Structure and function of the skin

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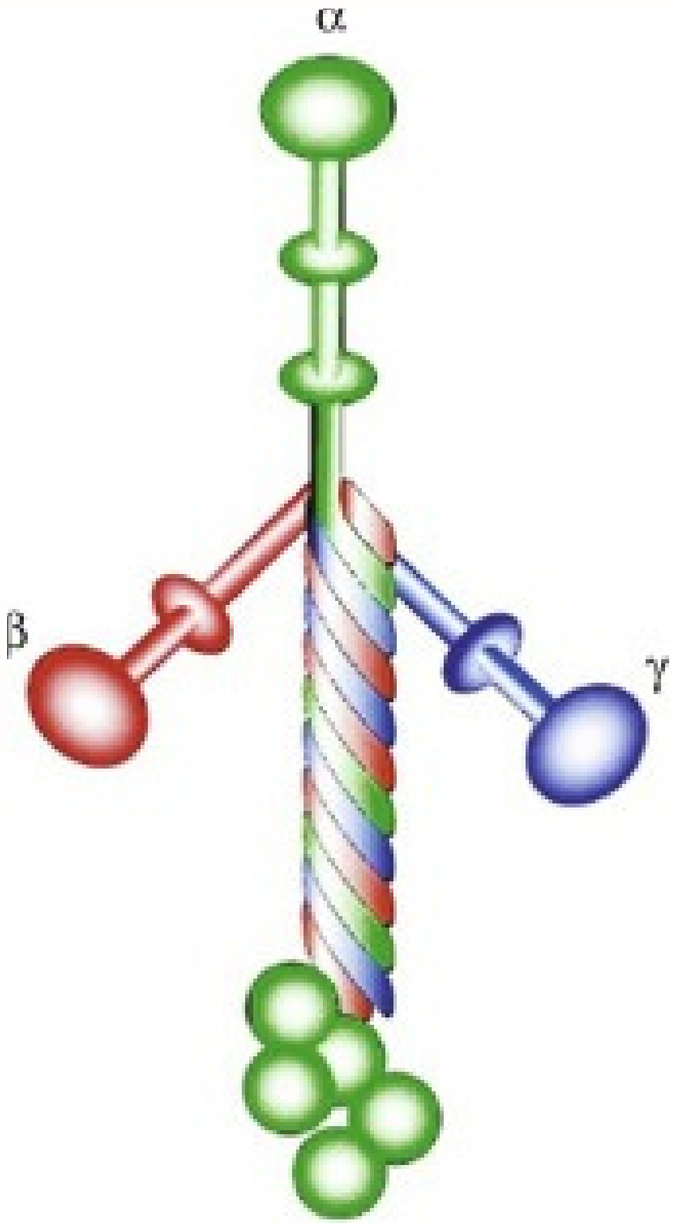
LAMININS

What are laminins?

- Laminin, a multidomain glycoprotein, is the major non-collagenous constituent of basement membrane.
- Laminins are heterotrimeric proteins with a high molecular mass (~400 to ~900 kDa).
- Each laminin molecule consists of three polypeptide subunits, α, β and γ chains (formerly, A,B1 and B2) which form a cruciform structure with three short arms and one long arm when visualised by rotary shadowing electron microscopy.
- The laminins molecules are named acoording to their chain composition.Thus, laminin-511 contains α-5, β-1 and γ-1 chains.



LAMININ

- Out of 16 different laminin identified, atleast 4 of them are present in skin.
- STRUCTURE: cruciform structure with three short polypetide subunits α, β and ϒ chains. Cell binding of laminin is mediated by integrins (α6β4 in BMZ).

Table 2.1 Chain composition of the major laminins in the skin.

Type	Chain composition	Old designation	Distribution in basement membranes
111	α1β1γ1	1	Blood vessels, LD
332	α3β3γ2	5	LL/LD
311	α3β1γ1	6	LL/LD
511	α5β1γ1	10	LL/LD

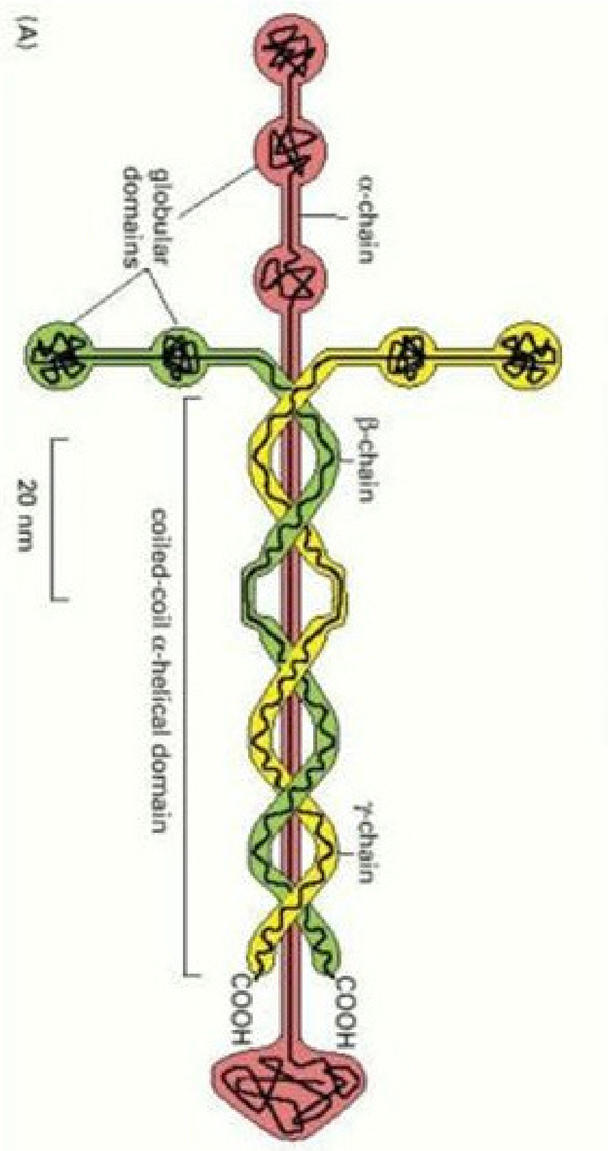
LD, lamina densa; LL, lamina lucida.

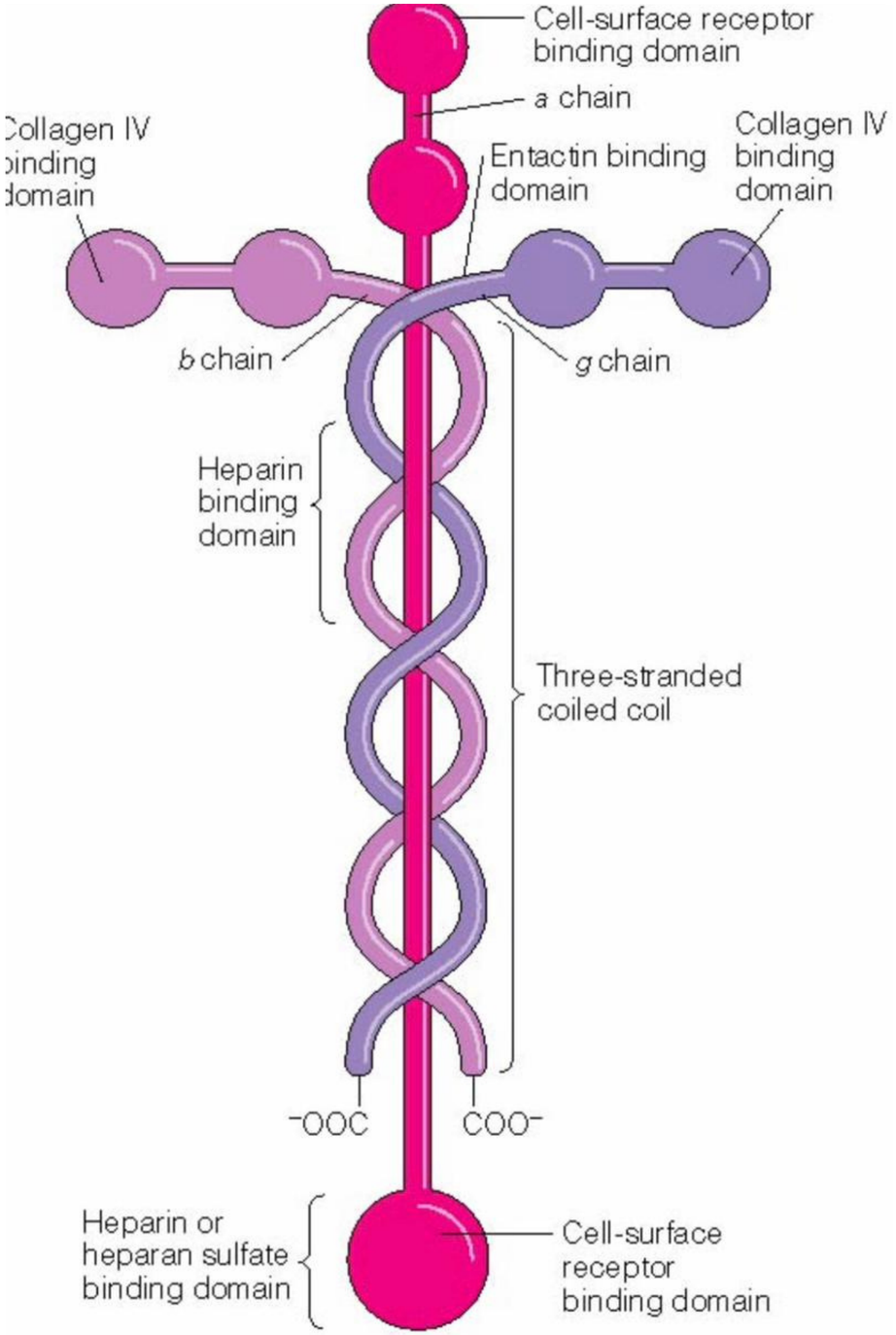
Anatomy of multidomain glycoportein

- Laminin is a large mosaic protein composed of many district domains with different structures & functions. Laminins chains are designated A(Mw : 400kDa), B1 (MW: 210kDa) and B2(Mw: 200kDa)

- Globular and rodlike domains are arranged in an extended four-armed, cruciform shape that is well-suited for mediating between distant sites on cells and other components of the extracellular matrix.

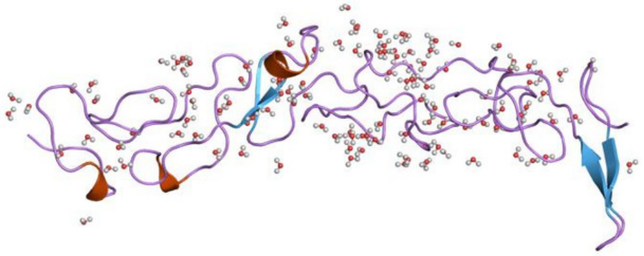
- The alpha-helical coiled-coil domain of the long arm is involved in the specific assembly of the three chains (A,B1,B2 and possible variants) of laminin and is the only domain composed of multiple chains.




Cell-surface receptor binding domain
a chain
Collagen IV binding domain
Entactin binding domain
Collagen IV binding domain
b chain
g chain
Heparin binding domain
Three-stranded coiled coil
⁻OOC
COO⁻
Heparin or heparan sulfate binding domain
Cell-surface receptor binding domain

Functions of laminins

- Laminins form independent networks and are associated with type IV collagen networks via entactin, fibronectin, and perlecan. They also bind to cell membranes through integrins and other plasma membrane molecules such as the dystroglycan glycoprotein complex. Through these interactions, laminins critically contribute to
- Cell attachment & differentiation.
- Cell shape & movement.
- Maintenance of tissue phenotype.
- Promotion of tissue survival.
- Role in peripheral nerve repair (laminins are enriched at the lesion site after peripheral nerve injury and are secreted by Schwann cells. Neurons of peripheral nervous system express integrin receptors that attach to laminins and promotes neuroregeneration after injury.)



Name	Source	Storage Temp	Target Cells For Attachment	Concentration For Use	Cat. No.
Laminin, aqueous solution	from Engelbreth-Holm-Swarm murine sarcoma basement membrane	−20°C	Epithelial cells, endothelial cells, muscle cells, tumor cells, hepatocytes, Schwannoma	1 - 2 µg/cm^2	L2020-1MG
Laminin, liquid	from human placenta	−70°C	Epithelial cells, endothelial cells, muscle cells, tumor cells, hepatocytes, Schwannoma	1 - 2 µg/cm^2	L6274-.5MG

Use of laminins in cell culture

More Basal Lamina Proteins

Perlecan is a large multidomain heparan sulfate proteoglycan of the extracellular matrix which regulates systemic metabolism with dynamic changes in adipose tissue and skeletal muscle.

Nidogen (previously called entactin), a glycoprotein that interacts with type IV collagen either alone or as a laminin-nidogen complex. Genetic analysis have shown that these are not required for the overall architecture of the basement membrane. Instead, nidogens appear to play a critical role in development of basement membranes in tissues undergoing rapid growth or turnover.

Fibronectin (fibro + nectere : to bind), a high-molecular weight (440kDa) glycoprotein of the extracellular matrix that binds to membrane-spanning receptor proteins called integrins. It crosslinks and stabilizes other components of Extra-cellular matrix.

Hemidesmosomes

(A cell-basement membrane adhesion site)

- **Hemidesmosomes are very small stud-like structures which extend from the intracellular compartment of the basal keratinocytes to the lamina lucida in the upper portion of the dermal-epidermal basement membrane.**
- **It has three plaques .**

Inner Plaque

↓ **Plectin**

↓ **BPAG1 (BP230)**

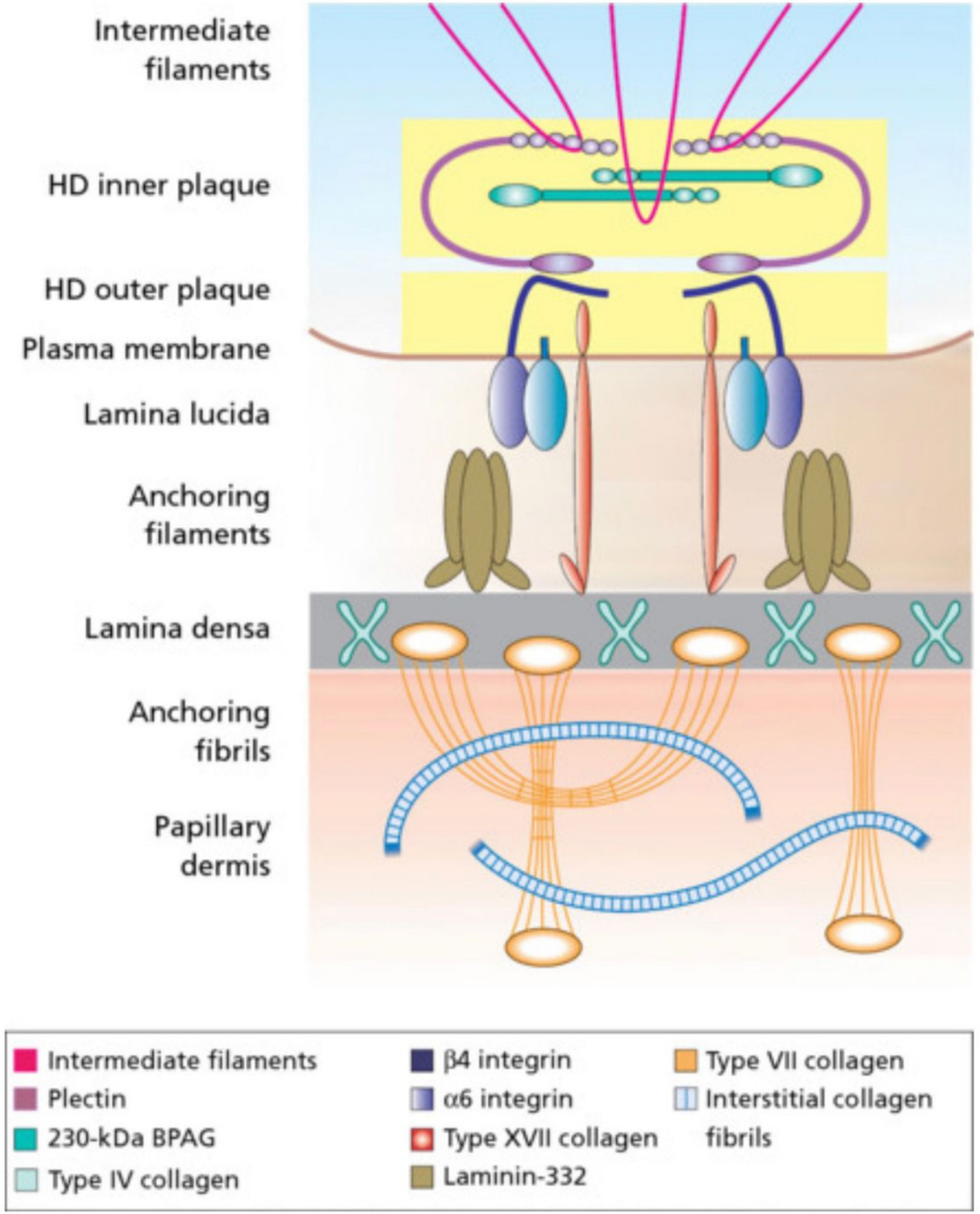
Outer Plaque

↓ **BP-180 (Collagen 17)**

↓ **α6β4 Integrin**

Sub basal dense plaque

The intracellular domains of hemidesmosomes within the basal keratinocytes attach to the keratin intermediate filament network, while in the extracellular space within the lamina lucida, the hemidesmosomes are contiguous with anchoring filaments; this unit is termed the **hemidesmosomes-anchoring filament complex.**



- **Initially 5 major components of hemidesmosomes were recognized namely HD1 to HD5.**
- **They were later renamed as:**

HD1	**PLECTIN**
HD2	**230-kDa BULLOUS PEMPHIGOID ANTIGEN**
HD3	**β4 INTEGRIN SUBUNIT POLYPEPTIDE**
HD4	**180-kDa BULLOUS PEMPHIGOID ANTIGEN**
HD5	**α6 INTEGRIN PEMPHIGOID ANTIGEN**

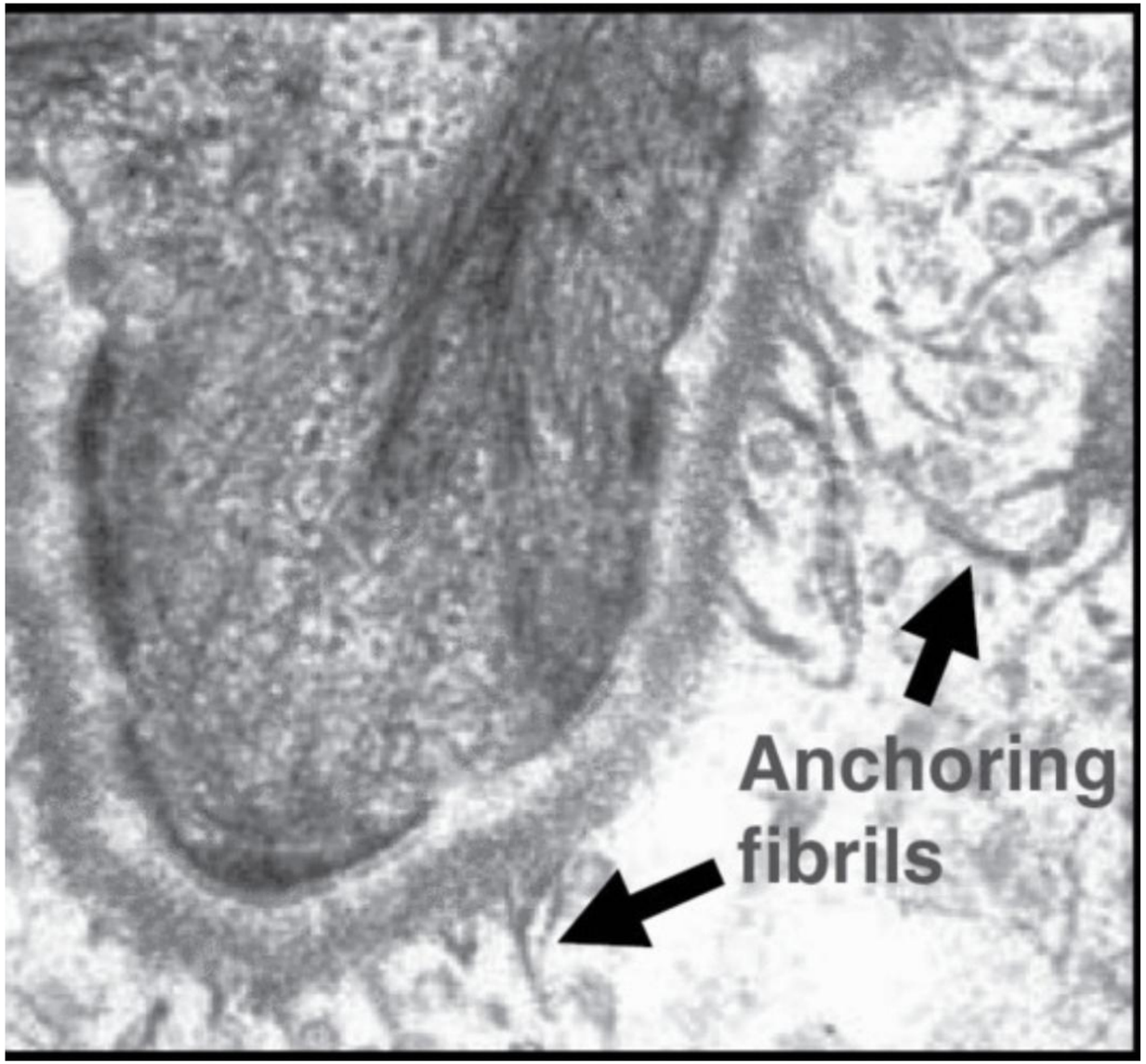
Hereditary skin diseases of hemidesmosomes

- **The critical importance of this network structure in securing the adherence of the epidermis to the underlying dermis is reflected in the group of diseases, epidermolysis bullosa, in which components of hemidesmosomes, anchoring filaments or anchoring fibrils are genetically altered or missing. As a result, fragility at the dermal-epidermal junction ensues, clinically manifesting as erosions and blisters following minor trauma.**
- **Mutations of plectin results in epidermolysis bullosa simplex with progressive muscular dystrophy.**
- **Mutations in type XVII collagen (BP180 : BPAG2) causes junctional epidermolysis bullosa.**

ANCHORING FIBRILS

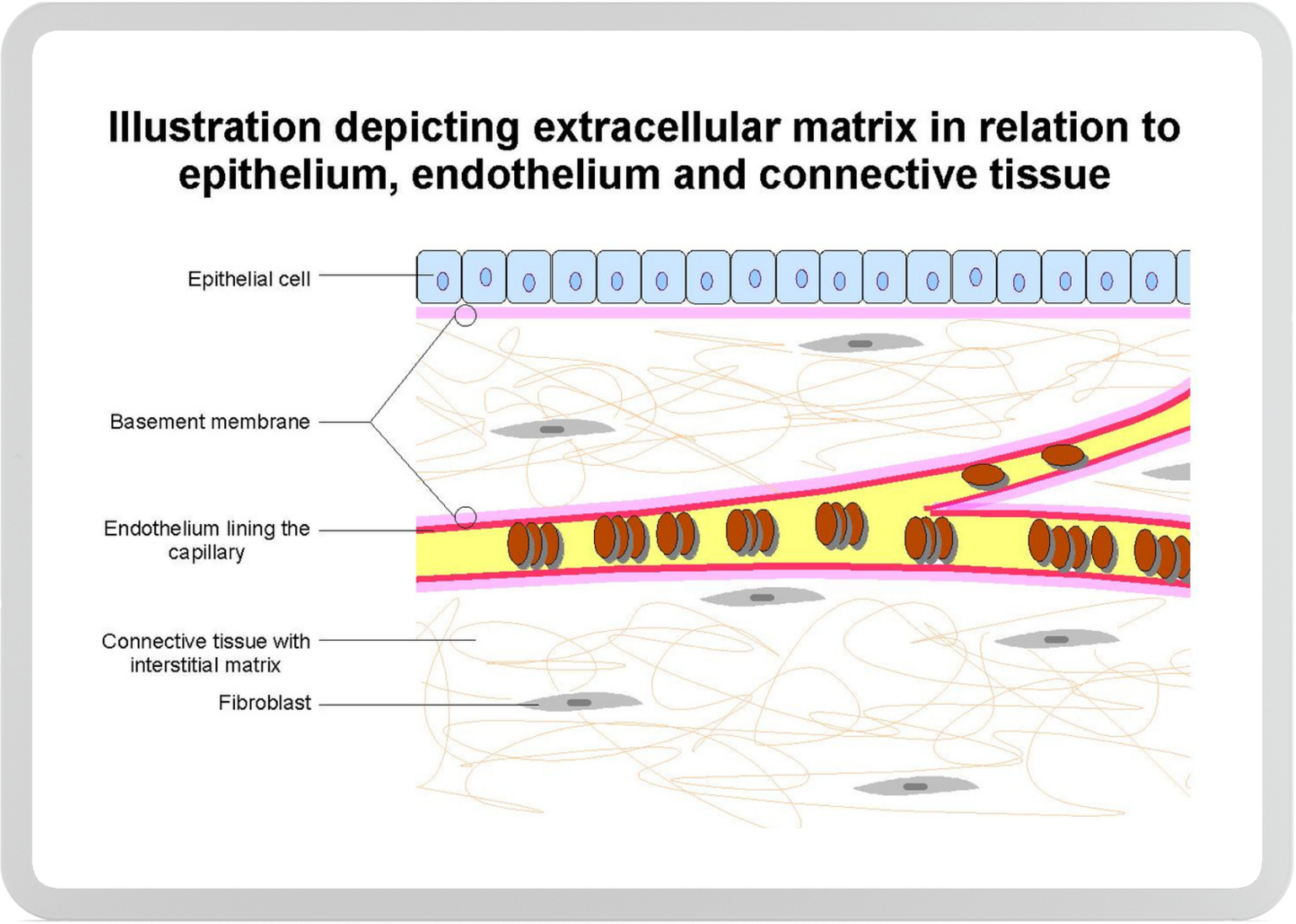
- Short, U-shaped structures that extend from the lower part of the lamina densa to the upper reticular dermis.
- Major component ⟷ Type VII Collagen
- The critical importance of the anchoring fibrils in securing the adhesion of the dermal-epidermal basement membrane to the underlying dermis as well as in wound healing is illustrated by the dystrophic forms of EB.
- Specifically, a complete absence of type VII collagen results in severe, generalized, recessive dystrophic EB with fragility of the skin & mucous membranes, leading to mutilating scarring of the hands and feet.

- **Transmission electron microscopy of the dermal-epidermal junction revealing wheatsheaf-shaped anchoring fibrils beneath the lamina densa.**

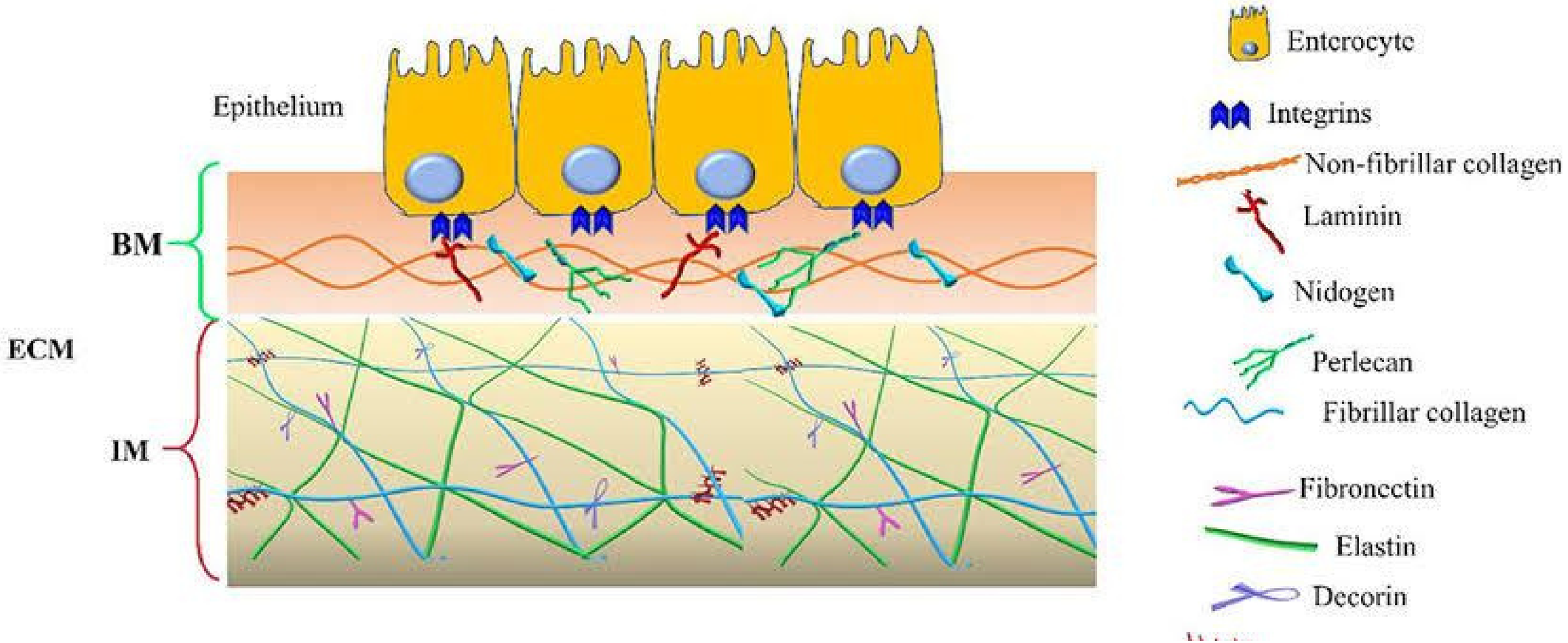


Extracellular Matrix

ECM is a non-cellular, three-dimensional network consisting of extracellular macromolecules such as : collagens,proteoglycans,elastin and glycoproteins that provide structural and biochemical support to surrounding cells.



Structure of ECM



Composition of Extracellular Matrix (ECM)

- **Cells (mesenchymal origin)**

1. **fibroblasts**
2. **smooth muscle cells**
3. **chondroblasts**
4. **osteoblasts & epithelial cells**

- **Organic fibrillar matrix**
- **Organic nonfibrillar matrix**
- **Water**

Function of ECM

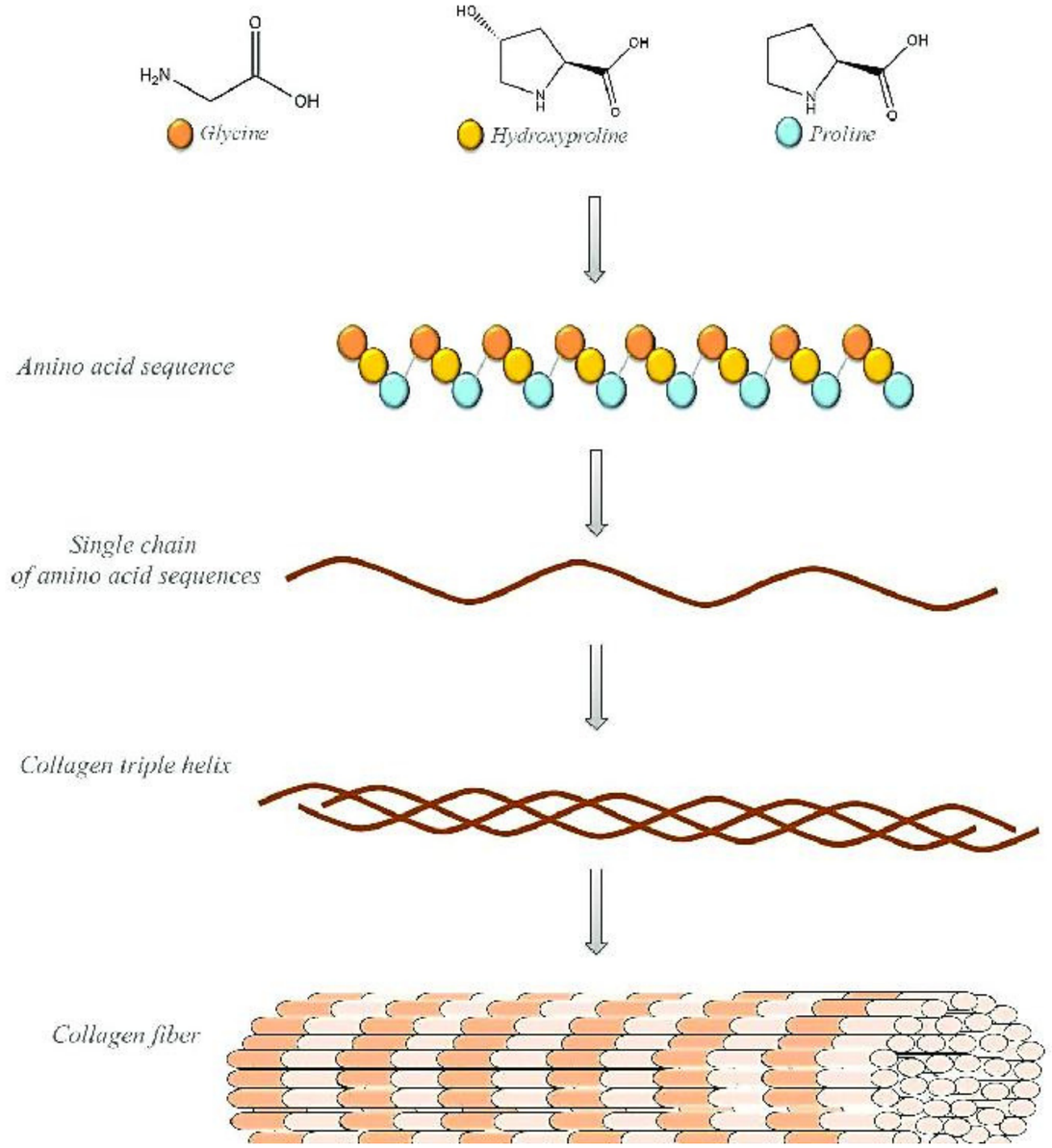
- Provide support and anchorage for cells.
- Regulates and determine cell dynamic behaviour
  - polarity of cells
  - cell differentiation
  - adhesion
  - migration
- Provide mechanical support for tissues and organ architecture
  - growth
  - regenerative and healing process
  - determination and maintenance of the structure
- Place for active exchange of different metabolites, ions, water.

Collagen

- Collagen is the most abundant protein in the human body.
- Collagen contributes to the stability of tissues & organs.
- It maintains their structural integrity.
- It has great tensile strength.
- The main component of fascia, cartilage, ligaments, tendons, bone and skin.
- Plays an important role in cell differentiation, polarity, movement.
- Plays an important role in tissue and organ development.

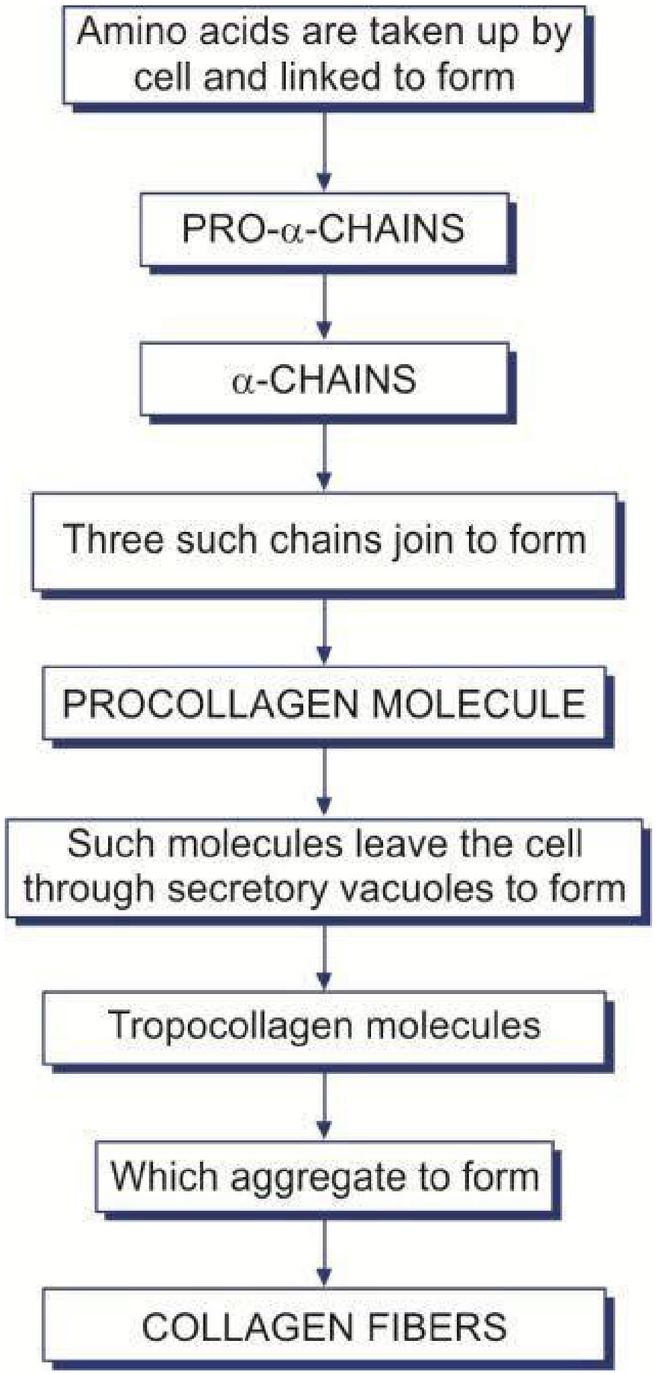
Collagen Structure

- **Collagen consists of amino acids bound together to form a triple helix of elongated fibril known as collagen helix.**



Collagen Synthesis

- Transcription of collagen gene
- Translation to pre-procollagen chain
- α-chain synthesis
- Procollagen assembly
- Stable triple helix formation
- Cleavage of propeptides
- Fibril formation
- Collagen fiber



Types of collagen

- **19 types of collagens are found.**
  - **Fibril-forming collagens (I, II,III, V, X)**
  - **-Fibril-associated collagens (FACITs)**
  - **-Network forming**
  - **-Beaded filaments**
  - **-Anchoring fibrills**
  - **-Growth plate specific**
  - **-Miscellaneous**

  Variations occur due to:
- **Differences in the assembly of basic polypeptide chains.**
- **Different lengths of the helix.**
- **Various interruptions in the helix**
- **Differences in the terminations of the helical domains.**

Our Main Collagen Types		
	Category	Tissues
Type I	Fibrillar	bone, skin, tendons, ligaments, cornea, fibrous cartilage, connective tissue, teeth, muscle
Type II	Fibrillar	cartilage, vitreous body, nucleus pulposus
Type III	Fibrillar	skin, blood vessel, intestine, muscle, reticular fibers
Type IV	Network-forming collagen	basement membranes
Type V	Fibrillar	lung, liver, cornea, bones, placental/embryonic tissue
Type IX	FACIT	cartilage, vitreous humor, cornea

Collagen Biology

- **“The regulation of collagen gene expression has to be tightly controlled in order to maintain normal amounts and ratios of genetically distinct collagens under physiological conditions.”**

- **“An important control mechanism is at the level of collagen mRNA formation through regulation of the transcriptional activity of the corresponding genes. ”**

- **“The transcriptional regulation of collagen gene expression involves a number of both cis-acting elements and trans-acting factors.”**

- **“Such factors can either up-regulate or suppress the transcriptional promoter activity. ”**

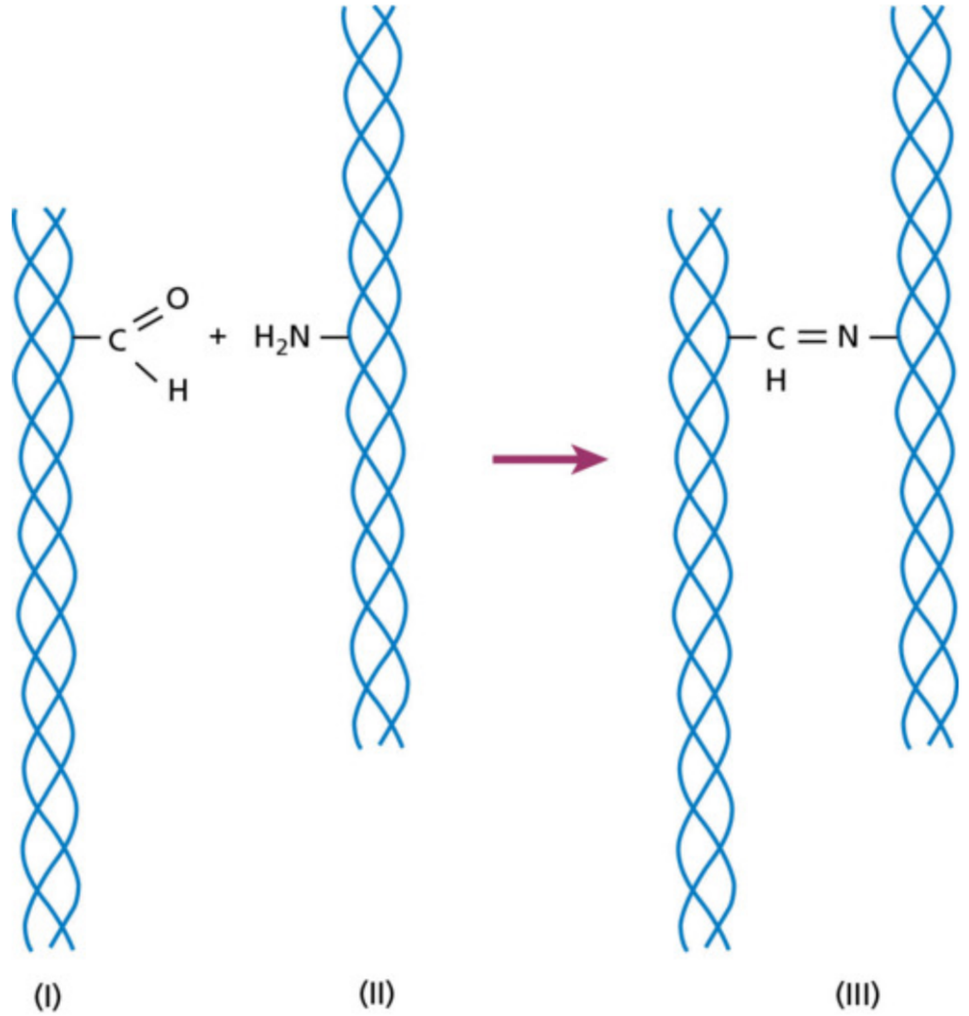
- **“Collagen gene expression can also be modulated by a number of cytokines and growth factors, and one of the most powerful modulators of connective tissue gene expression is TGF-β”**

- **In general, TGF-β is pro-fibrotic and it has been shown to up-regulate the expression of a number of extracellular matrix protein genes, including those encoding collagen types I, III, IV, VI and VII.”**

Collagen cross-linking

- “The alignment of collagen molecules into their specific supramolecular organization occurs spontaneously, but these fibre structures do not attain the necessary tensile strength until the molecules have been covalently linked together by specific intra- and intermolecular cross-links”
- “The first step in the cross-linking process is enzymatic synthesis of aldehyde residues from lysyl and hydroxylysyl residues by removal of the ε-amino group of these amino acids .

“Formation of intermolecular cross-links between individual collagen molecules. The cross-linking is initiated by the conversion of lysine or a hydroxylysine residue that contains an ε-amino group to a corresponding aldehyde (I). The aldehyde then reacts with an unmodified ε-amino group in an adjacent collagen molecule (II) to form a Schiff base-type covalent cross-link (III).”



Collagen degrading

- Collagen fibres, once fully matured by the cross-linking processes, are relatively stable and can exist in tissues under normal physiological conditions for long periods.

- However, there is continuous, yet slow, degradation and turnover of collagen in normal situations, as attested by continuous urinary excretion of hydroxyproline as a marker of collagen degradation.

فَبِأَيِّ آلاءِ رَبِّكُمَا تُكَذِّبَان

Then which of the favors of your Lord will ye deny?