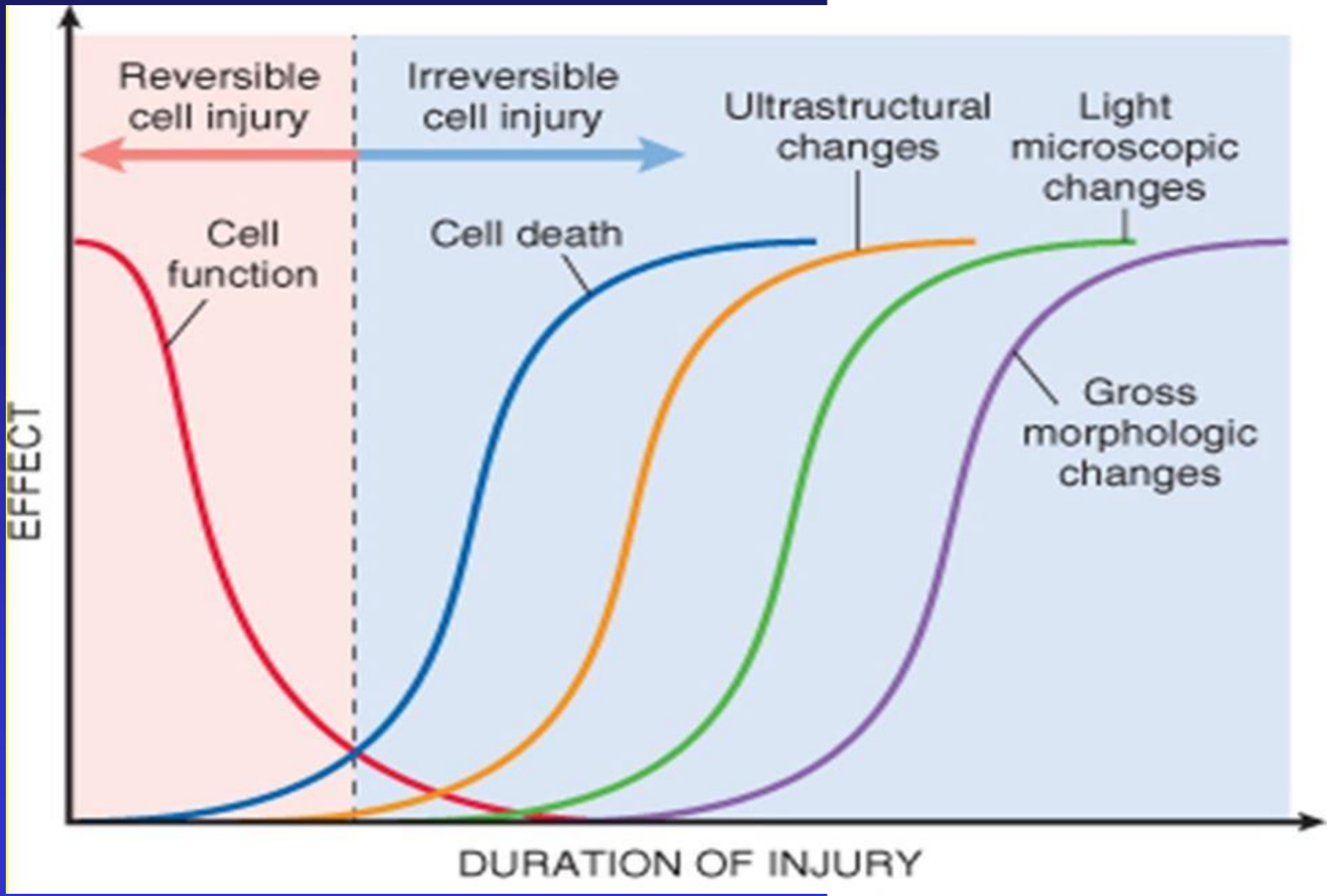


Skin Aging



APOPTOSIS

Skin Aging


Reversible cell injury
Irreversible cell injury
Ultrastructural changes
Light microscopic changes
Cell function
Cell death
Gross morphologic changes
EFFECT
DURATION OF INJURY

Skin Aging

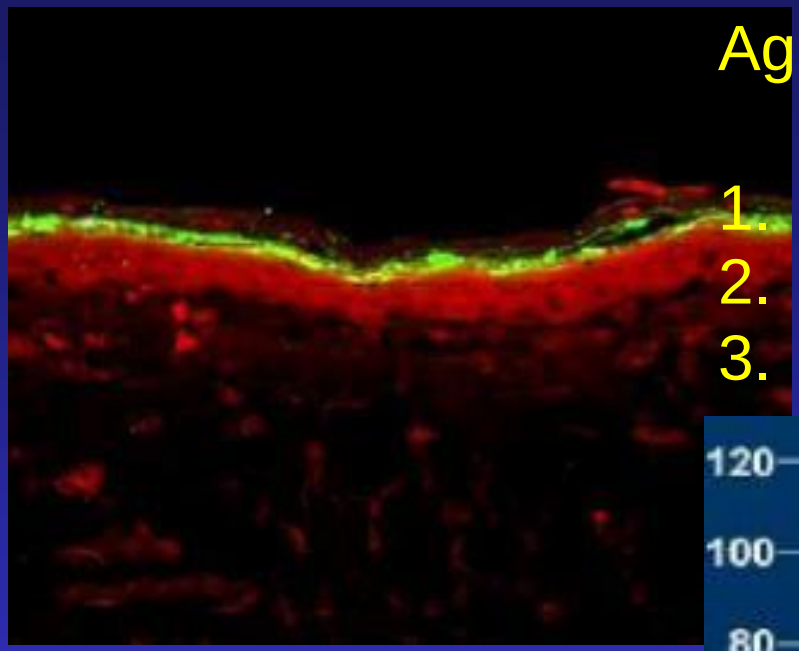
Main manifestations

Texture: Wrinkles, dilated pores

Coloration: Hyperpigmentation

Vascular: Telangiectasias

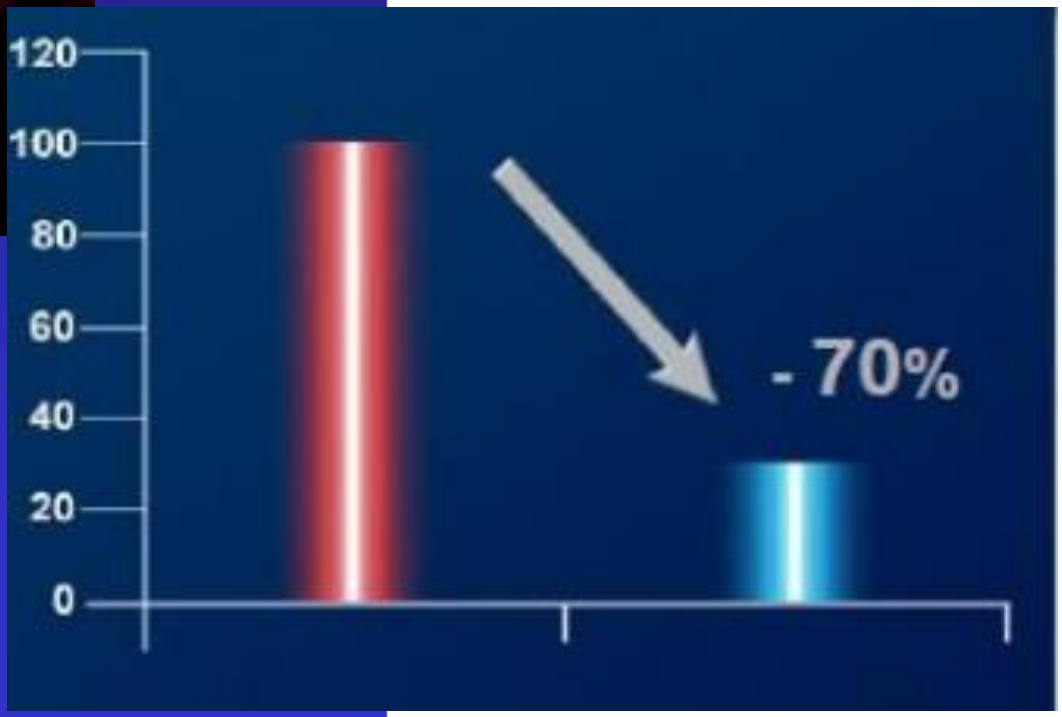
Skin Aging



Aging causes serious decrease in:

1. metabolic activity of fibroblasts
2. protein synthesis
3. quantity of collagen

Loss of adhesion capacity of fibroblast to collagen fibers and disorganization of elastic fibers



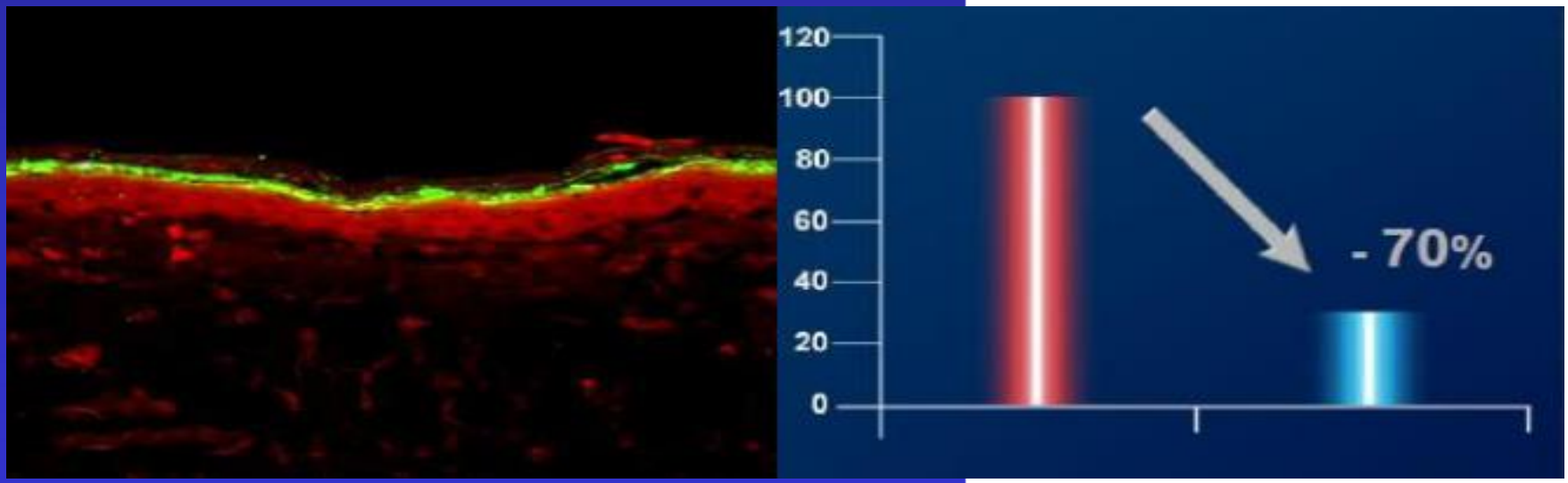
Normal fibroblast

Wrinkle fibroblast

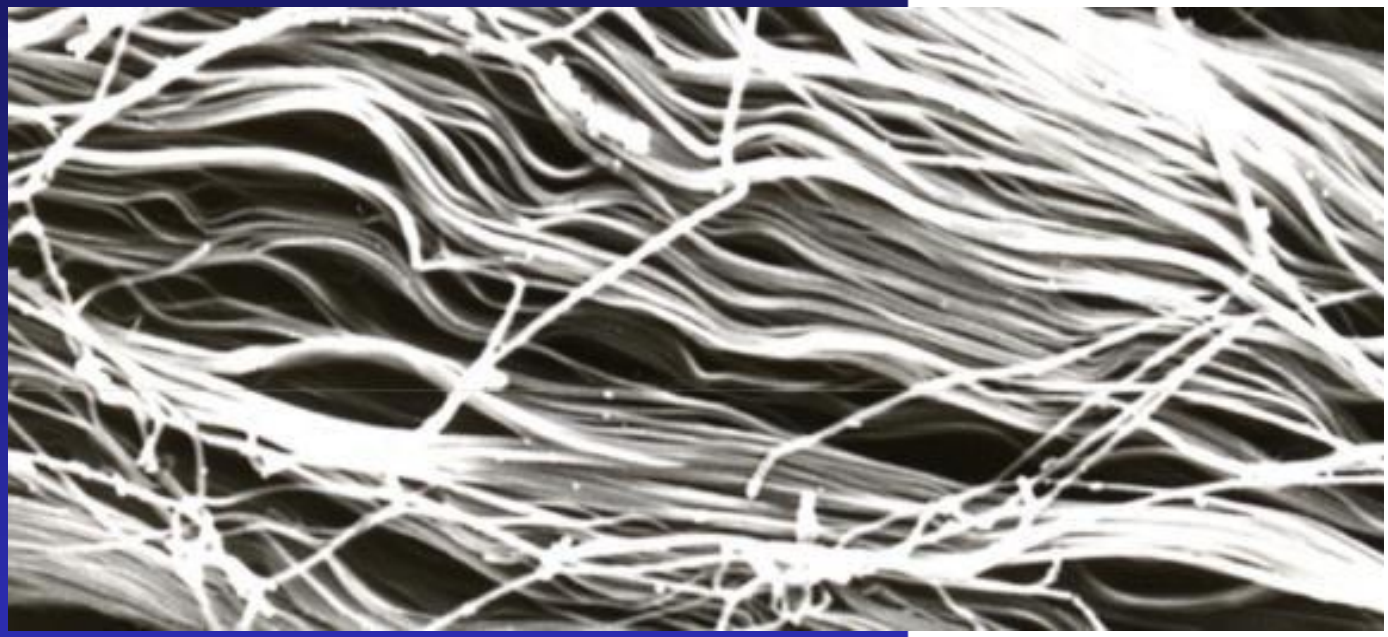
Skin Aging

Inside the wrinkle (Aging manifestation)

1. Reduced % collagen production by 70%
2. Formed contractile bundles of actinomyosin
3. Modified composition of dermis and structure of macromolecules of skin



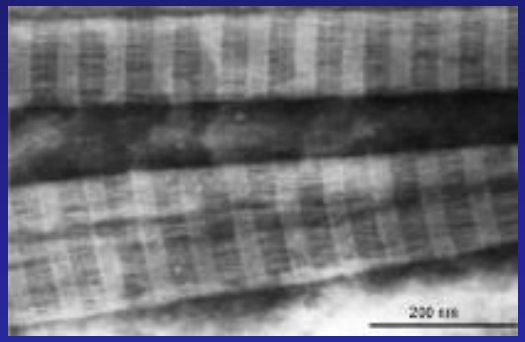
Skin Aging



Extracellular Matrix fills extracellular spaces forming around cells sort of connective substance, which enforces consistency adhesion and structure of tissues

Skin Aging

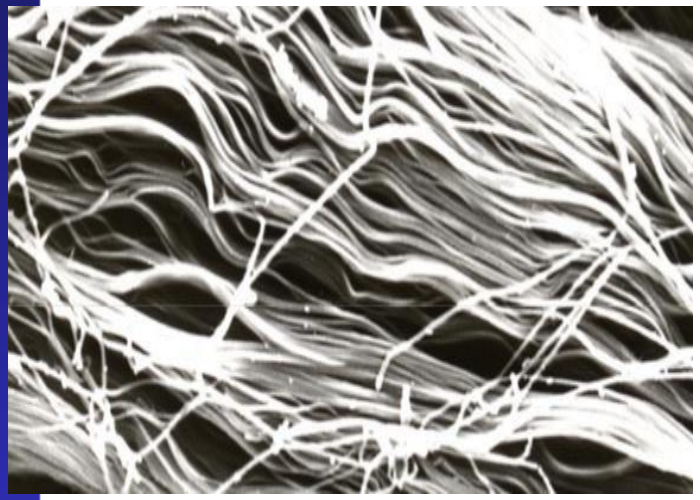
Key components of extracellular matrix

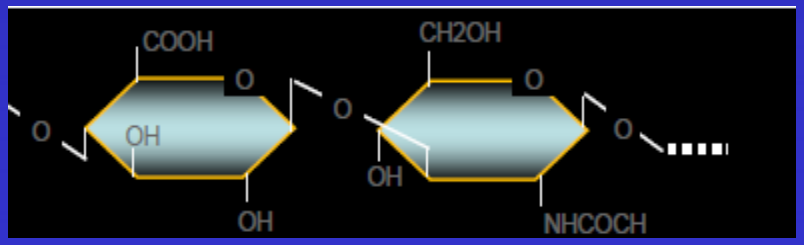


Collagen



Elastin





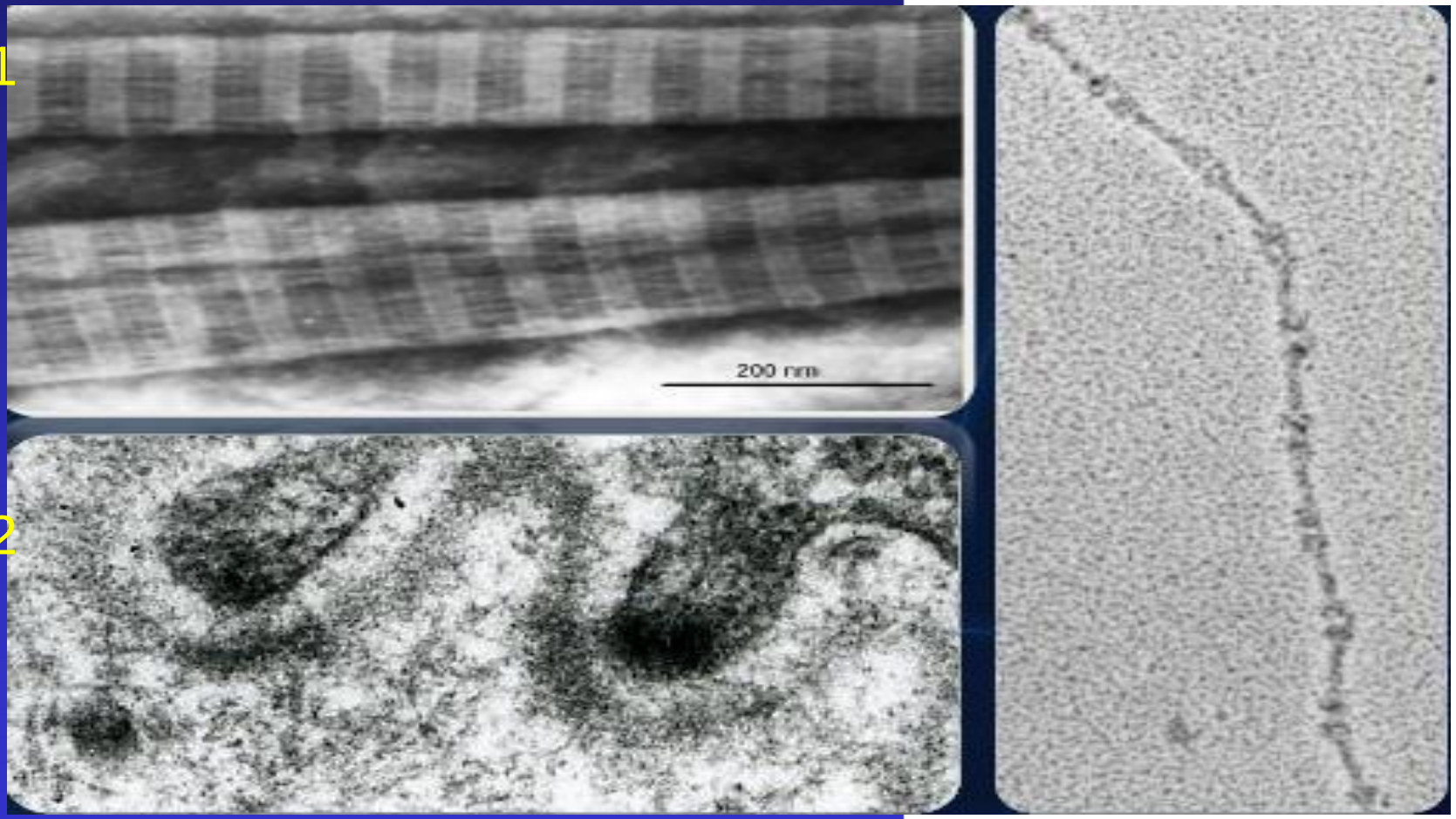
Hyaluronic acid

Skin Aging

Collagens

1

2



Skin Aging

Collagens

1893 Component of connective tissue which produces gelatin in boiling (Oxford Dictionary)

1960 Several types of collagen fibers, which are collectively responsible for the biological, mechanical and structural properties of tissues

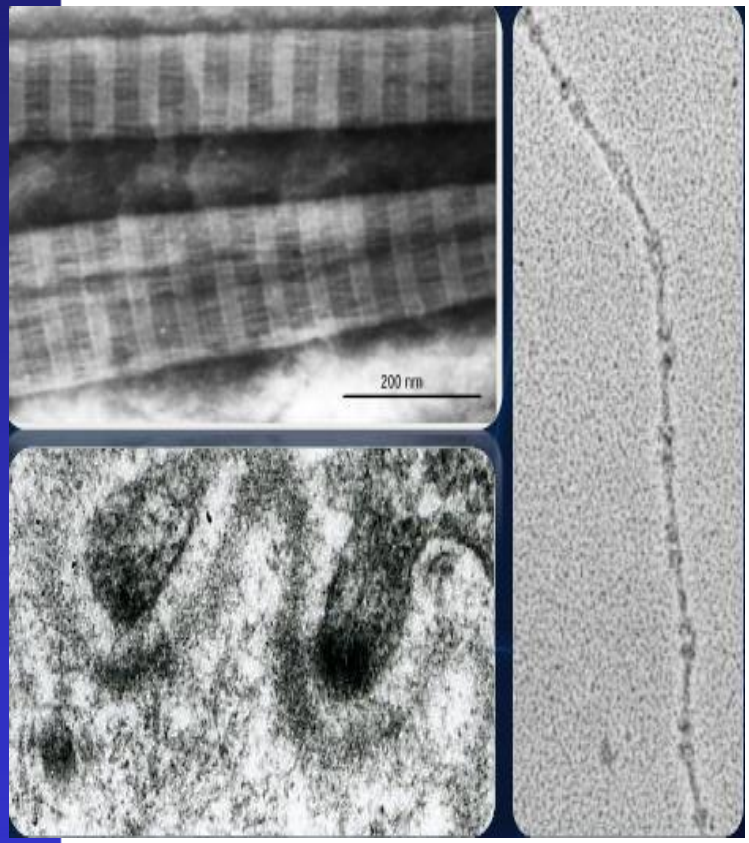
2005 Collagens consist of a family of proteins with specialized properties

41 genes 27 collagens all genetically distinct

Skin Aging

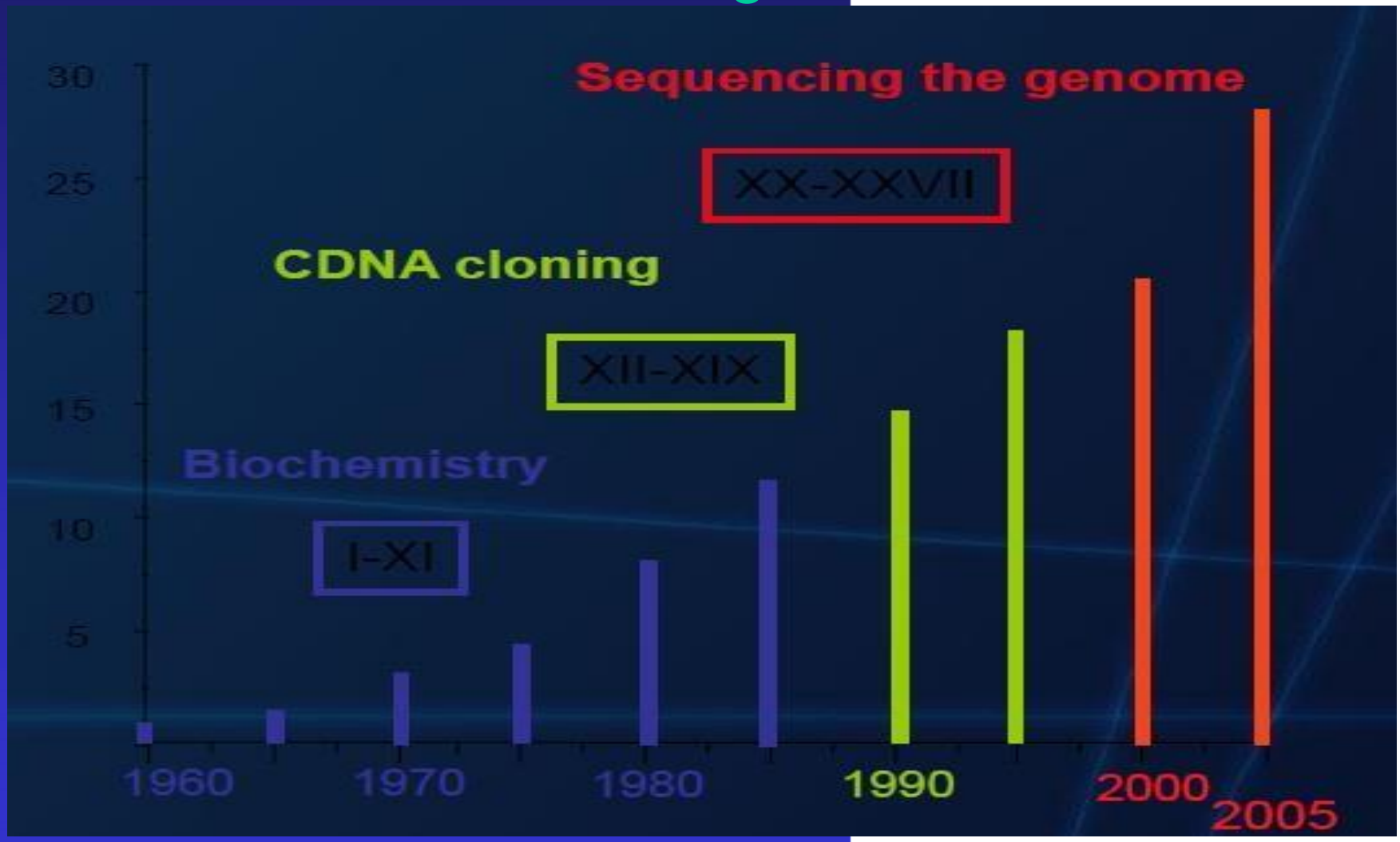
Collagens various functions

- Life of cells (differentiation, migration, proliferation, etc.)
- Extracellular matrix (morphogenetic development and remodeling)
- Tissue repair, healing of scars



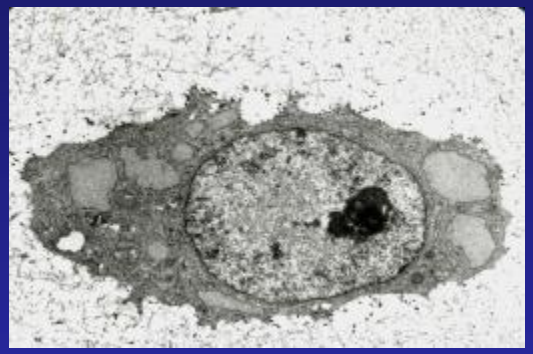
Skin Aging

Number of known Collagens

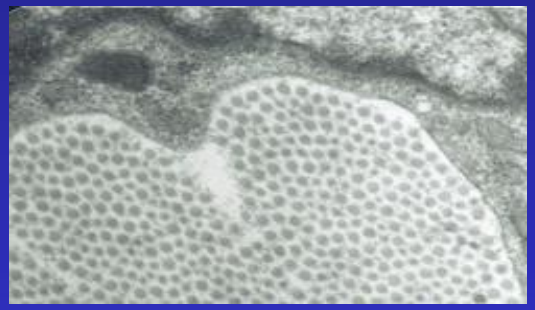


Skin Aging

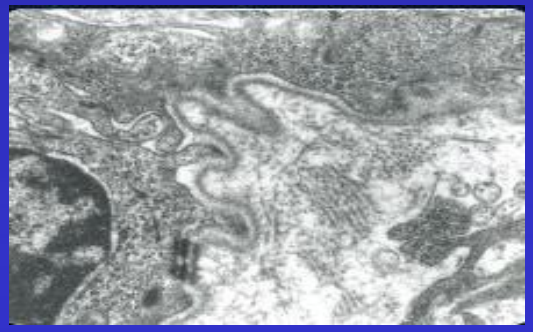
Collagens



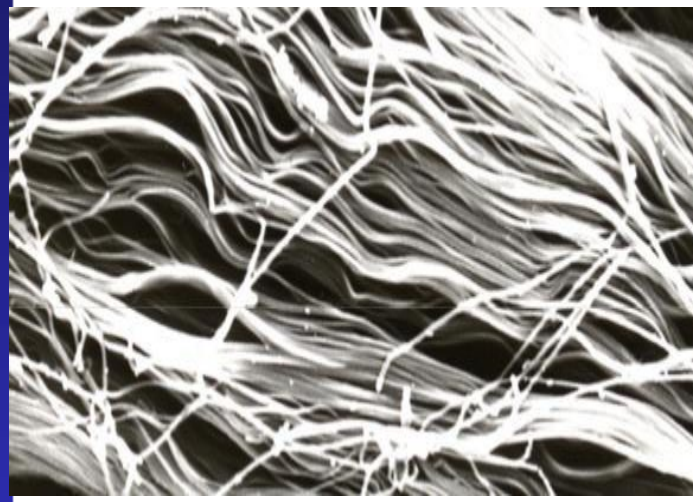
Cartilage
II, IX, X, XI



Tendon
I, V, VI



Skin
Dermis I, III, V, XII, XIV, XVI
DE Junction VII, XVII, XXII, …



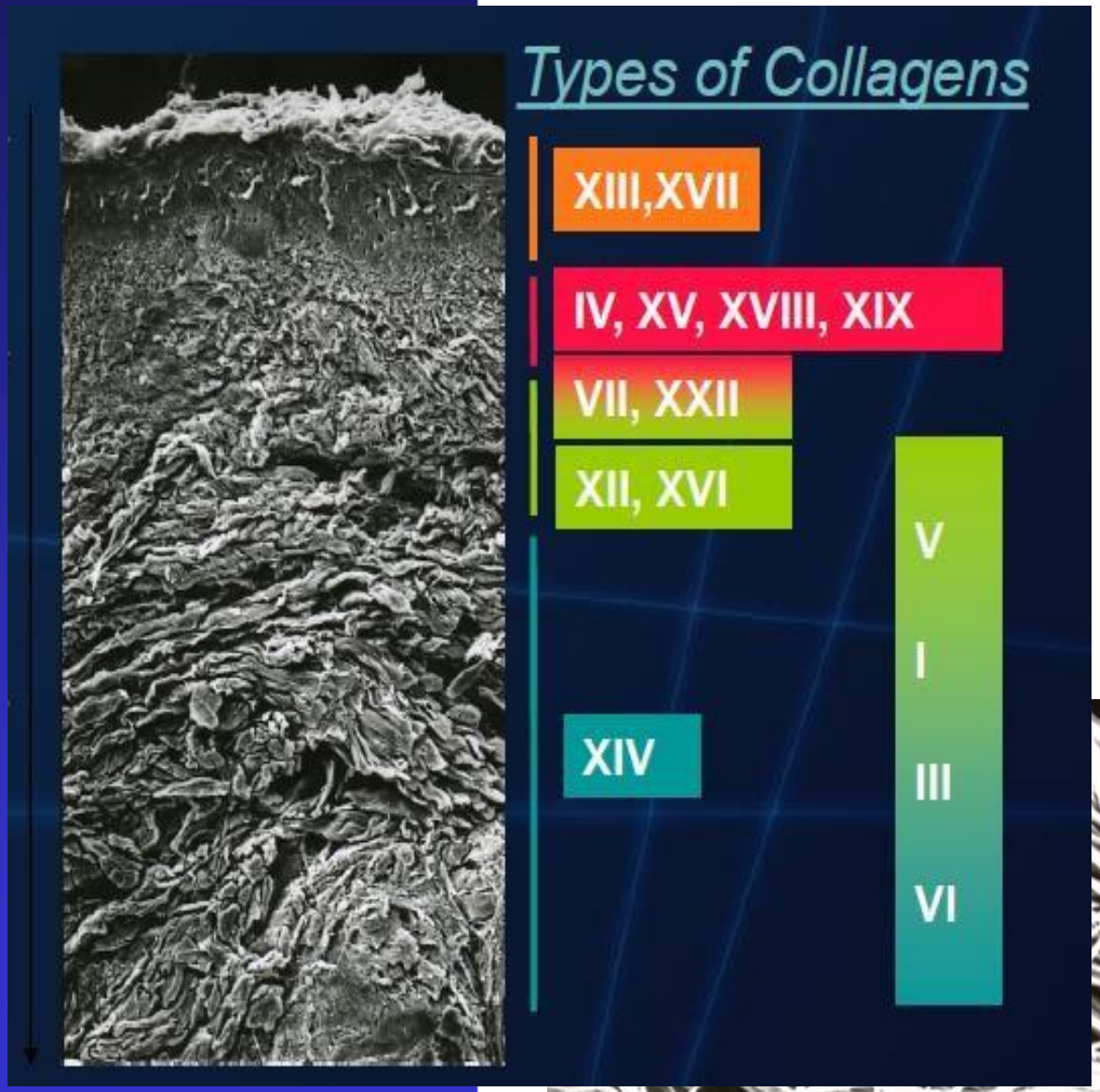
Skin Aging

Collagens

Epidermis
D-E Junction

Papillary dermis

Reticular dermis



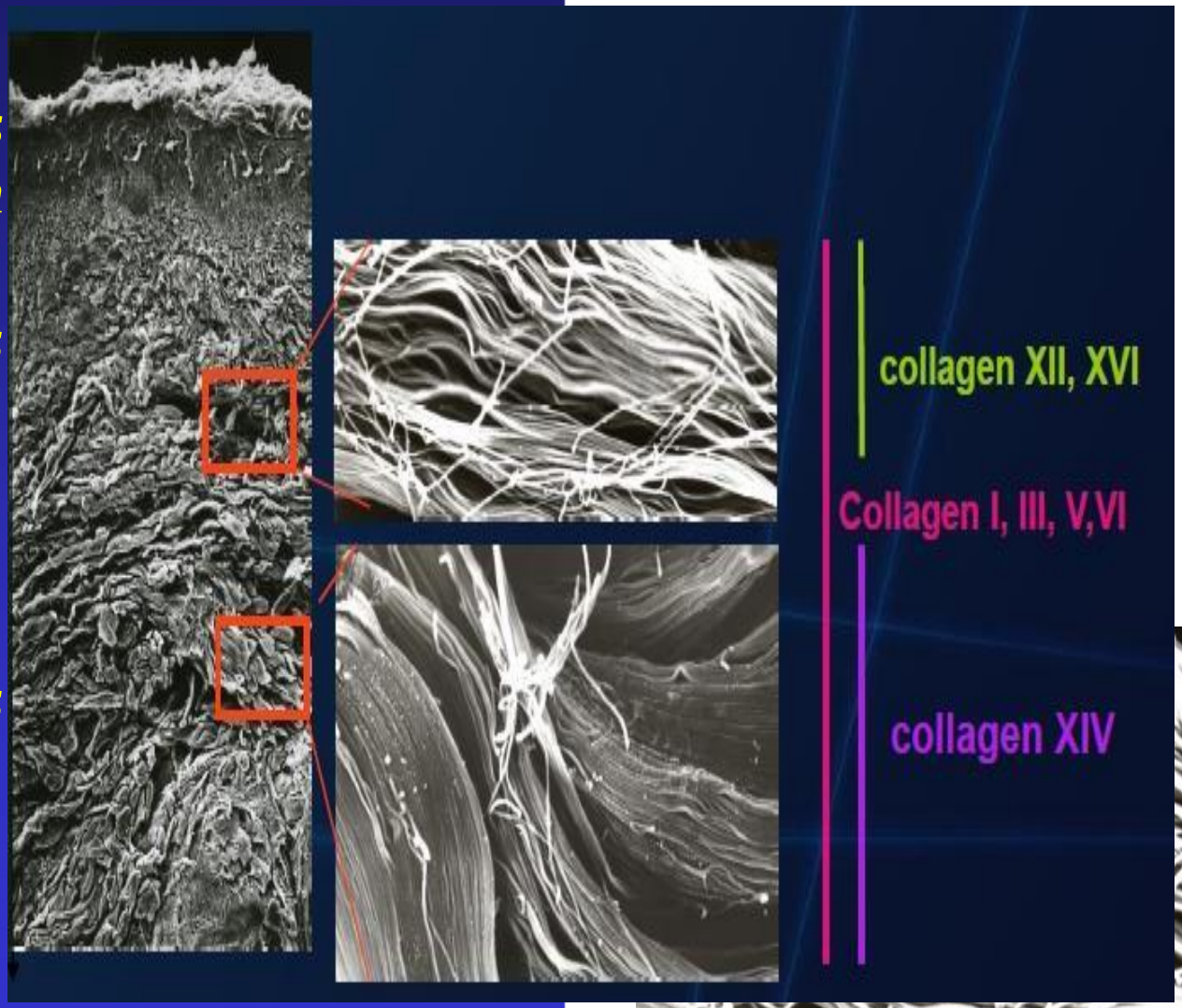
Skin Aging

Collagens *in the Dermis*

Epidermis
D-E Junction

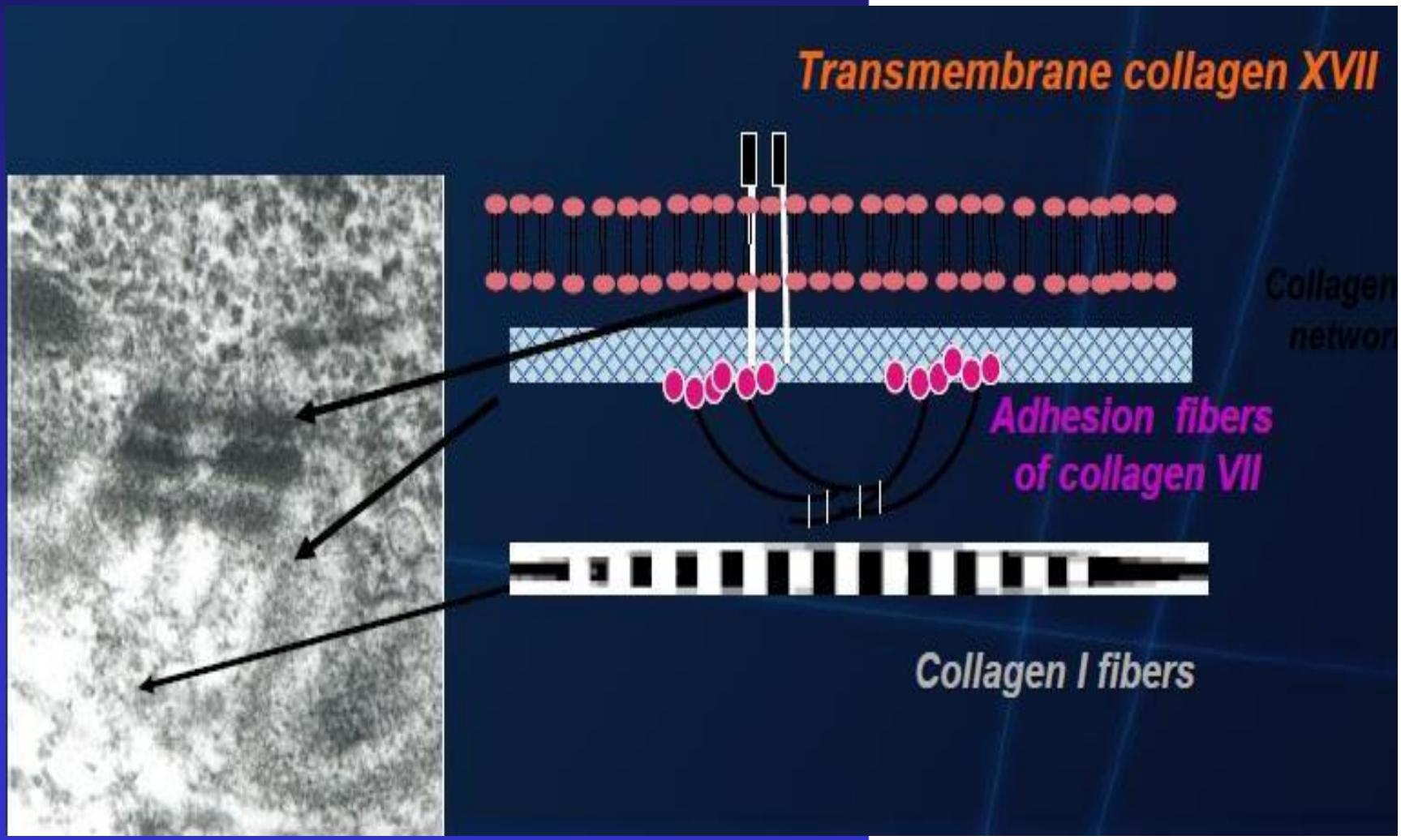
Papillary dermis

Reticular dermis



Skin Aging

Collagens *in Dermoepidermal junction*

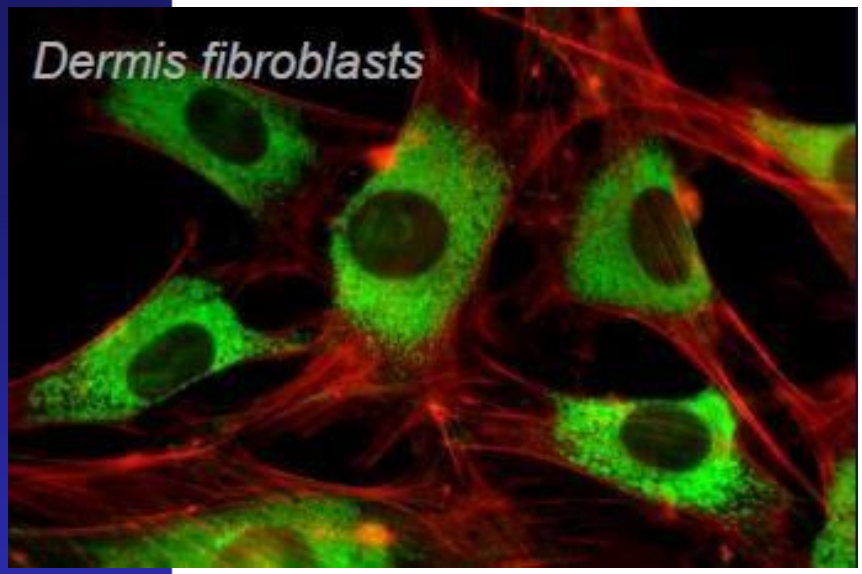


Skin Aging

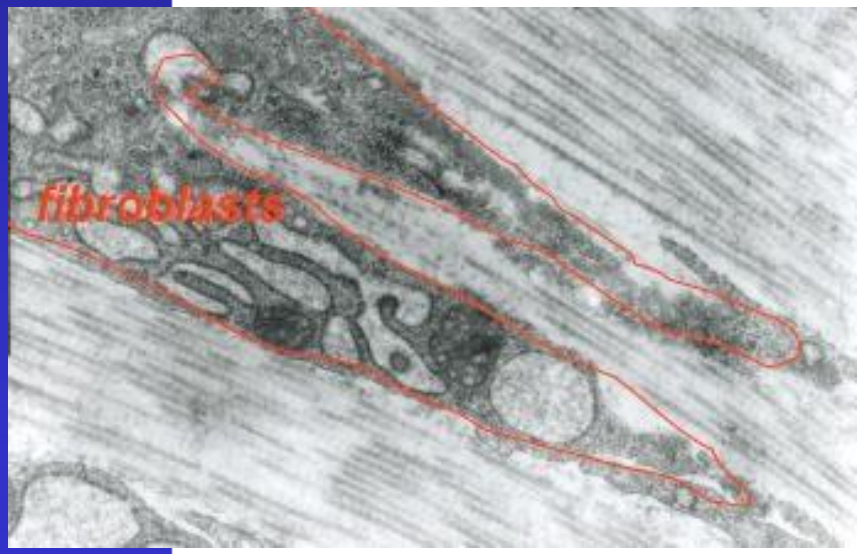
Collagen Biosynthesis

Collagen I

Cellular skeleton (actin)

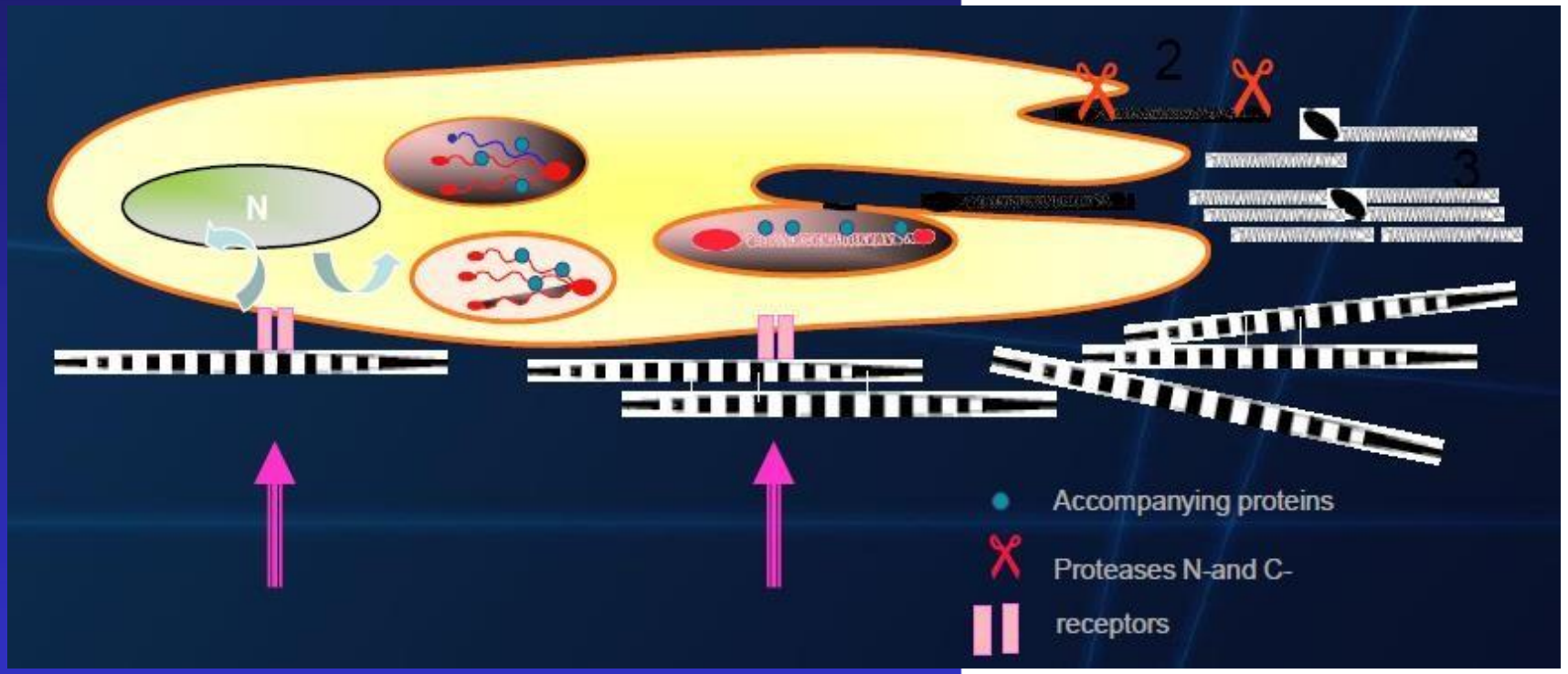


Collagen fibers gather in diverticulum of fibroblasts

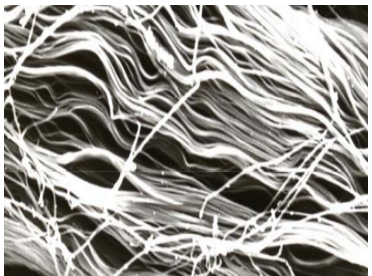


Skin Aging

Collagen Biosynthesis

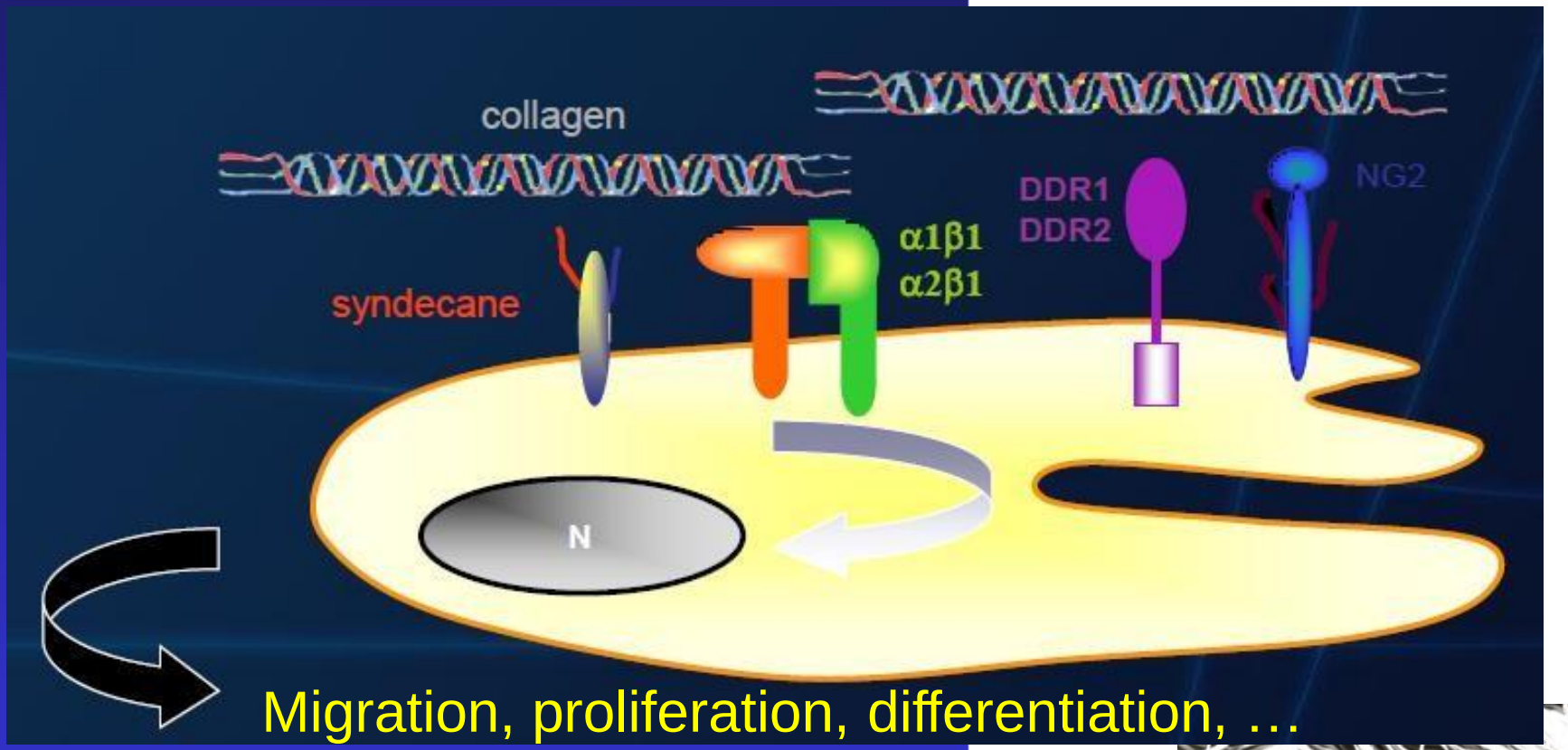


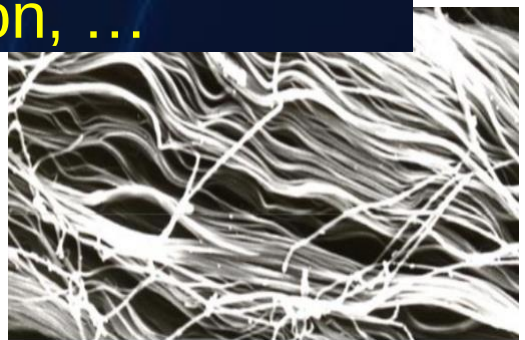
1. Triple helix formation (intracellular)
2. Maturation (intracellular)
3. Formation of fibrils and network (extracellular)



Skin Aging

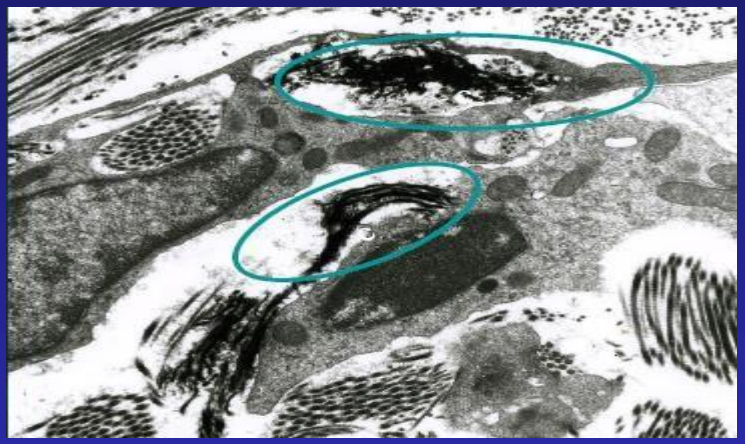
Collagen *Multiple membrane receptors*

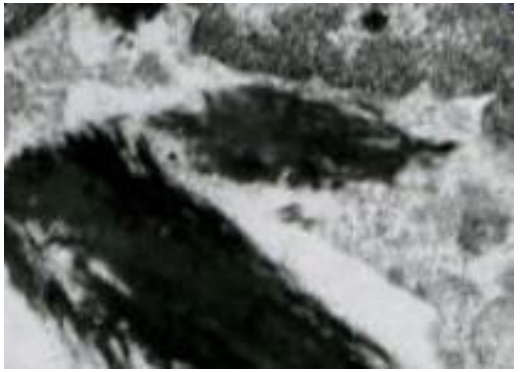




Skin Aging

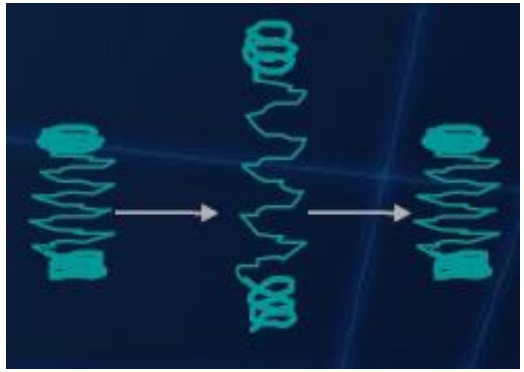
Elastin *"Spring" molecule*





Dermis with Electron emission Microscopy (EEM)





EEM after shading of cartilage homogenization

Skin Aging

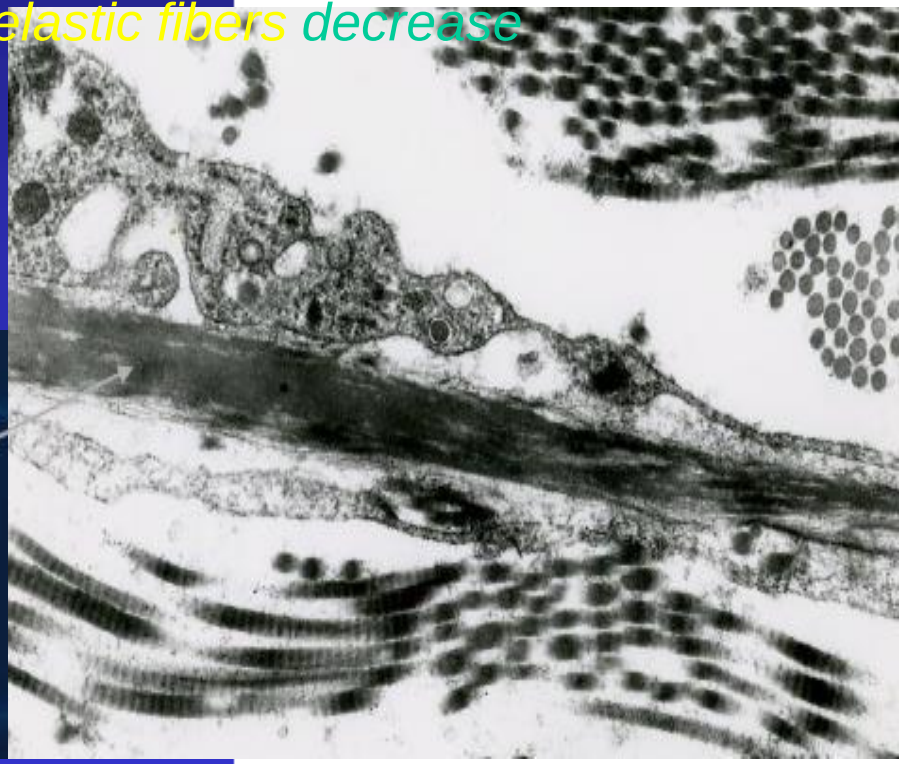
Elastin *"Spring" molecule*

"The stock of skin in elasticity"

- *Synthesized by fibroblasts of Dermis*
- *Responsible for elasticity, plasticity and expansion*
- *Production and composition of elastic fibers decrease significantly after puberty*

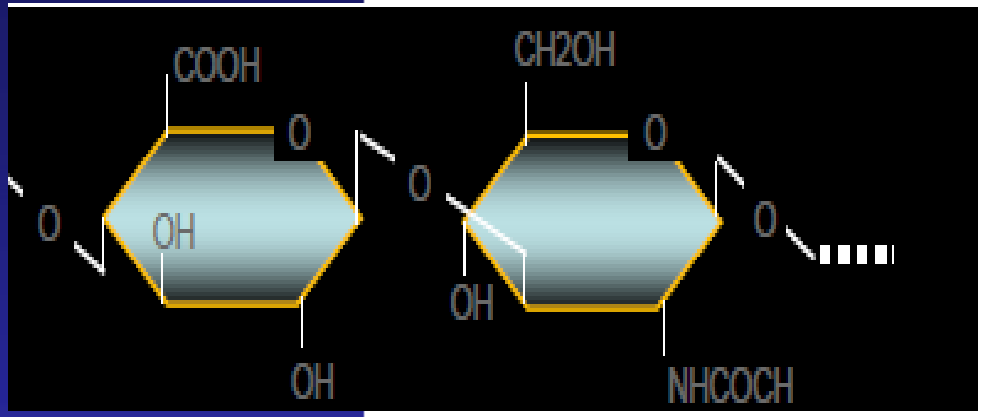
- *High elastic potential*
- *Highly insoluble substance*





Skin Aging

Hyaluronic acid

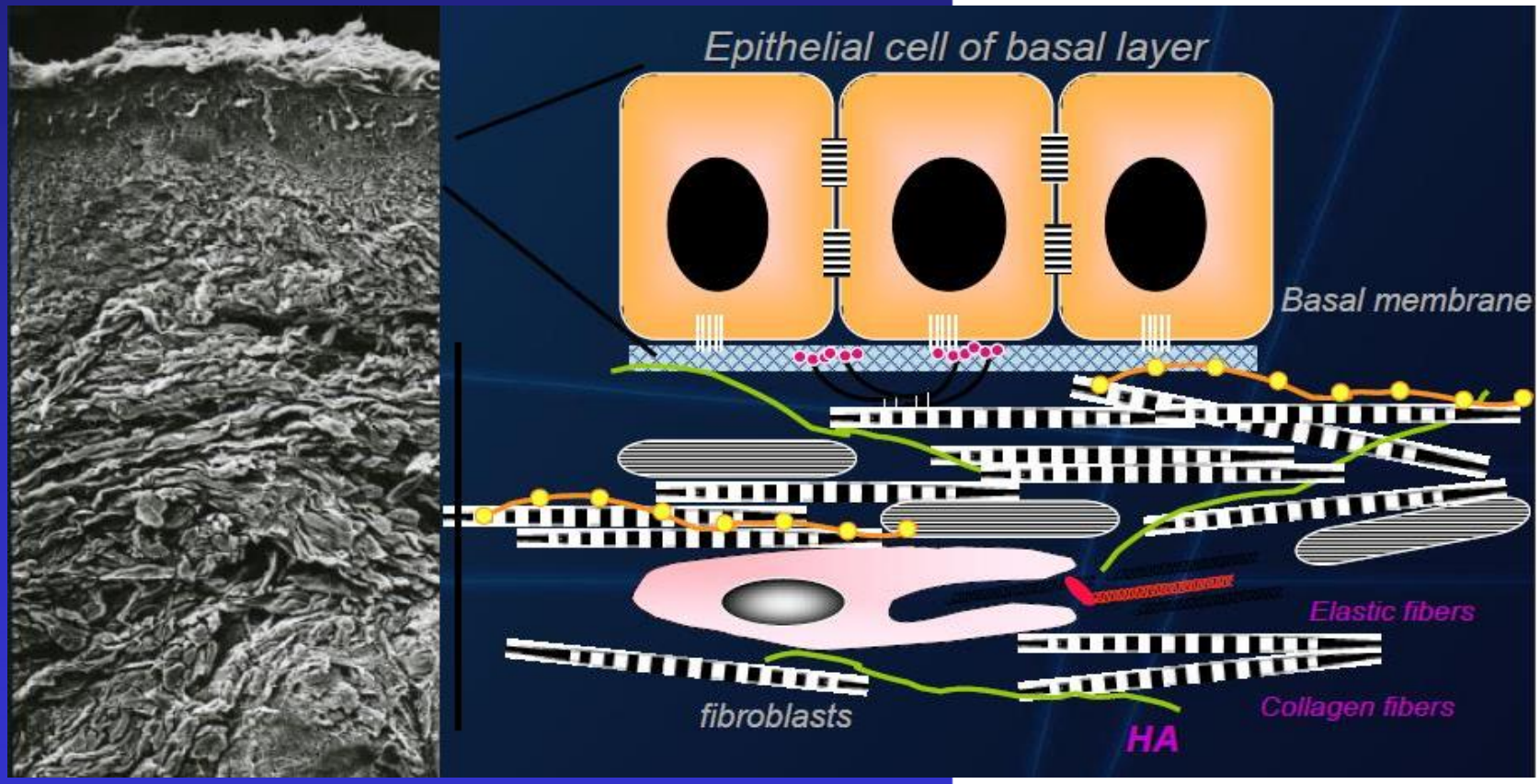


- *large polysaccharide with linear structure and unique rheological, elastic and hygroscopic properties*
- *interacts with other components of extracellular matrix*
- *plays important role in healing of scars*



Skin Aging

Skin *The complex "skeleton" structure of extracellular matrix proteins ensures and regulates preservation of bio-mechanical and functional properties of epidermis (collagens, elastin, hyaluronic acid)*



Skin Aging

When aging starts?

INTRINSIC AGEING (organic) *(DNA, heredity)*

EXTRINSIC AGEING *(environment, nutrition, way of life)*

HISTORICAL AGEING *(emotions, psychology)*

Skin Aging

ADDRESSING INTRINSIC AGING

Impossible till new concepts come up with DNA control via genetic studies



Skin Aging

ADDRESSING EXTRINSIC AGING

Medical (plastic surgery, dermatology, geriatrics, nutrition etc.)

Biology Biochemistry (implants, injectables, organic products)

Cosmetology (cosmetics)

Environmental studies, Aesthetics, SPA, etc …

Skin Aging

Etiology of Skin Aging

- *Impaired production of collagen and elastin*
- *Thickening of stratum corneum*
- *Laxity*
- *Impaired tone, texture and elasticity*
- *Disorders of nails and hair*
- *Skin Cancer*
- *Dermatitis*
- *Fat atrophy*
- *Loss of support*

Skin Aging

Effects of aging and sun exposure on skin

- *Hyperpigmentations*
- *Telangiectasias*
- *Skin laxity*
- *Skin elastosis*
- *Fine wrinkles*
- *Enlarged pores*

Skin Aging

Solar UV radiation

- The main environmental factor
- Causes premature aging of skin (photoaging)

  Wrinkles, altered pigmentation, loss of skin tone

Factors affect UV radiation

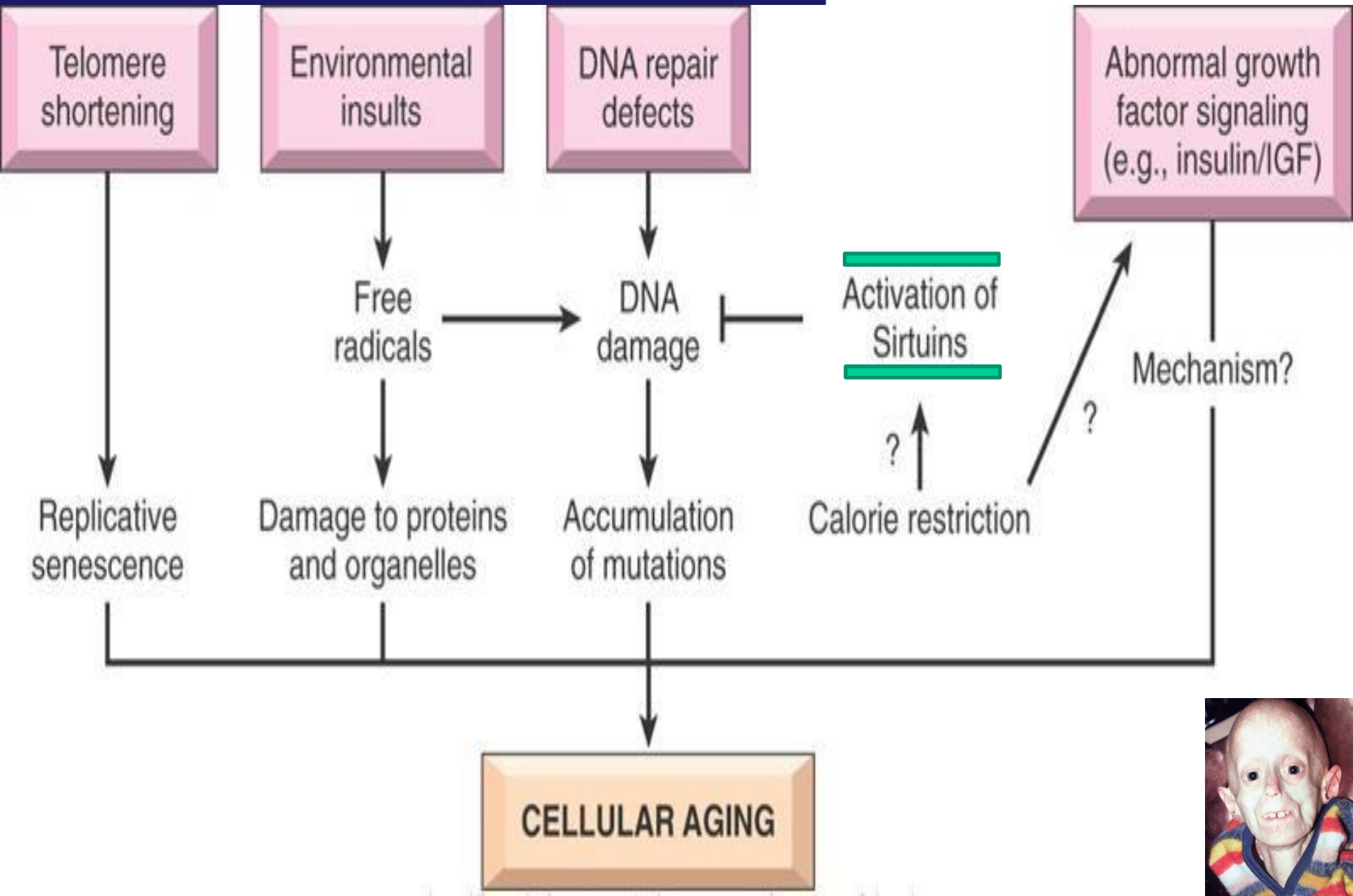
- Cumulative process
- Degree of sun exposure
- Level of skin pigment

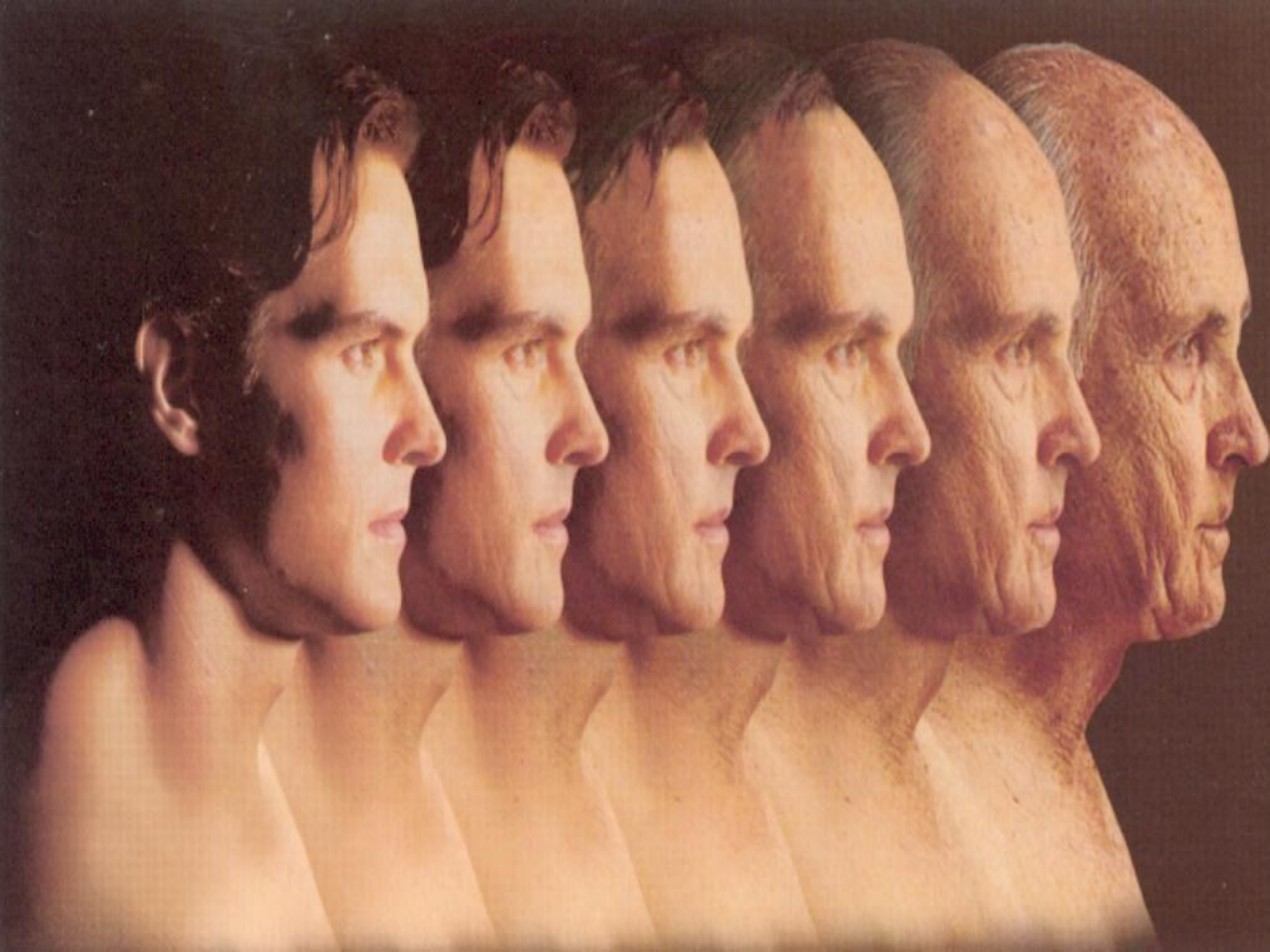
Skin Aging

Solar UV radiation

- Induces matrix metalloproteinases (MMPs) → impaired integrity of collagenous extracellular matrix
- Attacks keratinocytes and fibroblasts → activation of cell surface receptors
- Breakdown of collagen in extracellular matrix and shutdown of new collagen synthesis

Skin Aging


Telomere shortening
Environmental insults
DNA repair defects
Abnormal growth factor signaling (e.g., insulin/IGF)
Free radicals
DNA damage
Activation of Sirtuins
Mechanism?
?
?
Replicative senescence
Damage to proteins and organelles
Accumulation of mutations
Calorie restriction
CELLULAR AGING



Skin Aging

Treatments
Conventional surgery and technology

Lasers: Wrinkles, pores, pigmented lesions, vascular lesions, collagen, elastin stimulation, rejuvenation

Surgery: Face lift , blepharoplasty, suture lifts, fat transfer, injectables, etc.

Combination: surgery and lasers

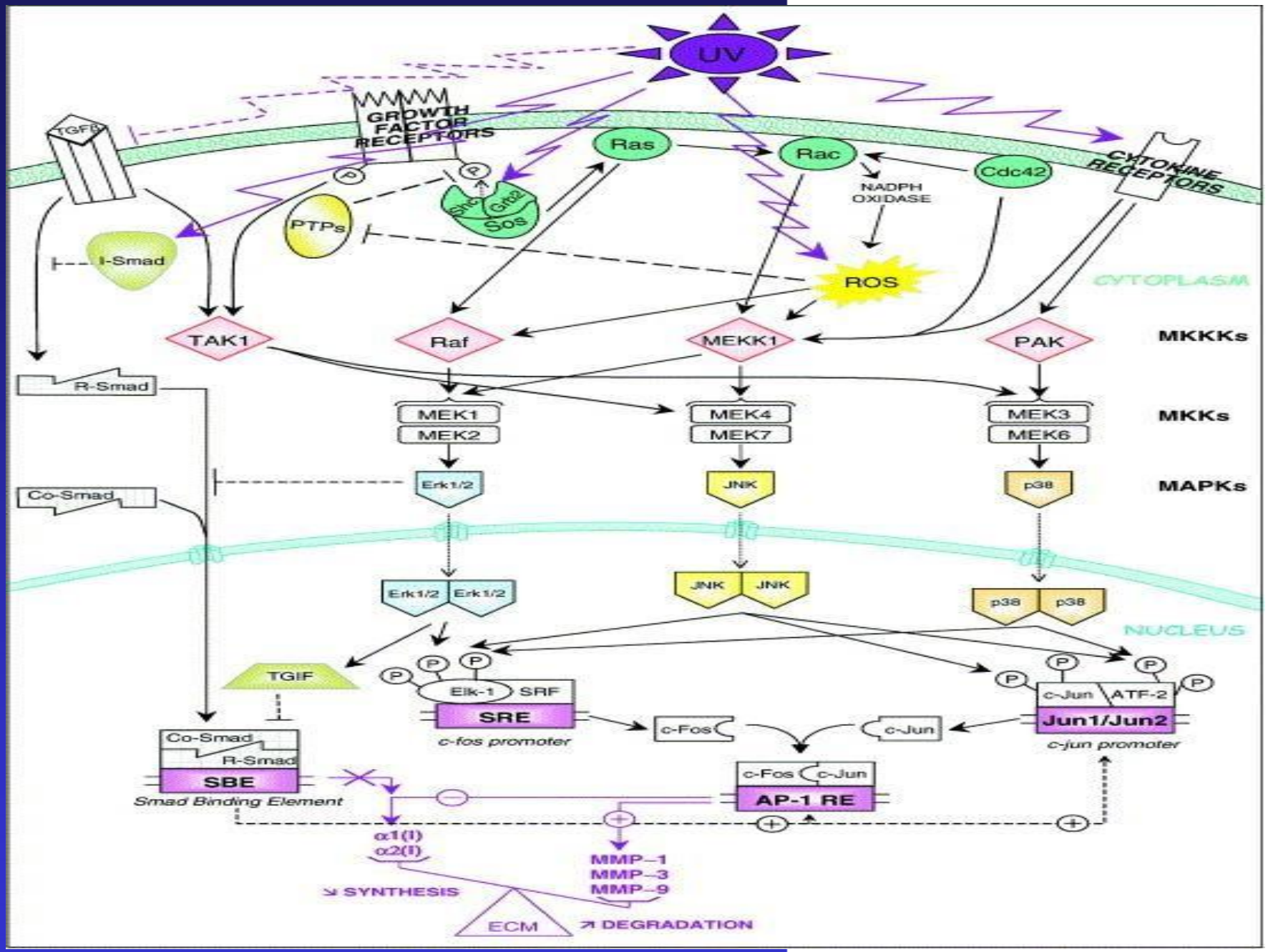
Other: Cooling, heating, ultrasound etc …

Skin Aging

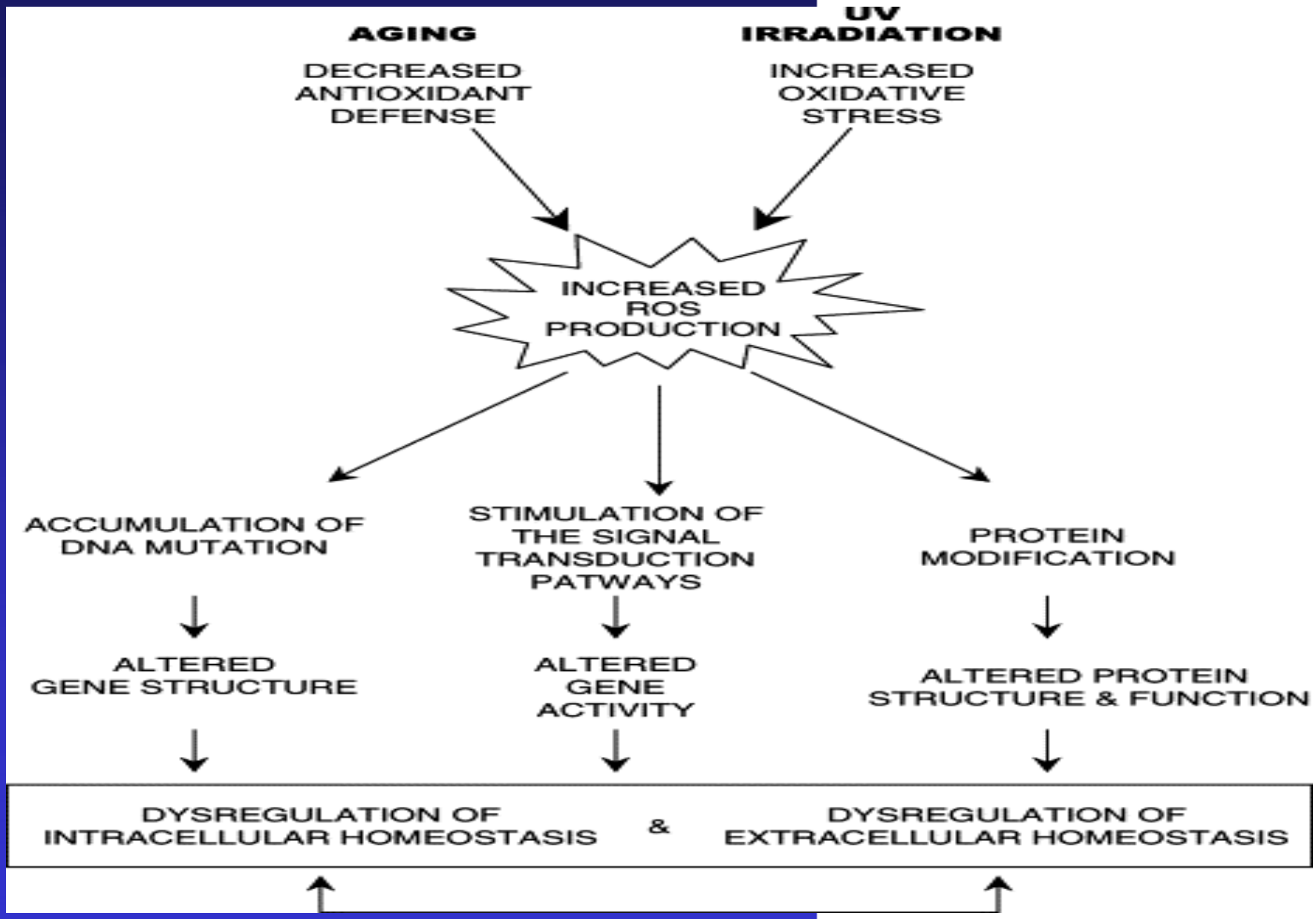
Acknowledgement

Dr. Paraskevas (Vakis) P. Kontoes

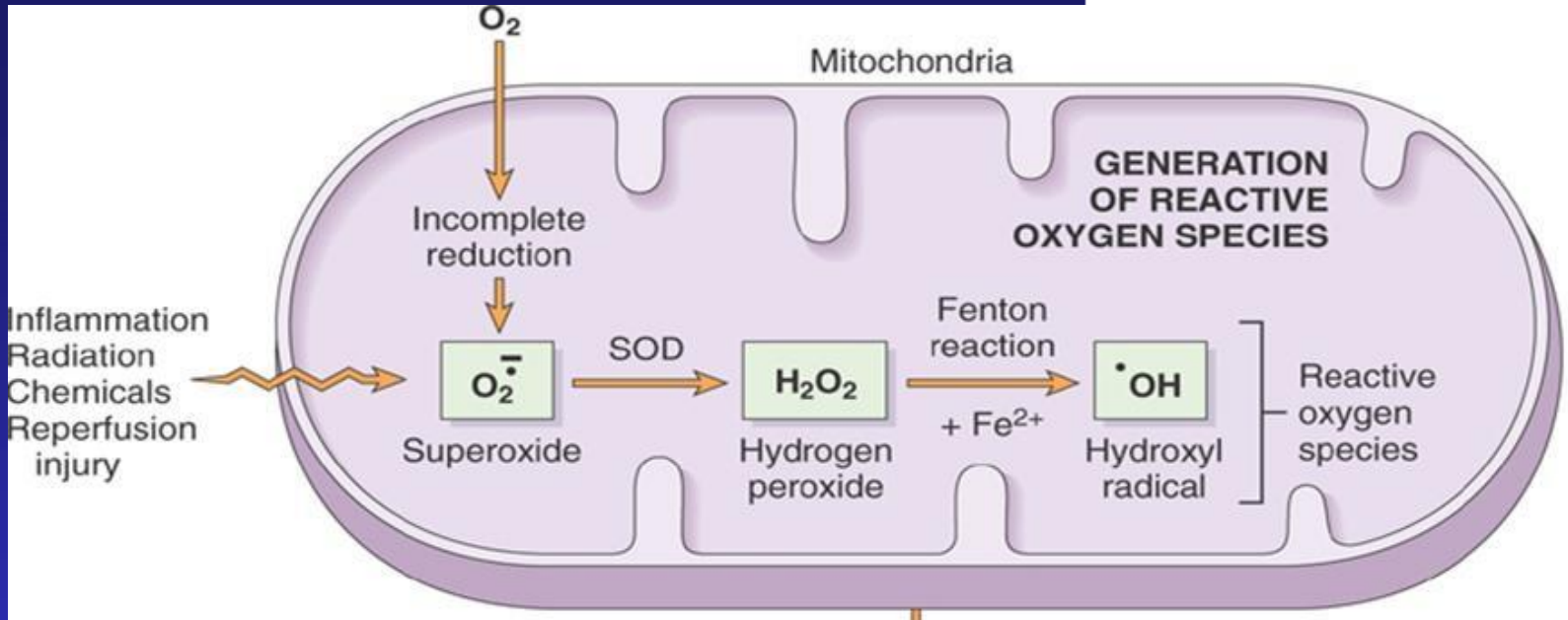
THANK YOU


UV
GROWTH FACTOR RECEPTORS
TGFβ
Ras
Rac
Cdc42
NADPH OXIDASE
CYTOKINE RECEPTORS
Shc
Grb2
Sos
PTPs
I-Smad
ROS
CYTOPLASM
TAK1
Raf
MEKK1
PAK
MKKKs
R-Smad
MEK1
MEK2
MEK4
MEK7
MEK3
MEK6
MKKs
Co-Smad
Erk1/2
JNK
p38
MAPKs
Erk1/2
Erk1/2
JNK
JNK
p38
p38
NUCLEUS
TGIF
Elk-1
SRF
SRE
c-fos promoter
c-Fos
c-Jun
c-Jun
ATF-2
Jun1/Jun2
c-jun promoter
Co-Smad
R-Smad
SBE
Smad Binding Element
c-Fos
c-Jun
AP-1 RE
α1(I)
α2(I)
↘ SYNTHESIS
MMP–1
MMP–3
MMP–9
ECM
↗ DEGRADATION

Skin Aging


AGING
DECREASED ANTIOXIDANT DEFENSE
UV IRRADIATION
INCREASED OXIDATIVE STRESS
INCREASED ROS PRODUCTION
ACCUMULATION OF DNA MUTATION
STIMULATION OF THE SIGNAL TRANSDUCTION PATWAYS
PROTEIN MODIFICATION
ALTERED GENE STRUCTURE
ALTERED GENE ACTIVITY
ALTERED PROTEIN STRUCTURE & FUNCTION
DYSREGULATION OF INTRACELLULAR HOMEOSTASIS
&
DYSREGULATION OF EXTRACELLULAR HOMEOSTASIS

Skin Aging



PATHOLOGIC EFFECTS OF ROS: CELL INJURY AND DEATH

ROS react with:

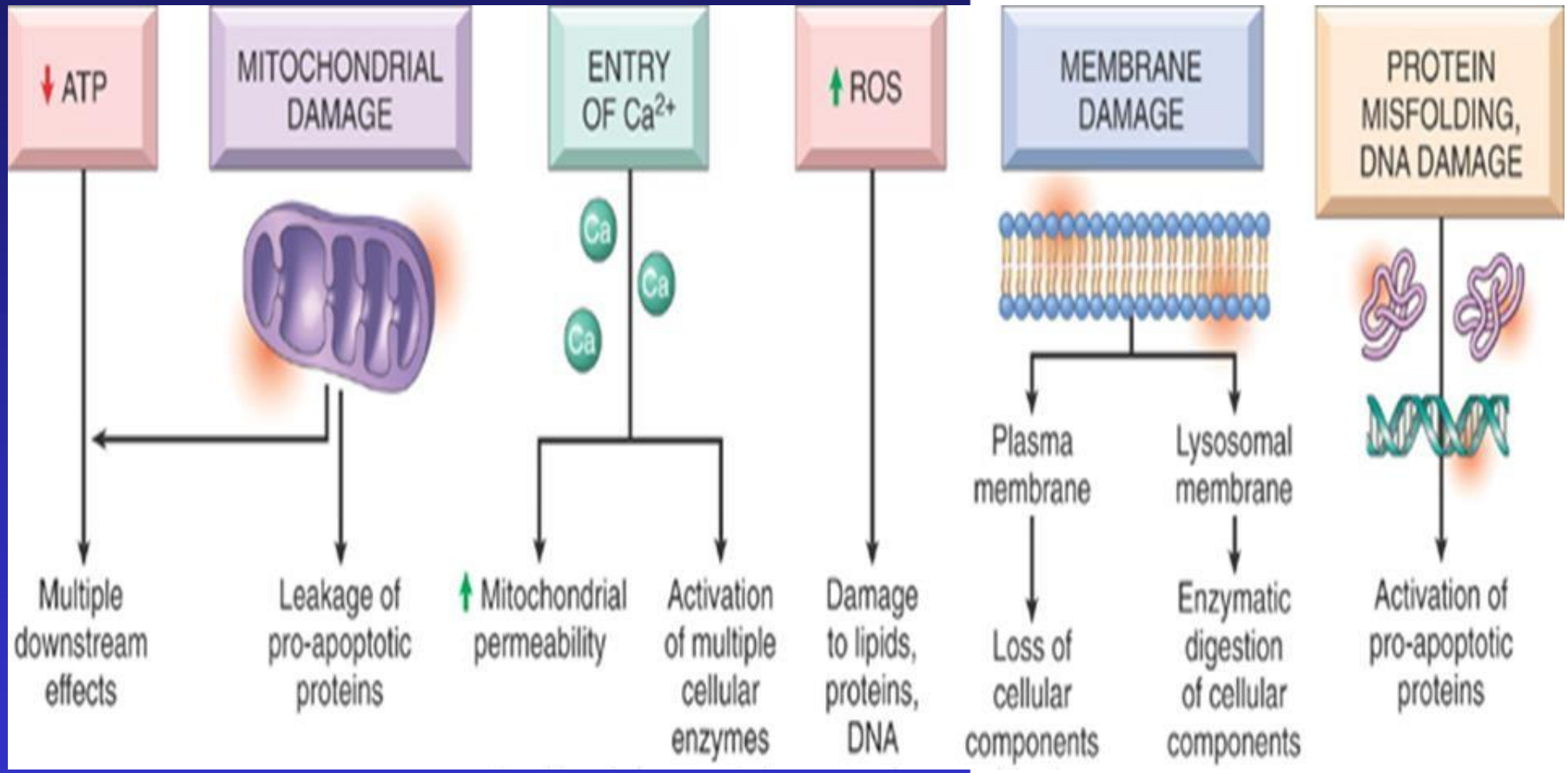
- Fatty acids → oxidation → generation of lipid peroxidases → disruption of plasma membrane, organelles
- Proteins → oxidation → loss of enzymatic activity, abnormal folding
- DNA → oxidation → mutations, breaks

REMOVAL OF FREE RADICALS

Antioxidant mechanisms:

- SOD (in mitochondria) converts $O_2^{\cdot -} \rightarrow H_2O_2$
- Glutathione peroxidase (in mitochondria) converts $^{\cdot}OH \rightarrow H_2O_2 \rightarrow H_2O + O_2$
- Catalase (in peroxisomes) converts $H_2O_2 \rightarrow H_2O + O_2$

Skin Aging


ATP
MITOCHONDRIAL DAMAGE
ENTRY OF Ca^{2+}
ROS
MEMBRANE DAMAGE
PROTEIN MISFOLDING, DNA DAMAGE
Ca
Ca
Ca
Multiple downstream effects
Leakage of pro-apoptotic proteins
Mitochondrial permeability
Activation of multiple cellular enzymes
Damage to lipids, proteins, DNA
Plasma membrane
Lysosomal membrane
Loss of cellular components
Enzymatic digestion of cellular components
Activation of pro-apoptotic proteins