MUSCULOSKELETAL BLOCK

CREATINE METABOLISM AND COLLAGEN DISEASES

OBJECTIVES

By the end of this lecture the First Year students will be able to:

- Study the importance of creatine in muscle as a storage form of energy
- Understand the biosynthesis of creatine
- Study the process of creatine degradation and formation of creatinine as an end product
- Understand the clinical importance of creatinine as a sensitive indicator of kidney function
- Study the structure, function, types, and biosynthesis of collagen
- Understand different diseases associated with collagen

CREATINE METABOLISM

End product

Energy source

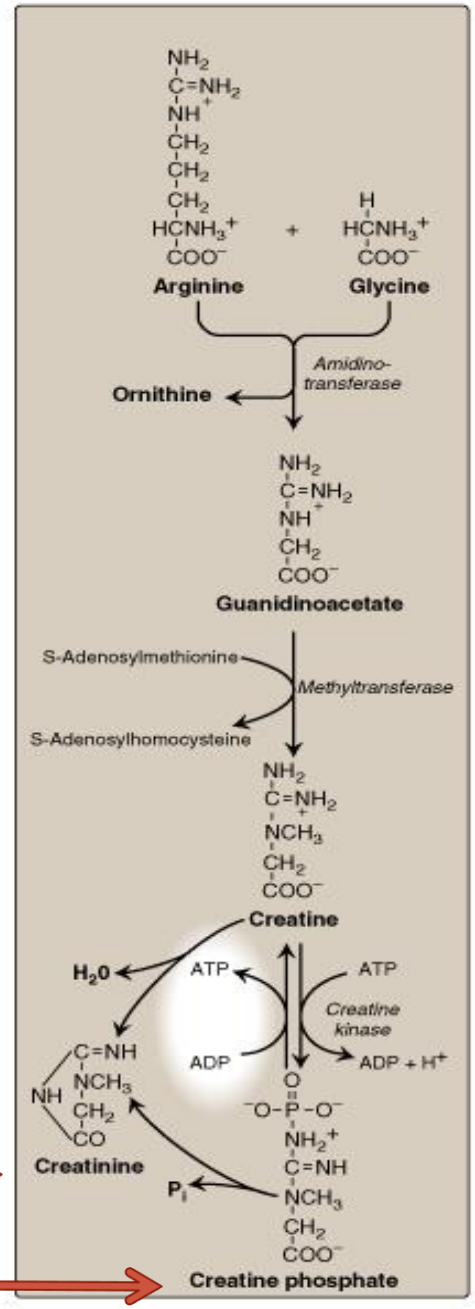


Figure 21.16
Synthesis of creatine.

CREATINE BIOSYNTHESIS

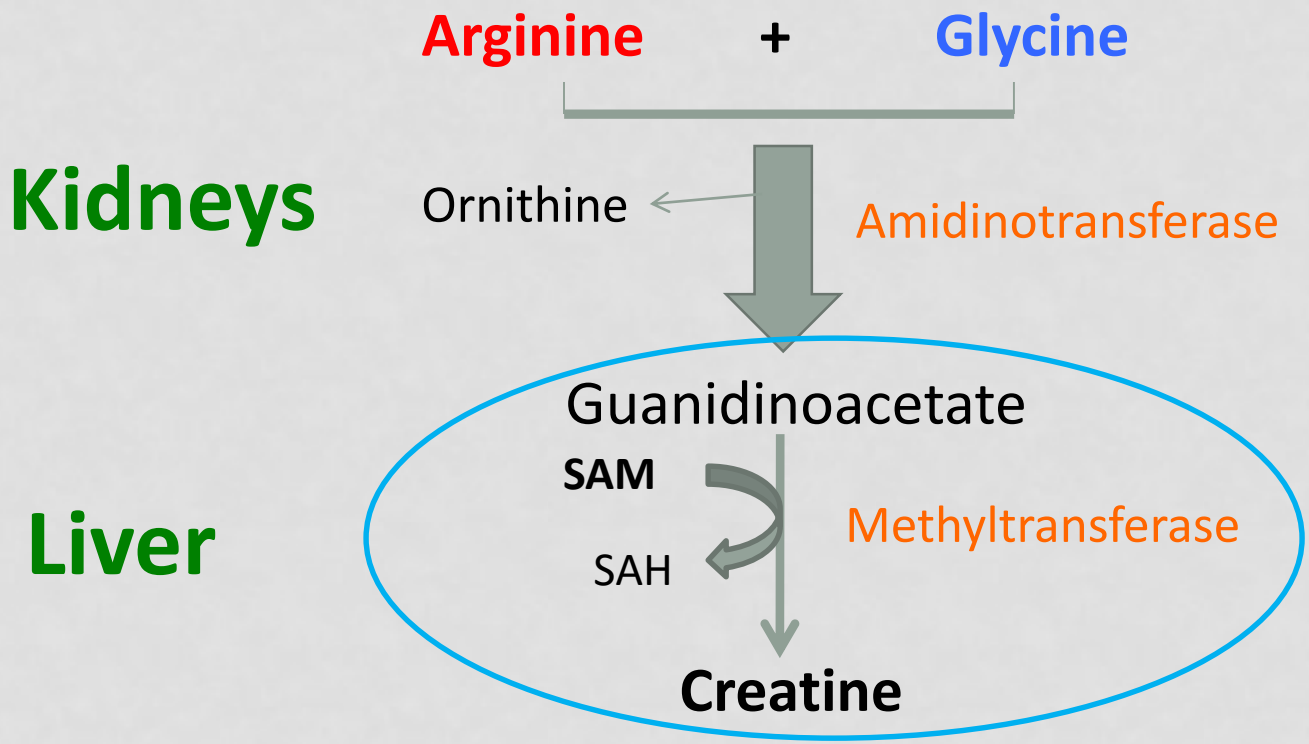
Three amino acids are required:

- Glycine
- Arginine
- Methionine (as *S*-Adenosylmethionine)

Sites of biosynthesis:

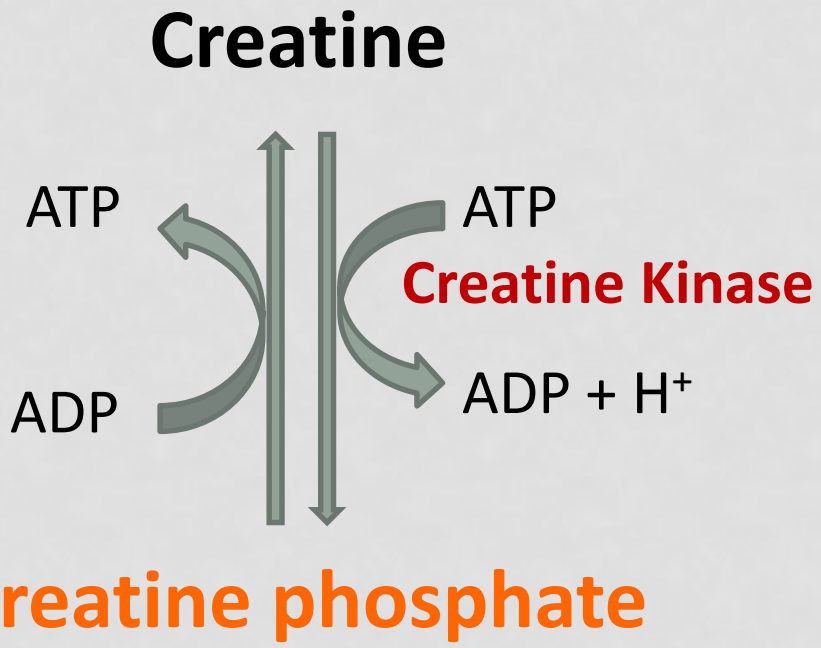
- Step 1: Kidneys
- Step 2: Liver

CREATINE BIOSYNTHESIS



DISTRIBUTION OF BODY CREATINE

- Transported from liver to other tissues
- 98% present in skeletal and heart muscles
- In skeletal muscle it is converted to high-energy source creatine phosphate (phosphocreatine)



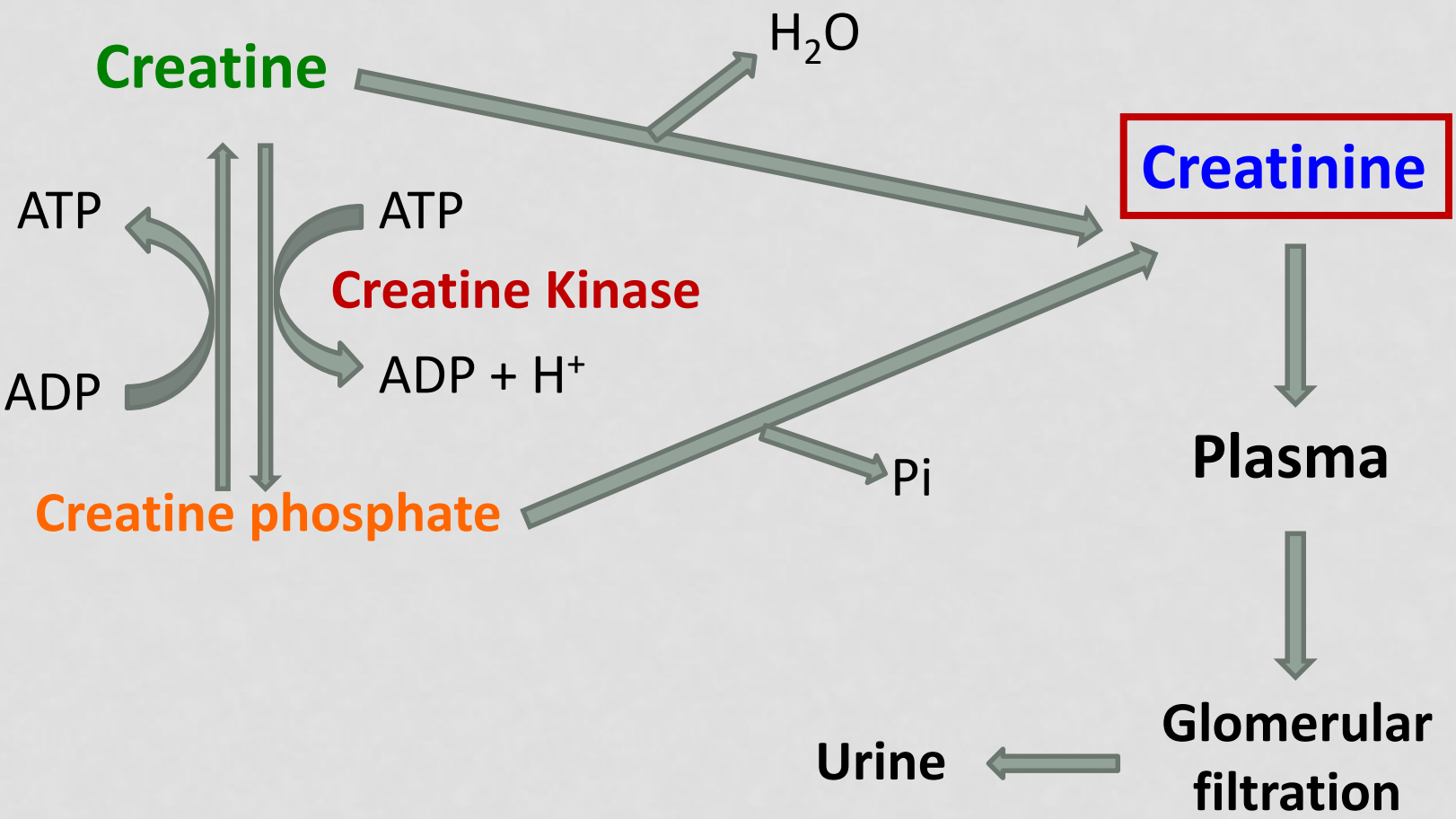
CREATINE PHOSPHATE

- A high-energy phosphate compound
- Acts as a storage form of energy in the muscle
- Provides small but, ready source of energy during first few seconds of intense muscular contraction
- The amount of creatine phosphate in the body is proportional to the muscle mass

CREATINE DEGRADATION

- Creatine and creatine phosphate spontaneously form creatinine as an end product
- Creatinine is excreted in the urine
- Serum creatinine is a sensitive indicator of kidney disease (kidney function test)
- Serum creatinine increases with the impairment of kidney function

CREATINE DEGRADATION

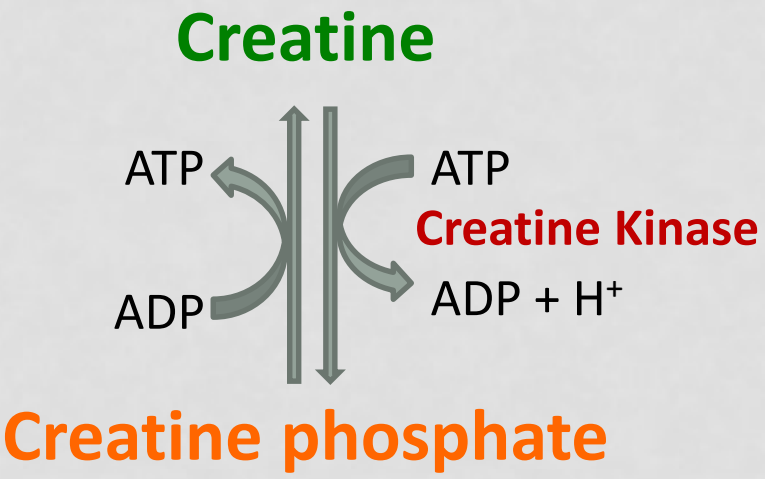


URINARY CREATININE

- A typical male excretes about 15 mmol creatinine/day
- Decrease in muscle mass (in muscular dystrophy, paralysis) leads to decreased level of urinary creatinine
- The amount of creatinine in urine is used as an indicator for the proper collection of 24 hours urine sample

CREATINE KINASE (CK)

- CK is responsible for generation of energy in contractile muscular tissues
- CK levels change in cardiac and skeletal muscle disorders



COLLAGEN

- Most abundant protein in the human body
- Collagen is a highly stable molecule with a half-life as long as several years
- A fibrous protein that serves structural functions
- Part of connective tissues, bone, teeth, cartilage, tendons, skin, blood vessels
- It has a long rigid structure

COLLAGEN STRUCTURE

- Collagen α-chain (~1,000 amino acids long) is rich in proline and glycine

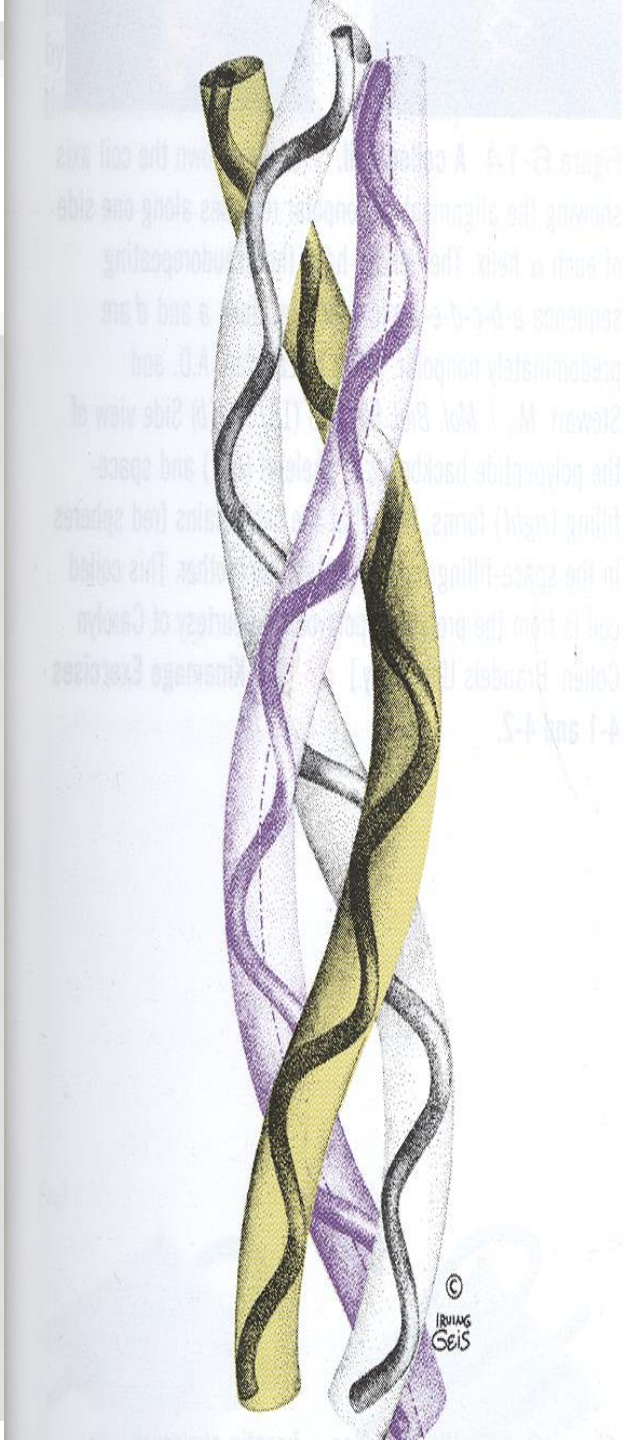
- The glycine residues are part of a repeating sequence:
- –Gly–X–Y–,
- X = Frequently proline
- Y = Often hydroxyproline
- $(–Gly–Pro–Hyp)_{333}$
- (Y can be also hydroxylysine)

COLLAGEN STRUCTURE

- Collagen consists of three α-chains wound around one another in a rope-like triple helix
- The three polypeptide chains are held together by hydrogen bonds
- Two examples of protein secondary structure: collagen helix and α-helix

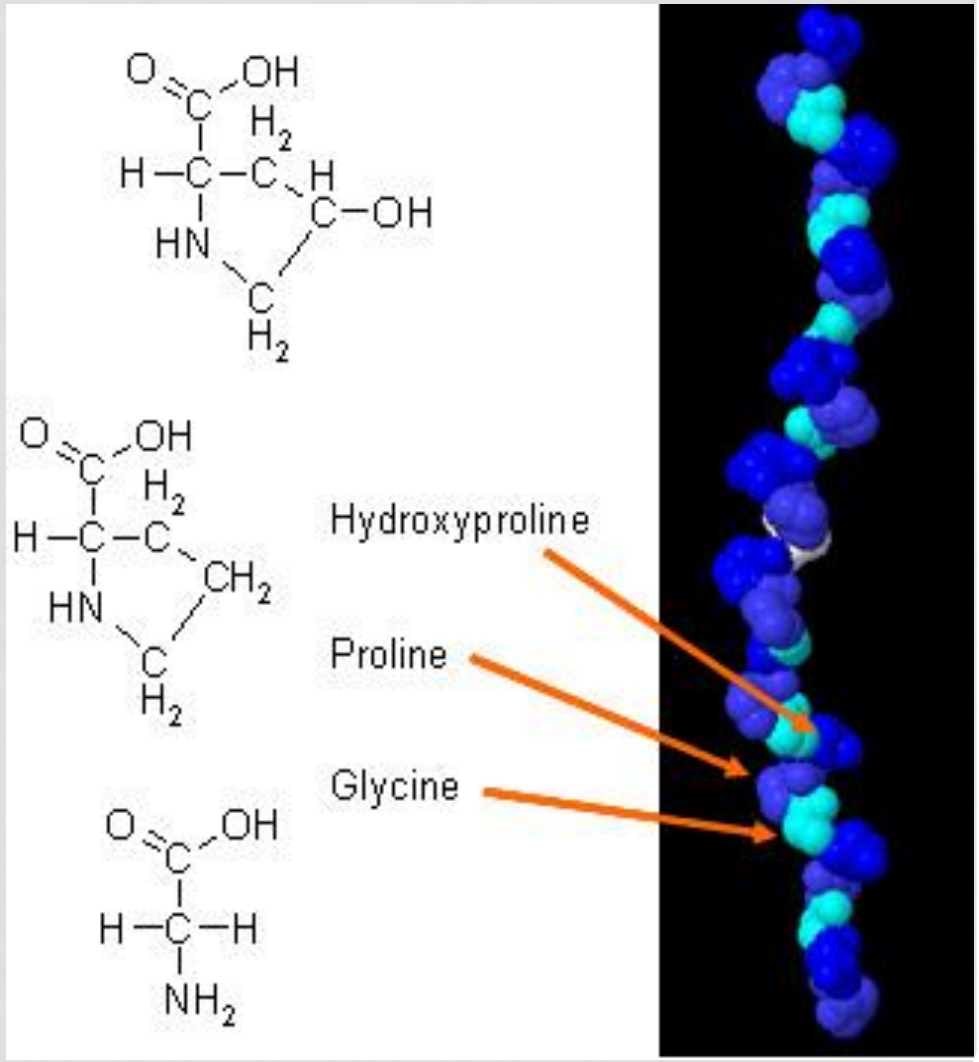
COLLAGEN STRUCTURE

- Rich in proline and glycine amino acids
- Proline prevents collagen chains to form α-helix because:
  - Proline has no back bone amino group (it is a ring structure with secondary amino group)
  - Therefore hydrogen bonding within the helix is not possible



NON-STANDARD AMINO ACIDS IN COLLAGEN

- Proline and lysine are converted to:
  - Hydroxyproline and Hydroxylysine
  - By hydroxylase enzymes
  - During post-translational modifications
- The enzyme requires vitamin C for its function



TYPES OF COLLAGEN

- Types of collagen depend on function
- Variations in the amino acid sequence of α-chains result in different properties

Examples:

- Type I: $(\alpha 1)_2\ \alpha_2$
- Type II: $(\alpha 1)_3$

TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, skin, muscle
	Network-forming
IV	Basement membrane
VIII	Corneal and vascular endothelium
	Fibril-associated
IX	Cartilage
XII	Tendon, ligaments, some other tissues

BIOSYNTHESIS OF COLLAGEN

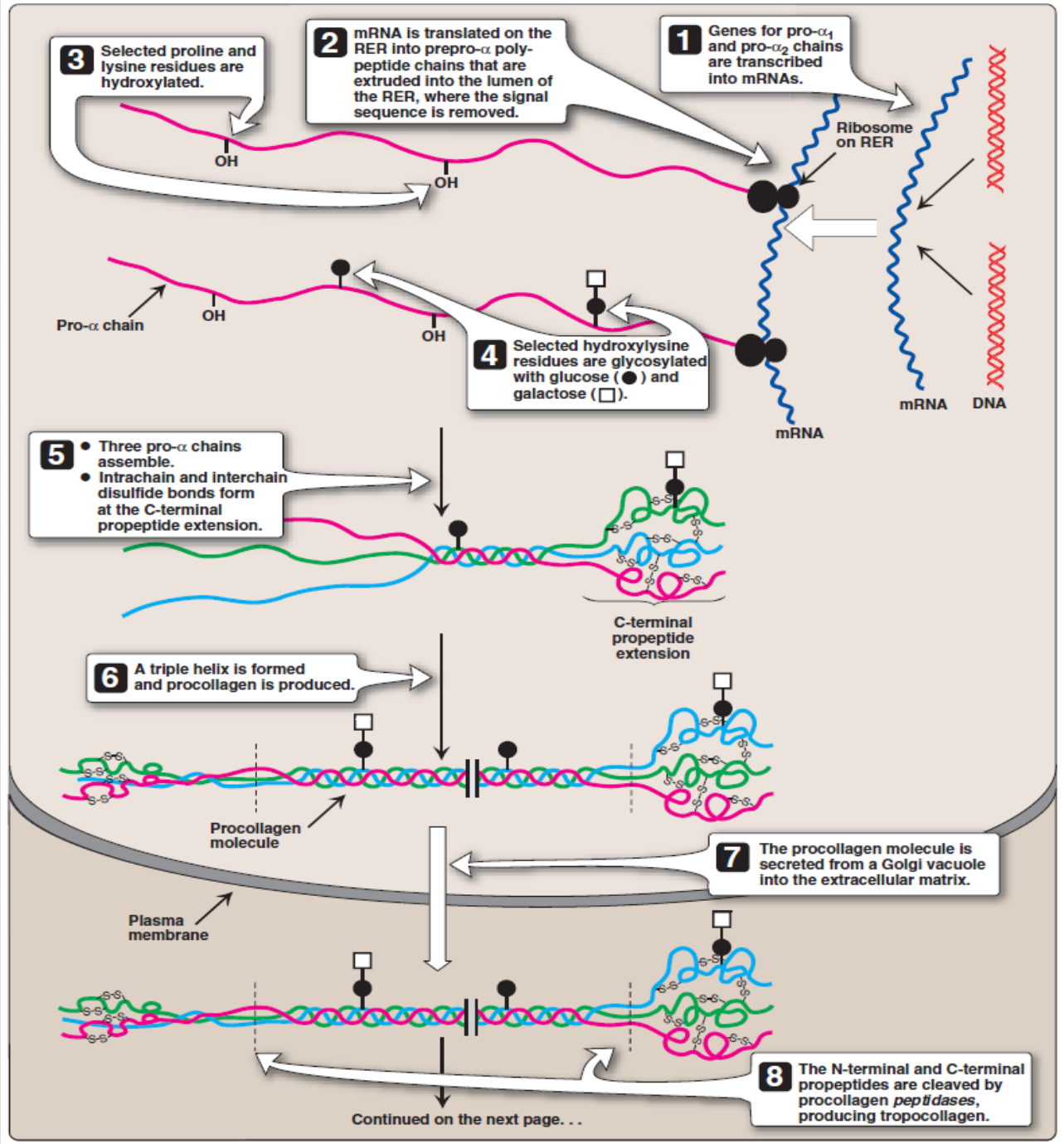
- Synthesized in fibroblasts, osteoblasts, chondroblasts
  - Pre-pro → Pro → Mature collagen
- Polypeptide precursors are enzymatically modified to form triple helix
- Hydroxylation of proline and lysine residues
- Glycosylation of some hydroxylysine residues with glucose or galactose

BIOSYNTHESIS OF COLLAGEN

- Secreted from Golgi vacoules into the extracellular matrix as procollagen
- Cleaved by N- and C- procollagen peptidases to release triple helical tropocollagen molecules
- Tropocollagen molecules spontaneously associate to form collagen fibrils

CROSSLINKING OF COLLAGEN FIBRILS

- Lysyl oxidase oxidatively deaminates some of the lysine and hydroxylysine residues in collagen
- The reactive aldehydes – allysine and hydroxyallysine condense with lysine or hydroxylysine residues in neighbouring collagen molecules to form covalent cross-links
- This produces mature collagen fibres


1 Genes for pro-α1 and pro-α2 chains are transcribed into mRNAs.
2 mRNA is translated on the RER into prepro-α polypeptide chains that are extruded into the lumen of the RER, where the signal sequence is removed.
3 Selected proline and lysine residues are hydroxylated.
OH
OH
Ribosome on RER
mRNA
DNA
mRNA
Pro-α chain
OH
OH
4 Selected hydroxylysine residues are glycosylated with glucose (●) and galactose (□).
5 • Three pro-α chains assemble.
• Intrachain and interchain disulfide bonds form at the C-terminal propeptide extension.
C-terminal propeptide extension
6 A triple helix is formed and procollagen is produced.
Procollagen molecule
7 The procollagen molecule is secreted from a Golgi vacuole into the extracellular matrix.
Plasma membrane
8 The N-terminal and C-terminal propeptides are cleaved by procollagen peptidases, producing tropocollagen.
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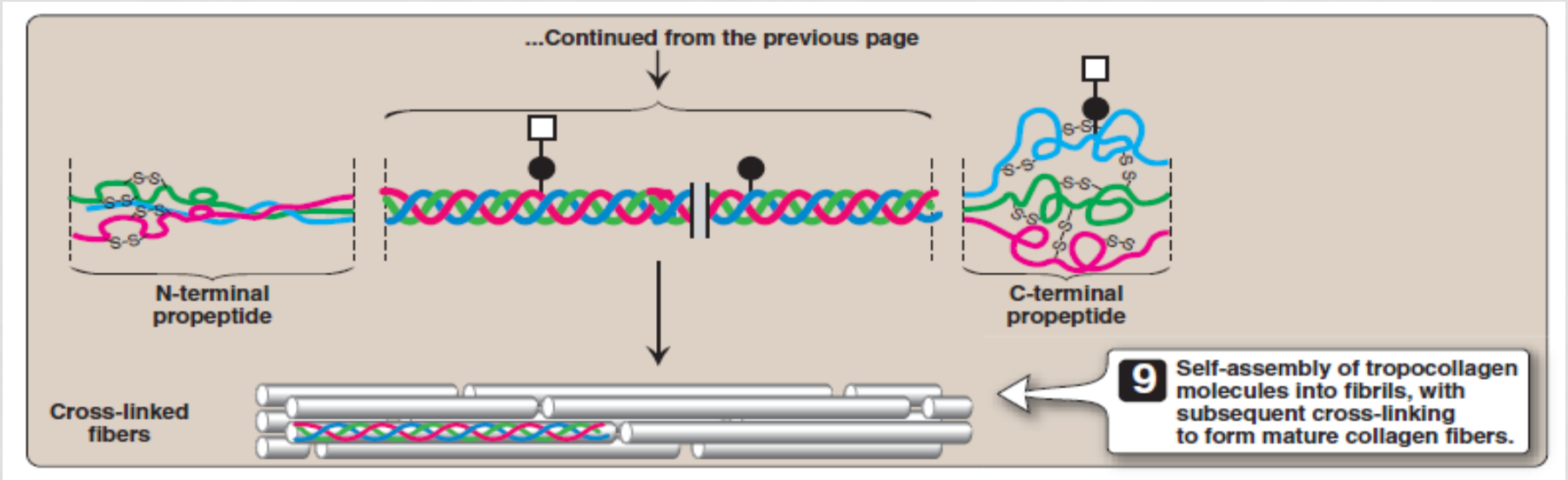
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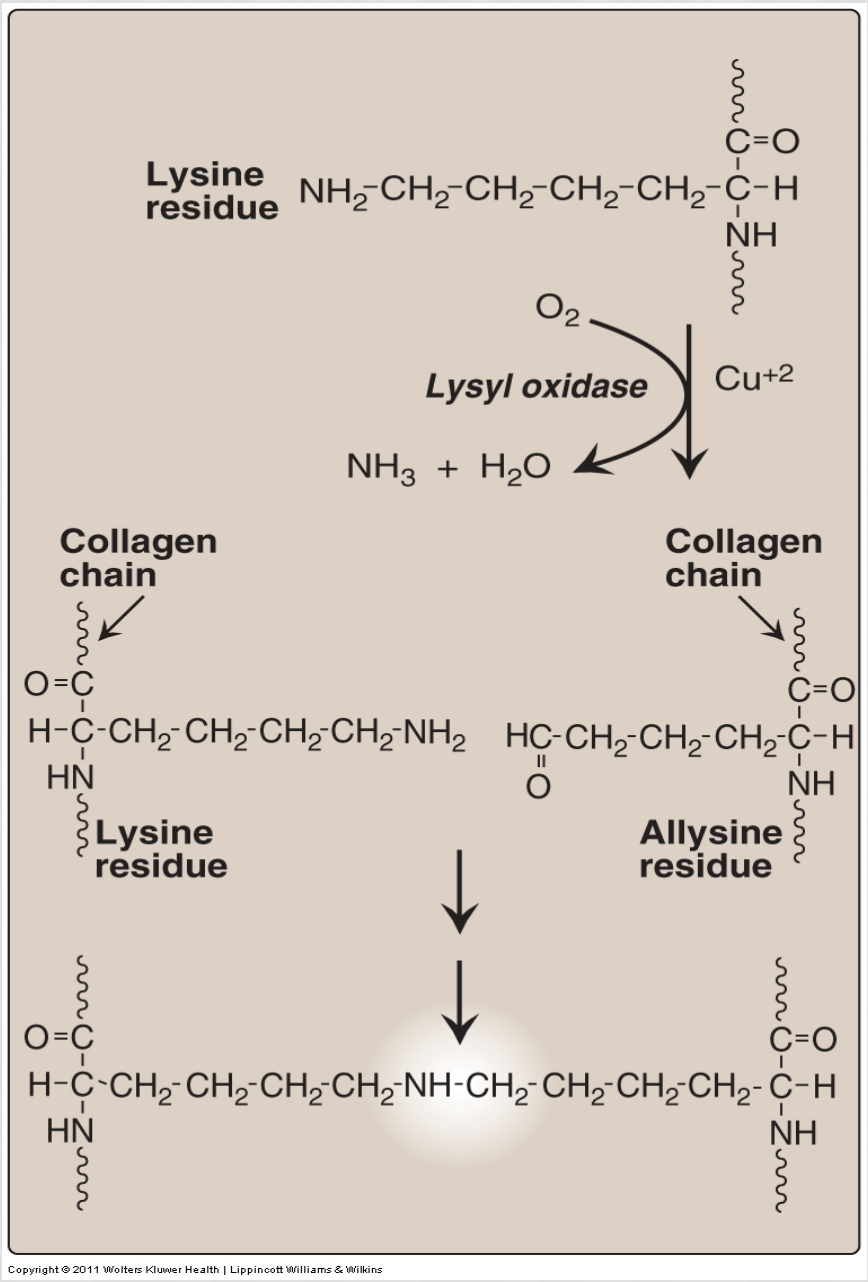
N-terminal propeptide
C-terminal propeptide
Cross-linked fibers
9
Self-assembly of tropocollagen molecules into fibrils, with subsequent cross-linking to form mature collagen fibers.



COLLAGEN DISEASES

Acquired disease:

- Scurvy due to vitamin C deficiency

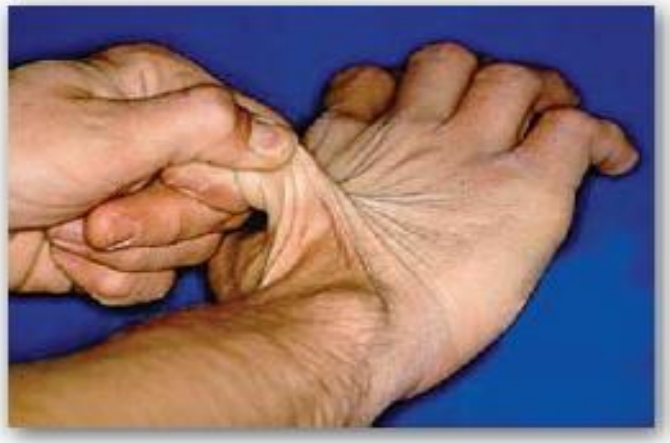
Geneticlly inherited diseases:

- Ehlers-Danlos syndromes (EDS)
- Osteogenesis imperfecta (OI)

COLLAGEN DISEASES

Ehlers-Danlos syndrome

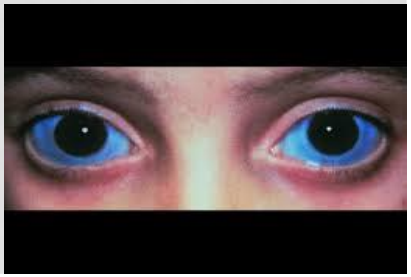
- Due to deficiency of lysyl hydroxylase or N-procollagen peptidase
- Mutations in the amino acid sequences of collagen I, III and V
- Characterized by hyper-extensibility of joints and skin



COLLAGEN DISEASES

Osteogenesis imperfecta (brittle bone disease):

- Bones fracture easily with minor or no trauma
- Mutations replace glycine with amino acids having bulky side chains preventing the formation of triple helical conformation
- Type I (most common) characterized by mild bone fragility, hearing loss and blue sclerae

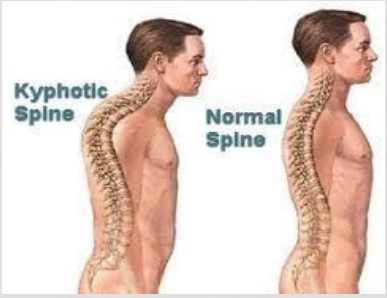


COLLAGEN DISEASES

Osteogenesis imperfecta (brittle bone disease):

- Type II (most severe) and lethal in the perinatal period (fractures *in utero*)

- Type III (severe form)
- Fractures at birth, short stature, spinal curvature
- Leading to a humped back (kyphotic) appearance and blue sclerae



REFERENCES

- Lippincott's Illustrated Reviews, Biochemistry, 5th edition, Denise R. Ferrier, Lippincott Williams & Wilkins, USA, pp. 43-49 and 287-288.

- Bishop's Clinical Chemistry 6th edition, pp. 223-227.