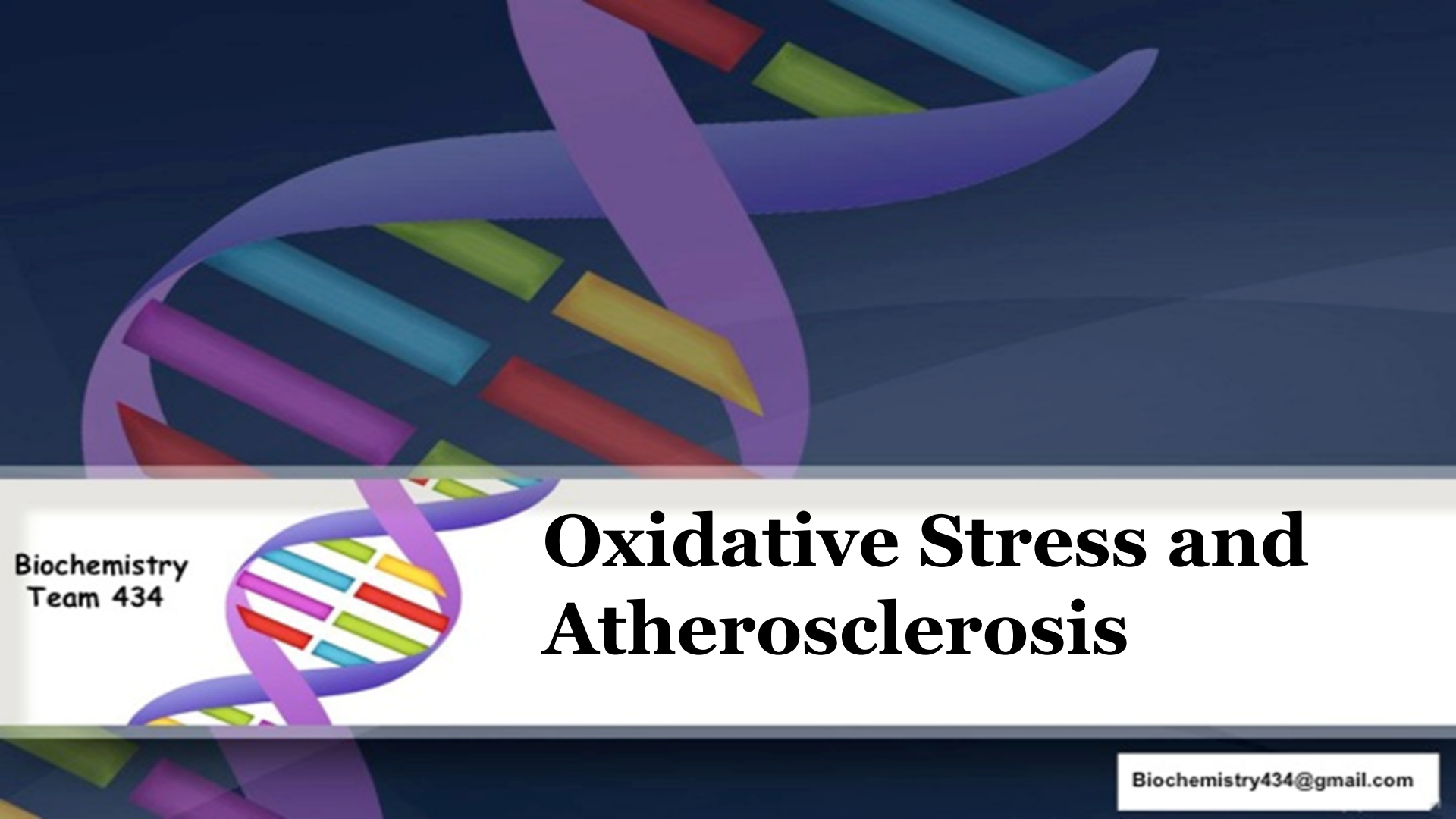

Biochemistry
Team 434

Oxidative Stress and Atherosclerosis

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Introduction

Some basic (extra) information before we start:

- Oxygen is important for humans as it serves as the final electron acceptor in the electron transport chain in the mitochondria
- Unfortunately, oxygen has the potential of transforming to other reactive oxygen species (ROS)
- This is very significant in practice & here are some examples of its importance:

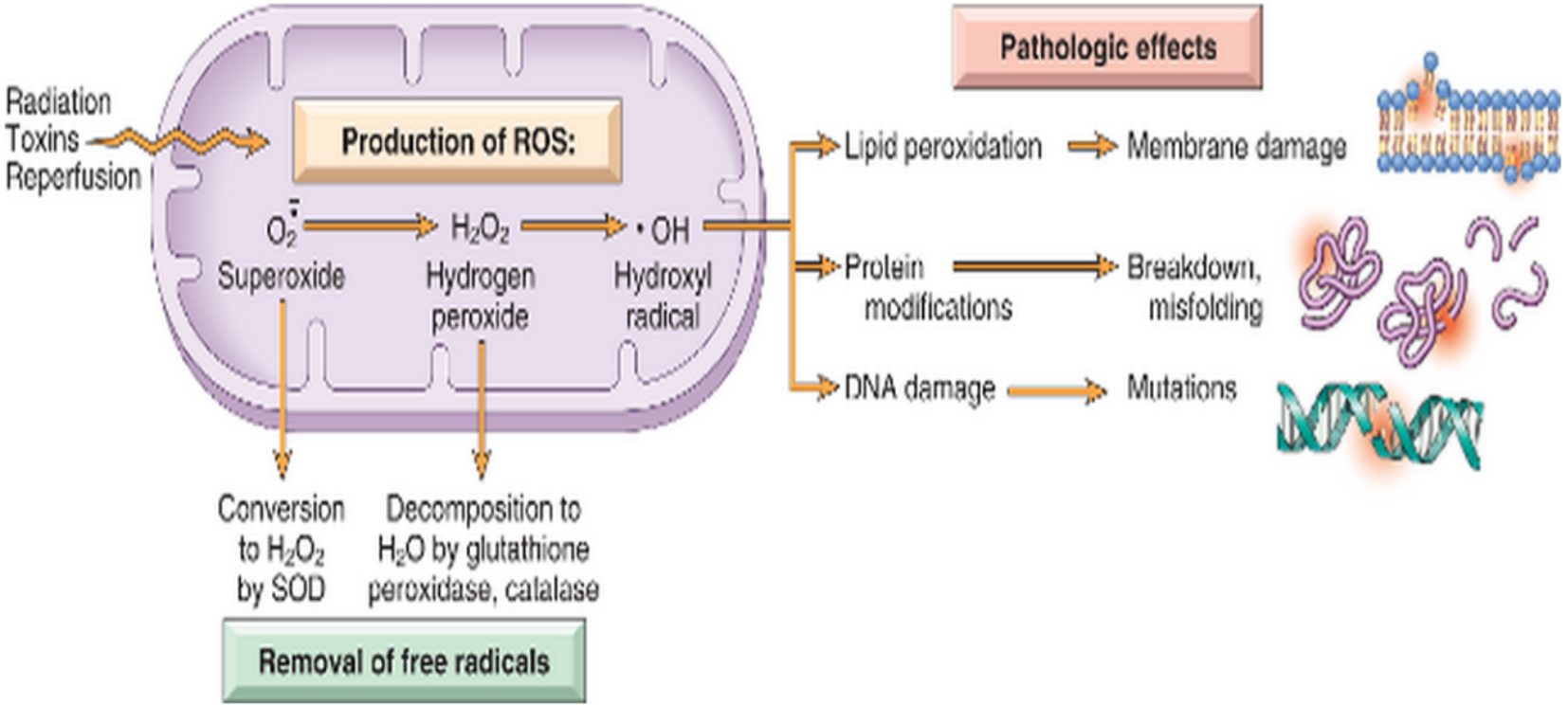
1) Reperfusion injury after thrombolysis in patients who suffered a MI
2) Respiratory distress syndrome (decreased surfactant in infants) → infants must receive supplemental oxygen → ROS cause damage to the retina potentially causing blindness (retinopathy of prematurity)

Now take a deep breath, (but not too deep to avoid any free radical injury), & enjoy the lecture

Oxidative stress

- Oxidative stress is an imbalance between oxidant production & antioxidant mechanisms
- Reactive species contribute to aging & to some serious diseases such as atherosclerosis
- Oxidative stress causes damage to DNA, proteins, & lipids
- Chronic inflammatory conditions, cancers, & obesity increase reactive species (example: Rheumatoid Arthritis)

Oxidative Stress


Radiation
Toxins
Reperfusion
Production of ROS:
$O_2^{\cdot-}$
Superoxide
H_2O_2
Hydrogen peroxide
$\cdot OH$
Hydroxyl radical
Conversion to H_2O_2 by SOD
Decomposition to H_2O by glutathione peroxidase, catalase
Removal of free radicals
Pathologic effects
Lipid peroxidation
Membrane damage
Protein modifications
Breakdown, misfolding
DNA damage
Mutations

ROS

- **Free radical:** a molecule that has an unpaired electron in its outer orbit (extra info) such as superoxide & hydroxyl radical
- **We can see from the previous figure that ROS include superoxide, hydrogen peroxide, & hydroxyl radical**

Antioxidant mechanisms:

- **Superoxide → Hydrogen peroxide (H_2O_2) by Superoxide dismutase**
- **H_2O_2 → H_2O by glutathione dismutase / or by catalase**
- **Vitamins A,C,E (remember ACE in pharm.) are antioxidants**
- **Vitamin C is also called ascorbic acid**
- **Selenium also an antioxidant but found in very small amounts (trace element)**

Sources of ROS

- **Sources:**
  - **During course of metabolism**

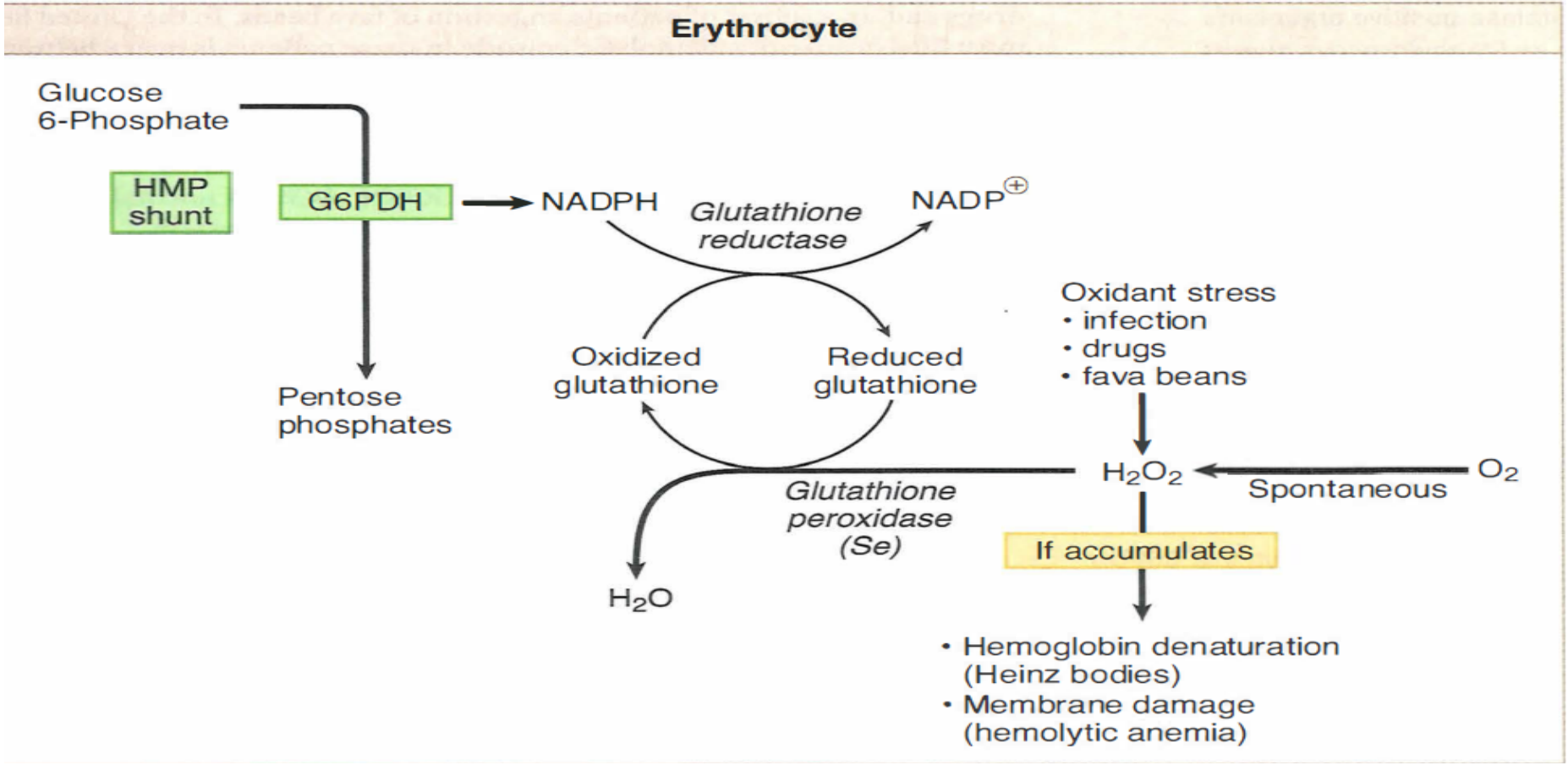
e.g., $O_2^{\cdot}$ by auto-oxidation of hemoglobin and xanthine oxidase

$OH^{\cdot}$ by Fenton reaction

$O_2^{\cdot}$, H_2O_2 , $OH^{\cdot}$ By partial reduction of molecular oxygen in electron transport chain in mitochondria

Ingestion of toxins, chemicals or drugs

Glutathione System



Glutathione system

Some notes on the previous image:

•Glutathione Is a silver amino acid composed of three amino acids: Glycine, Cysteine, and Glutamate that bound to silver group so, Glutathione has two forms: reduced form (2 G-SH) , and oxidase form (G-S-S-G).

- The function of the NADPH is to give reducing power to cells (extra info)
- G6PD produces NADPH in the red blood cells.
- NADPH is used by glutathione reductase to convert H2O2 to H2O
- If there is G6PD deficiency → there will be decreased levels of NADPH → increased levels of H2O2 → hemolysis.
- Selenium work as cofactor in Glutathione system enzymes.

Glutathione

Molecular & Vascular Effects of ROS

Molecular effects:

Lipid peroxidation (polyunsaturated fatty acids)
Protein denaturation
Inactivation of enzymes
DNA damage
Cell signaling effects
(e.g., release of Ca^{2+} from intracellular stores)
Cytoskeletal damage
Chemotaxis

Vascular effects:

Altered vascular tone
Increased endothelial cell permeability

Nitric Oxide (NO)

Free radical gas
Very short half-life (seconds)

Metabolized into nitrates & nitrites

Synthesis:
- Enzyme: NO synthase
- Precursor: L-Arginine

Effects:
- Relaxes vascular smooth muscle
- Prevents platelet aggregation
- Bactricidal & Tumoricidal effects
- Neurotransmitter in brain

Oxidative Stress: Role of Nitric Oxide (NO)

This may be both beneficial and detrimental, depending upon when and where NO is released
NO produced by endothelial NOS (eNOS) improving vascular dilation and perfusion (i.e., beneficial).

Vasodilators such as nitroglycerin is metabolized into NO and causes vasodilatation
In contrast, NO production by neuronal NOS (nNOS) or by the inducible form of NOS (iNOS) has been reported to have detrimental effects.
Increased iNOS activity is generally associated with inflammatory processes

Pathogenesis of Atherosclerosis

Modified (oxidized) LDL … Oxidative stress
(imbalance between oxidants and antioxidants)

↓

Endothelial injury of arterial wall

↓

Adherence of monocytes to endothelial cells and their movement into intima where it becomes macrophages

↓

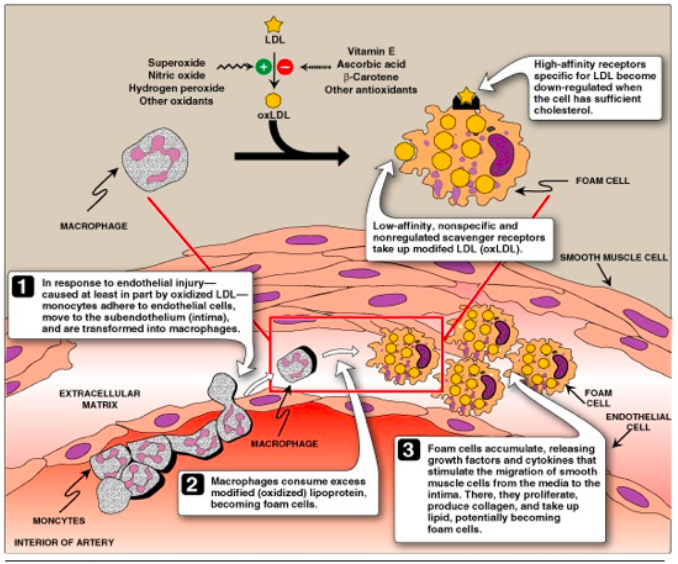
Uptake of oxLDL by macrophage scavenger receptor:
Scavenger receptor class A (SR-A)
Low-affinity, non-specific receptor
Un-regulated receptor

→

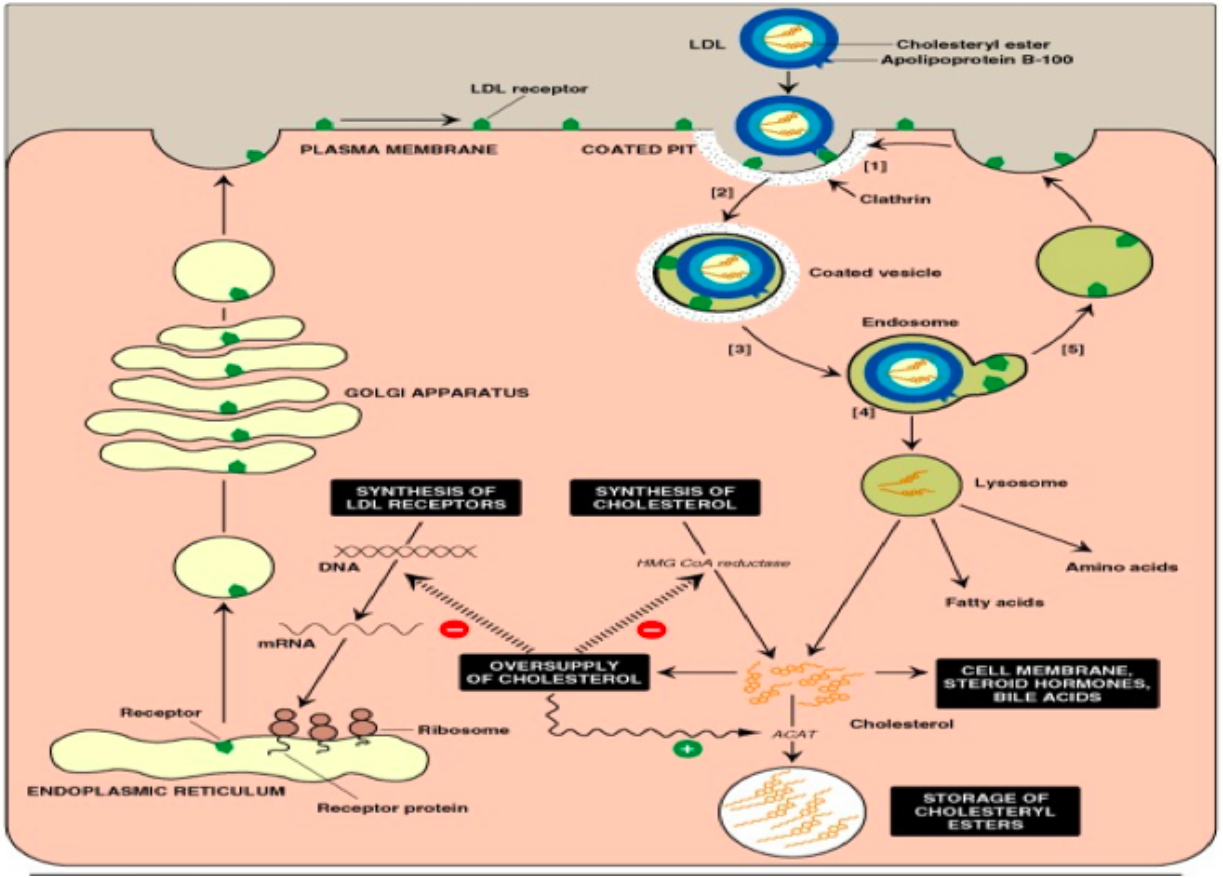
Foam cell transformation: Accumulation of excess lipids inside the cells (unregulated receptor)

↑

Atherosclerotic plaque formation



Compare to physiological uptake of LDL (unmodified) by high-affinity, specific & tightly regulated LDL-Receptor



LDL: Receptor-Mediated Endocytosis

SUMMARY

Oxidative Stress

"Imbalance between oxidant production and antioxidant mechanisms"

Oxidative Damage

- Proteins
- Fatty Acid
- DNA

Oxidative Disease

- Inflammatory condition
- Atherosclerosis
- Obesity
- Cancers
- G6PD deficiency hemolytic anemia

ROS

Non Free radical

(H_2O_2)

Free radical

$(O_2^{\cdot -})$
$(OH^{\cdot})$
$(ROO^{\cdot})$

Sources

- **During course of metabolism**

$O_2^{\cdot -}$: by auto-oxidation of hemoglobin and xanthine oxidase
$OH^{\cdot}$: by Fenton reaction
$O_2^{\cdot -}$, H_2O_2 , $OH^{\cdot}$ by partial reduction of molecular oxygen in electron transport chain in mitochondria

- **Ingestion of toxins, chemicals or drugs**

Molecular & Vascular Effects of ROS

- **Molecular effects:**

Lipid peroxidation (polyunsaturated fatty acids)
Protein denaturation
Inactivation of enzymes
DNA damage
Cell signaling effects (e.g., release of Ca^{2+} from intracellular stores)
Cytoskeletal damage
Chemotaxis

- **Vascular effects:**

Altered vascular tone.
Increased endothelial cell permeability.

Antioxidants

- **Enzymes:**
  - **Superoxide dismutase**
  - **Catalase**
  - **Glutathione system** (glutathione, NADPH, reductase, peroxidase & selenium)
- **Vitamins:**
  - **Vitamin C** (ascorbic acid)
  - **Vitamin A and β-carotenes**
  - **Vitamin E**
- **Trace elements:**
  - **Selenium**

Nitric Oxide (NO)

Free radical gas
Very short half-life (seconds)
Metabolized into nitrates & nitrites

Synthesis:

Enzyme:
NO synthase
Precursor:
L-Arginine

Effects:

- **Relaxes vascular smooth muscle.**
- **Prevents platelet aggregation**
- **Bactericidal & Tumoricidal effect**
- **Neurotransmitter in brain**

eNOS	beneficial
nNOS	detrimental
iNOS	detrimental

Atherosclerosis

- **Modified (oxidized) LDL ... Oxidative stress**
- **Endothelial injury of arterial wall**

Uptake of oxLDL by macrophage scavenger receptor:
Scavenger receptor class A (SR-A)

Foam cell transformation: Accumulation of excess lipids inside the cells (unregulated receptor)

Atherosclerotic plaque formation

QUIZ

1- WHICH OF THE FOLLOWING IS A NON-FREE RADICALS?

A- HYDROGEN PEROXIDE

B- HYROXYL RADICALS

C- SUPEROXIDE

2- WHICH OF THE FOLLOWING IS A POSSIBLE RESULT FROM HEMOLYTIC ANEMIA?

A- NADPH DEFICIENCY

B- FAD DEFICIENCY

C- REDUCTASE DEFICIENCY

3- WHICH OF THE FOLLOWING IS CONSIDERED AS A SOURCE OF REACTIVE OXYGEN SPECIES (ROS)?

A- PEROXYL RADICAL

B- INGESTION OF DRUGS

C- CARBOHYDRATE INTAKE

4- GLUATATHIONE SYSTEM IS CONSIDERED AS A?

A- OXIDANT PRODUCTION

B- VASCULAR EFFECTOR

C- ANTI-OXIDANT AGENT

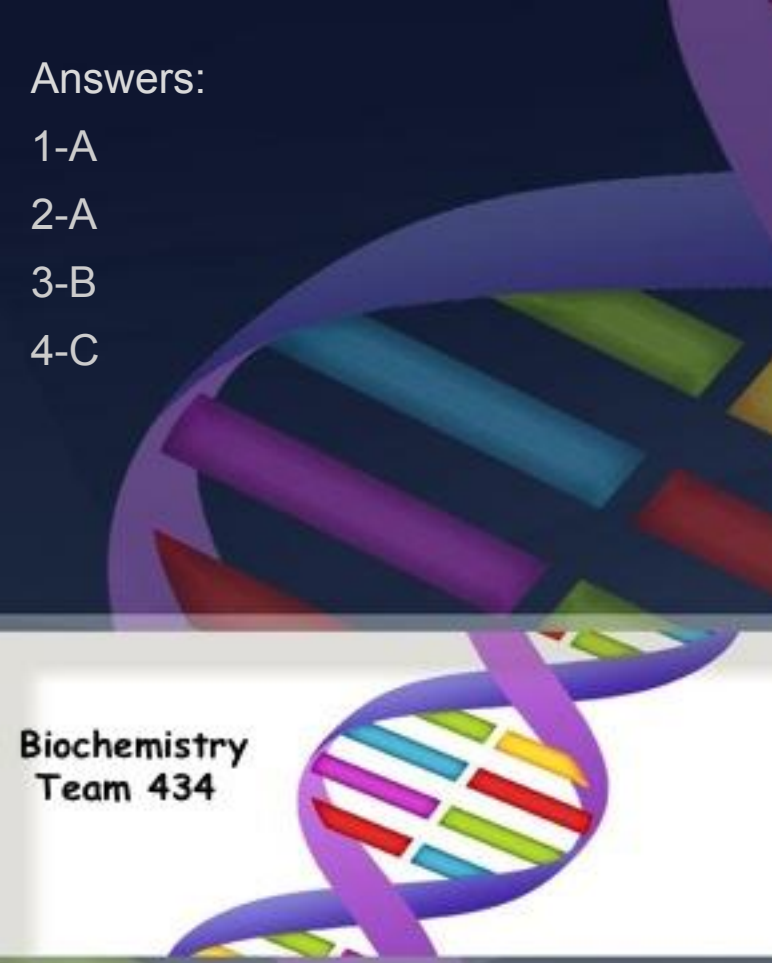
Answers:

1-A

2-A

3-B

4-C



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