Cell Injury

When the cell is exposed to an injurious agent or stress, a sequence of events follows that are loosely termed Cell Injury

For didactic use only

Causes of cell injury

External injurious stimuli:

Physical agents: extreme temperature, radiation, electric shock, mechanical trauma,…etc.

Chemical agents: simple chemicals, poisons, air pollutants,…

Drugs: alchohol, therapeutic drugs.

Infectious agents: viruses to worms

Internal injurious stimuli:

Genetic derangements: genetic abnormalities, enzyme defects,…

Nutritional imbalances: protein-calories deficiency, obesity, ….

Immunologic reactions: autoimmune diseases. Reactions to many external agents,..

Oxygen deprivation: Ischemia→Hypoxia

The consequences of an injurious stimulus depend on the type, status, adaptability, and genetic makeup of injuried cell.

Examples

- Skeletal muscle accomodates complete ischemia for 2 to 3h without irreversible injury.
- Cardiac muscle dies after 20 to 30 minutes.
- Neuron dies after few minutes.

Four intracellular system are particularly vulnerable.

- Cell membrane integrity, critical to cellular ionic and osmotic homeostasis;
- ATP generation, largely via mitochondrial aerobic respiration;
- Protein synthesis, folding, degradation, and refolding
- Integrity of the genetic apparatus

Biochemical mechanisms of cell damage and death.

Reduced ATP levels:

ATP molecule:

- Required in several cellular biosynthetic and degradative pathways (membrane transport, protein synthesis, etc.)
- Produced → oxidative phosphorylation of ADP in mitochondria
  → glicolysis

ATP depletion together with reduced ATP synthesis are consequences of ischemic and toxic damage.

Toxins interfere with endogenous substates or glicolytic enzymes, Citric Acid cycle and oxidative phosphorylation.

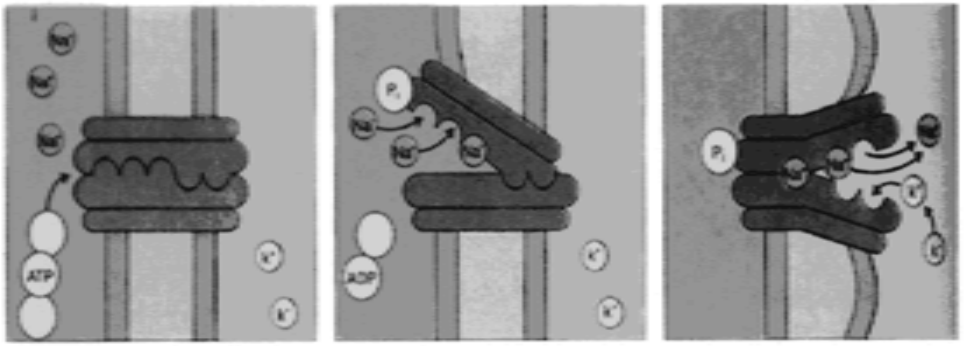
Cyanide → inactivates cytochrome oxidase

Fluorocetate → interferes with acid citric cycle ↓ ATP

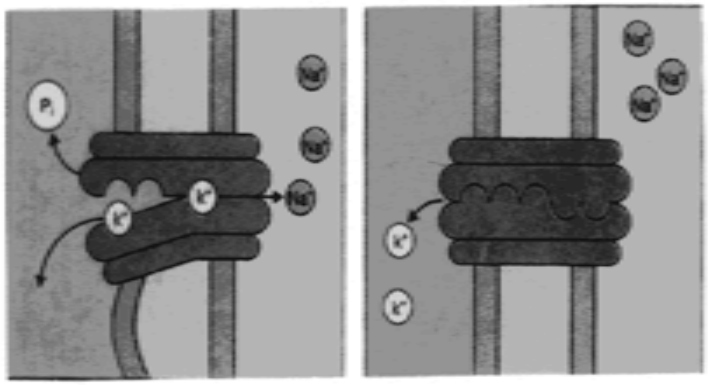
Plasma membrane damage

- Direct damage to plasma membrane (Viral protein, bacterial toxins, lytic component of complement)

- Indirect damage: ATP depletion (all the cell membranes)



- Loss of semi-permeability of plasma membrane. Typical feature of all kind of cell damage.

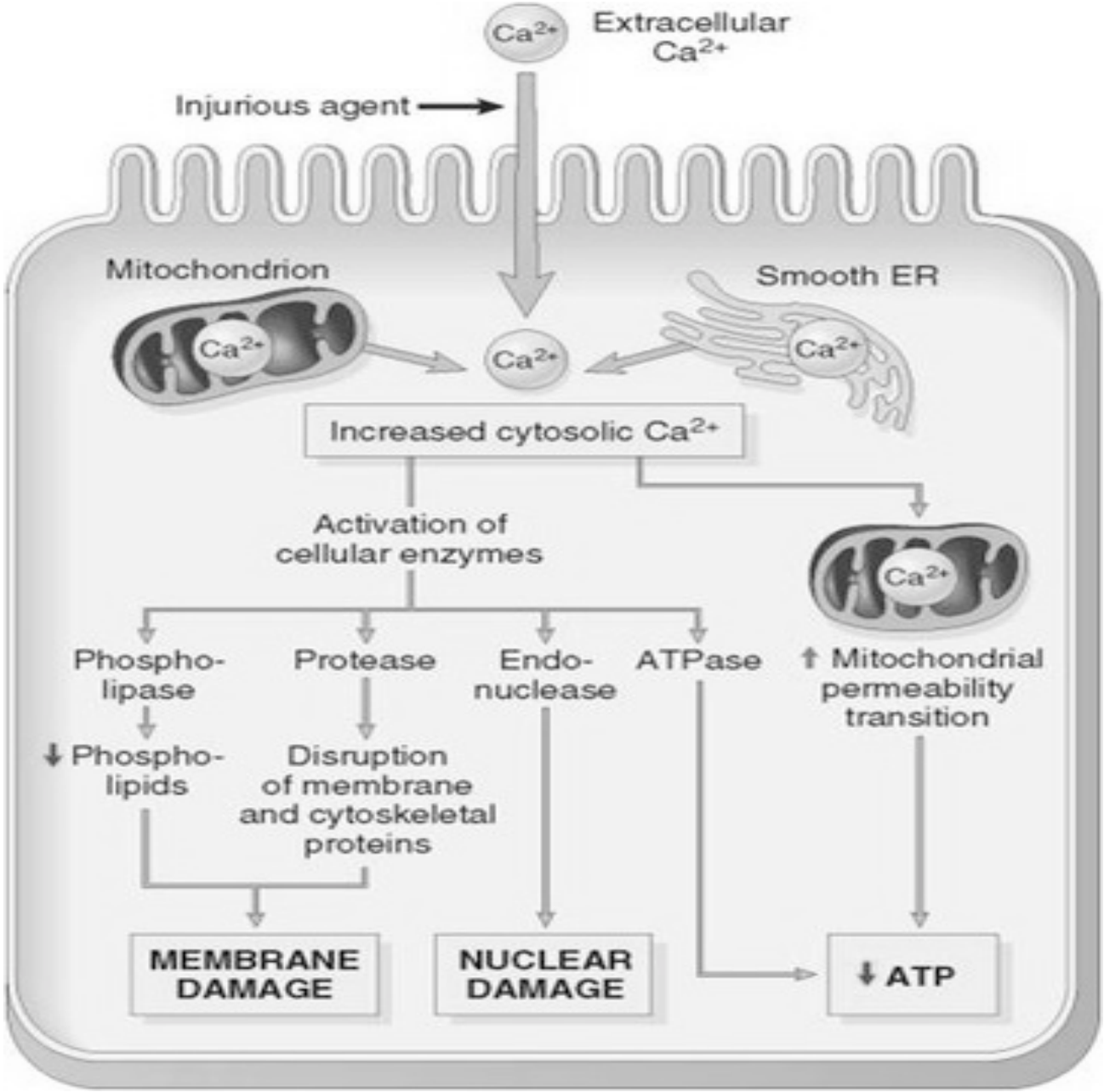


- Influx of Sodium and efflux of Calcium.

- Accumulation of water

Acute cell swelling

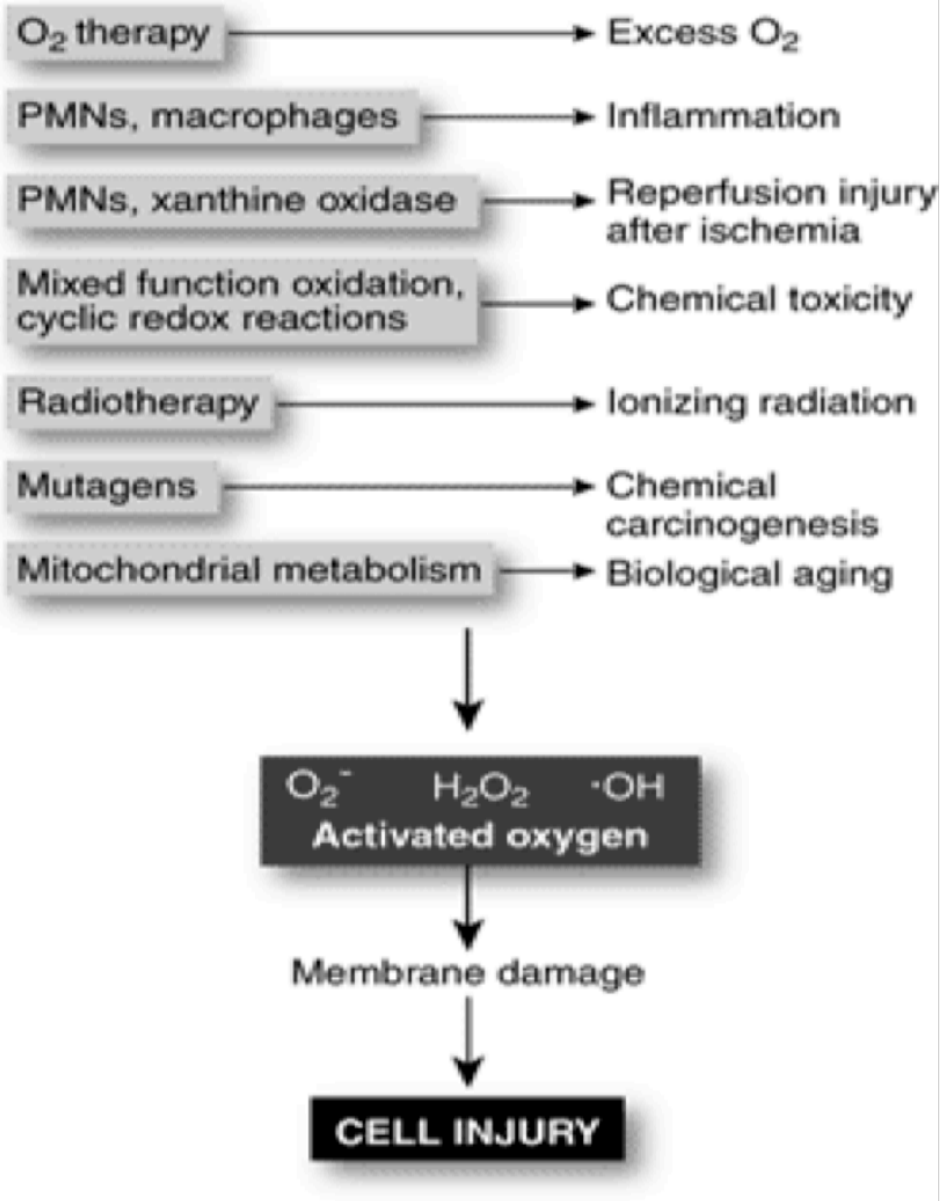
Loss of Calcium homeostatsis



>1,3 mM

< 0,1 μM

The role of activated oxygen species in human disease.



Reactive Oxygen Species (ROS)

Superoxide Anion O^{2-}

Hydrogen peroxide H_2O_2

Hydroxyl radical OH°

Peroxynitrite ONOO°

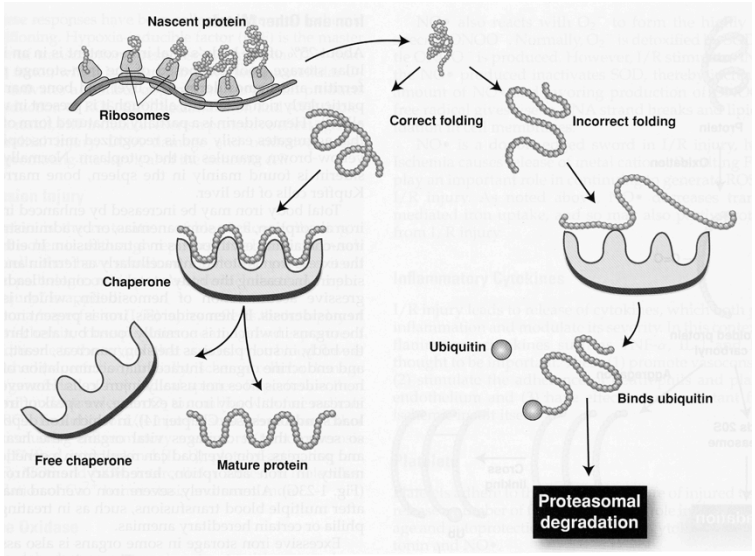
Lipid peroxid radical RCOO°

Hypochlorus acid HOCl

Protein Misfolding

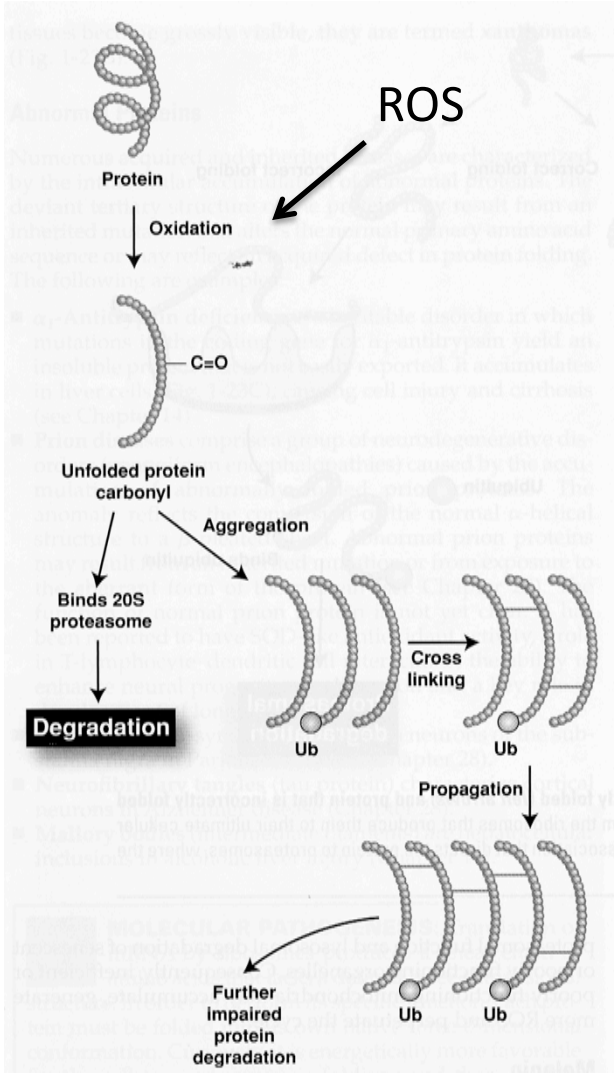
Oxidative stress, Hypoxia, or genetic mutations may lead to misfolded protein accumulation triggering the unfolded protein response.

Protein quality control system



Correctly folded proteins are chaperoned to final destination

Incorrectly folded proteins bid to uboquitin.



Oxygen deprivation

- Hypoxia is an extremely immportant and common cause of cell injury and cell death.
- It is an inadequate oxygenation of the blood due to cardiorespiratory failure

or

- Loss of oxygen-carrying capacity of the blood, as in anemia or carbon monoxide poisoning.
- Depending on the severity of the hypoxic state, cells may : adapt, undergo injury or die.

Hypoxia

- Most common cause of cell injury
- Major causes of Hypoxia
- Ischemia: decreased arterial blood flow to tissues: Atherosclerosis in coronary arteries due to deposition of lipid in intima of blood vessels.
- Hypoxiemia decrease in the amount of oxygen dissolved in plasma: Atelectasis, pulmonary embolus and interstitial fibrosis of lung
- Hemoglobin related abnormalities
- Anemia
- Carbon monoxide poisoning (Headaches)

Hypoxia: partial deficiency of oxygen

Hypoxic hypoxia: due to an inadequate supply of oxygen to the body as a whole. Caused by low partial oxygen tension in arterial blood.

Anemic hypoxia: due to reduced Hemoglobin content in blood associated to inefficient oxygen transport.

Ischemic, or stagnant hypoxia: due to local restriction in the flowof otherwised well-oxygenated bloood.

Histotoxic hypoxia: due to a failure of respiratory functions by toxicants.

Consequences:
Cellular Adaptations to hypoxia
Triggering apoptosis

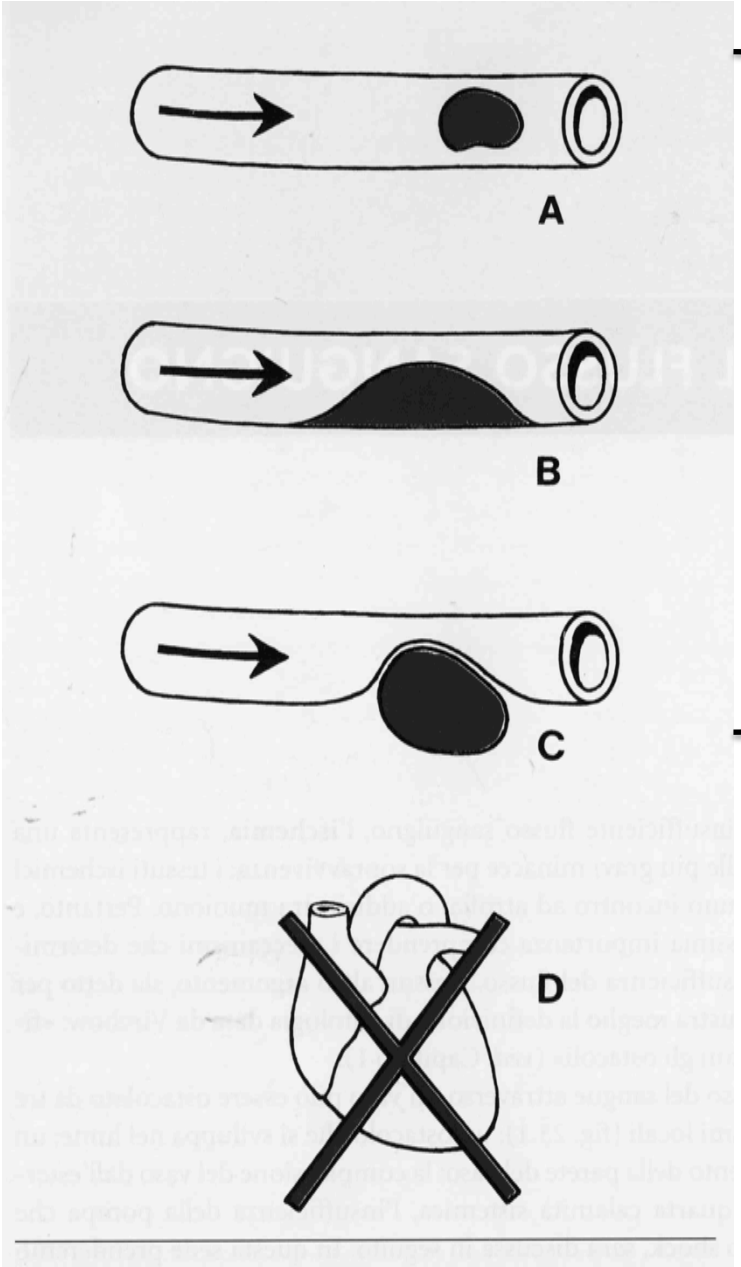
Obstructive mechanisms in blood flow

Within the vessels

On the walls

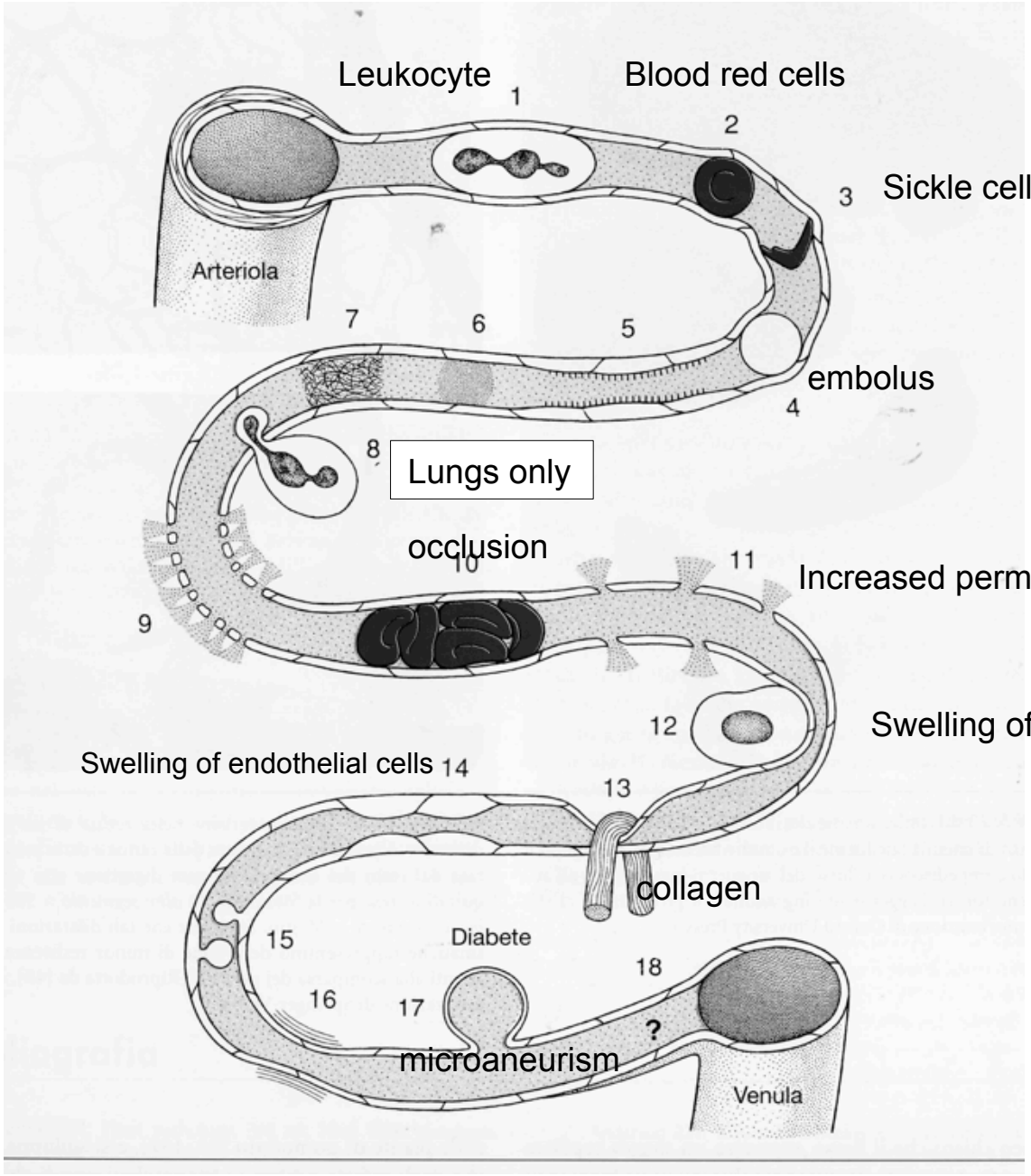
Compression

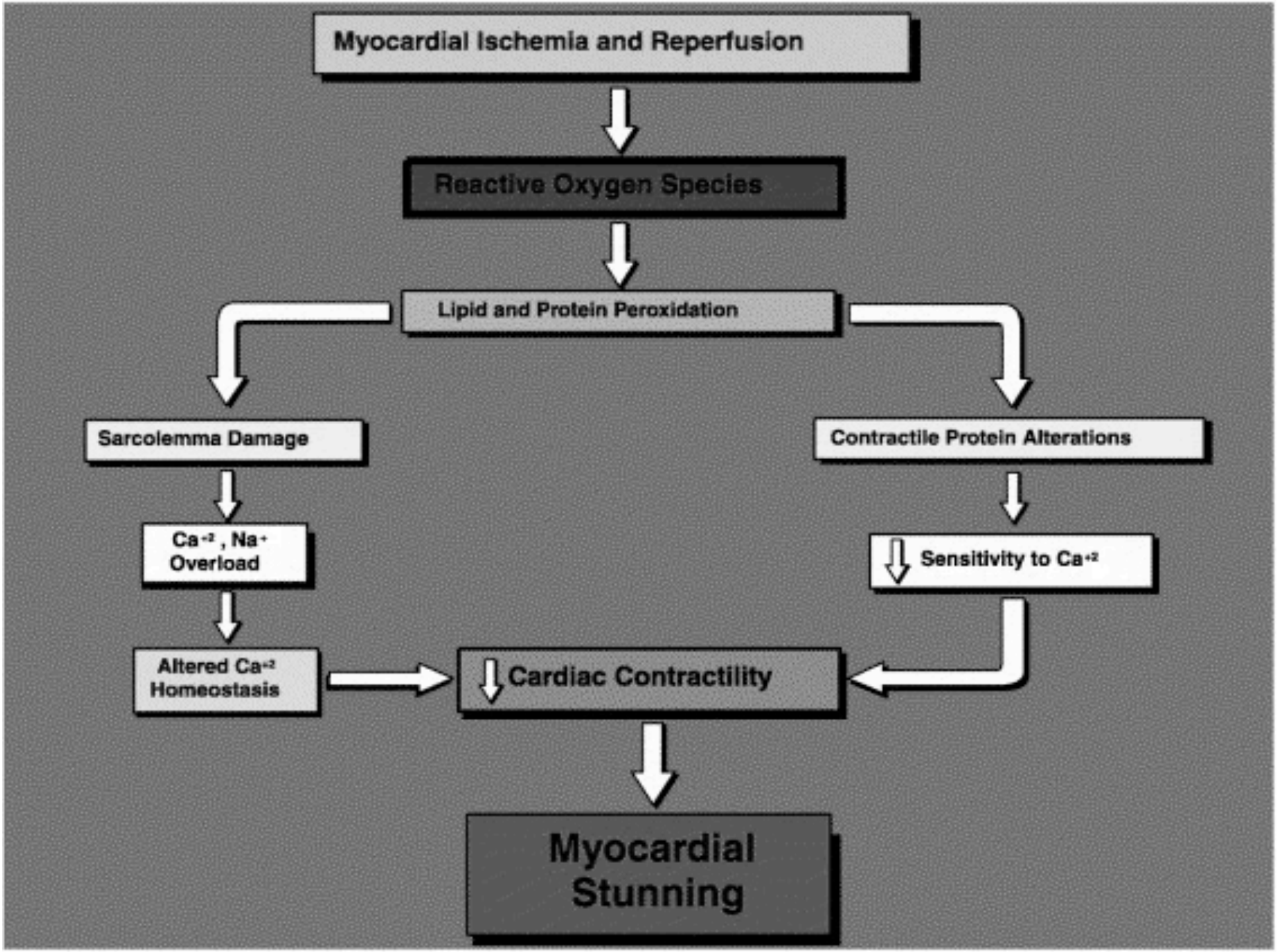
Shock:
a systemic
hypoperfusion



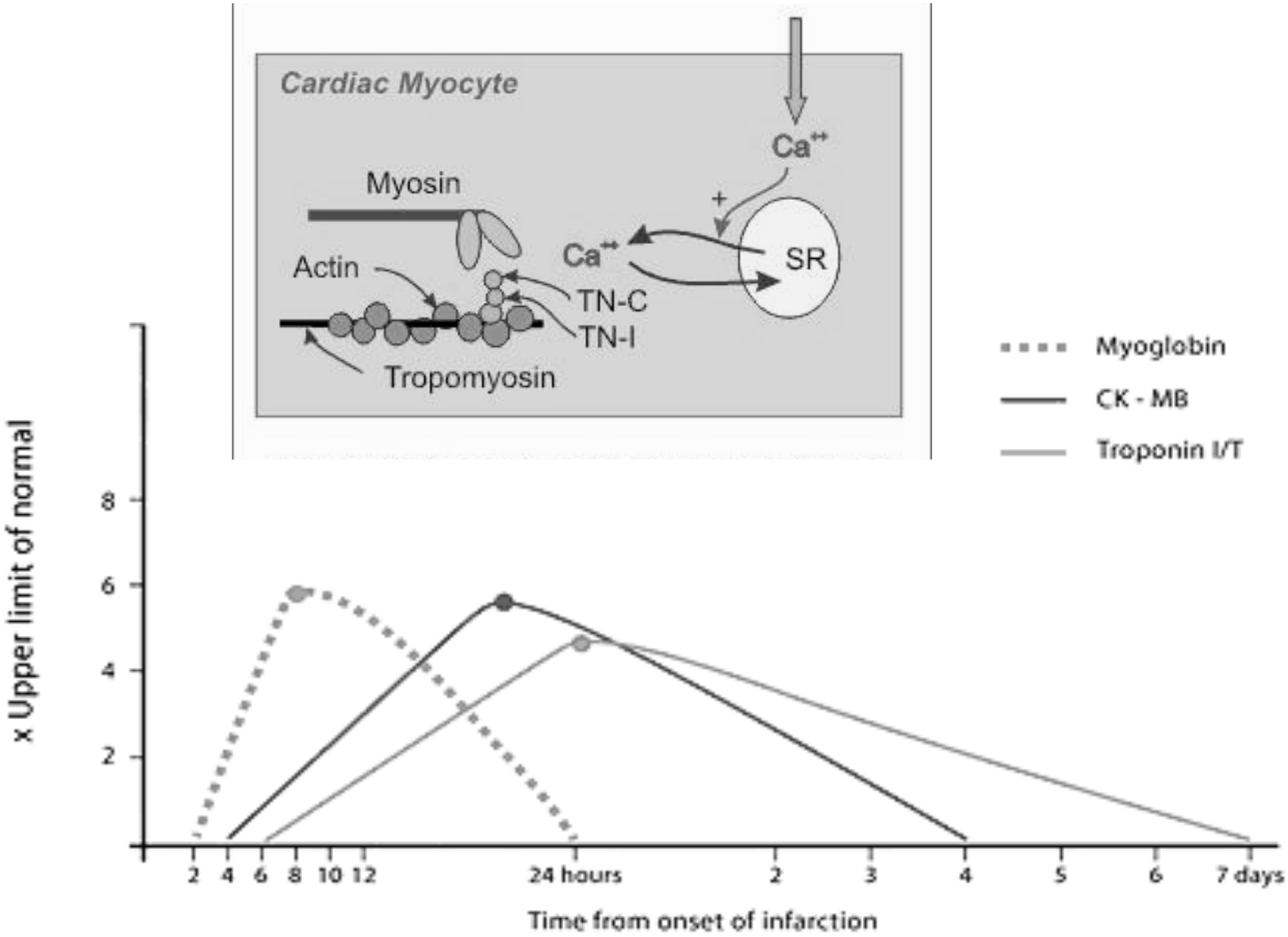
LOCAL

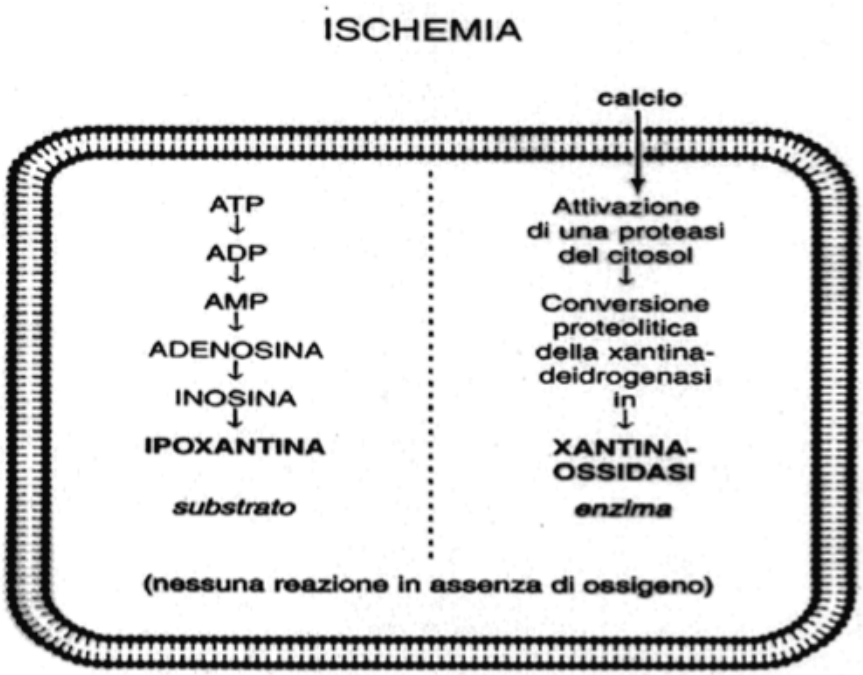
Pathogenetic mechanisms in capillaries obstructions




Myocardial Ischemia and Reperfusion
Reactive Oxygen Species
Lipid and Protein Peroxidation
Sarcolemma Damage
Contractile Protein Alterations
Ca+2 , Na+ Overload
Sensitivity to Ca+2
Altered Ca+2 Homeostasis
Cardiac Contractility
Myocardial Stunning

Post-infarction Time-course of myocardial enzymes in plasma

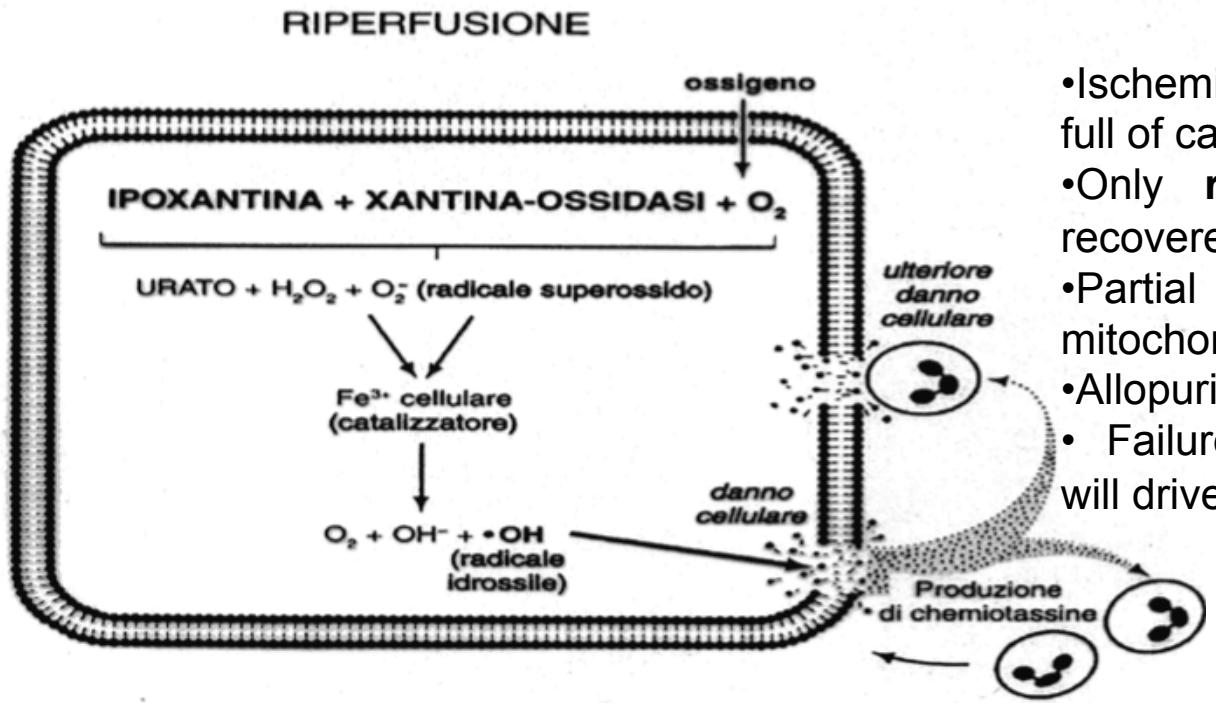




➢Metabolites accumulated during schemia mostly contribute to cell swelling.

➢Most part of damage is due to useless inflammation (PAF-piatelets).

➢**Reperfusion provides abundant molecular O2 to combine with free radicals to form ROS.**



•Ischemic cells are energy deprived and full of calcium.

•Only **reversibly injuried** cells are recovered by reperfusion..

•Partial reduction of O_2 in danaged mitochondria.

•Allopurinol inhibits xhantine-oxidase.

• Failure of antioxidant repair systems will drive to free radicals accumulation

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<u>Necrosis by Reperfusion</u>

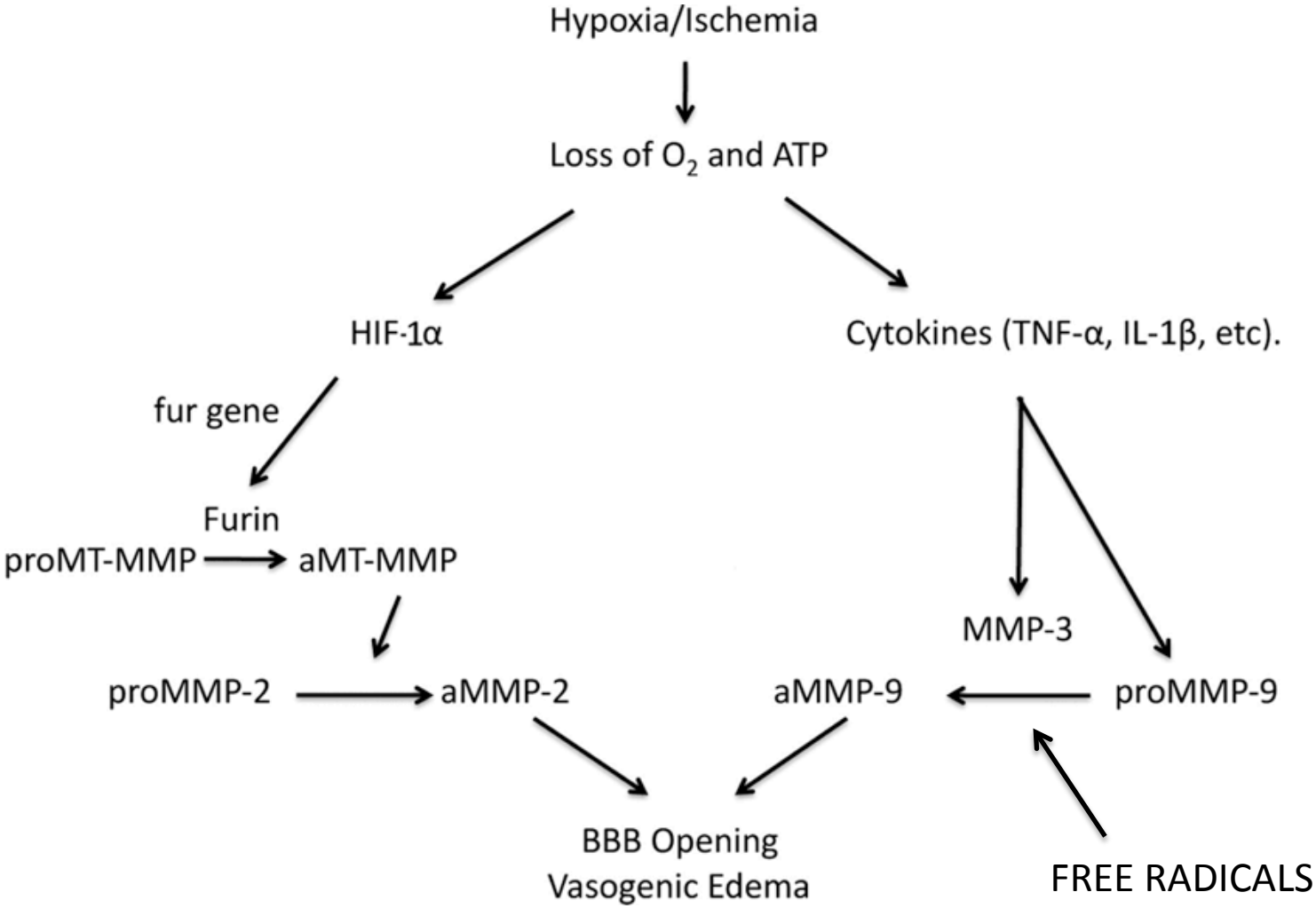
Matrix metalloproteinases and Blood Brain barrier disruption in acute ischemic stroke

- Acute ischemic stroke is the most common form of stroke and results from sudden blood vessel occlusion by a thrombus or embolism, resulting in an almost immediate loss of oxygen and glucose to the cerebral tissue.

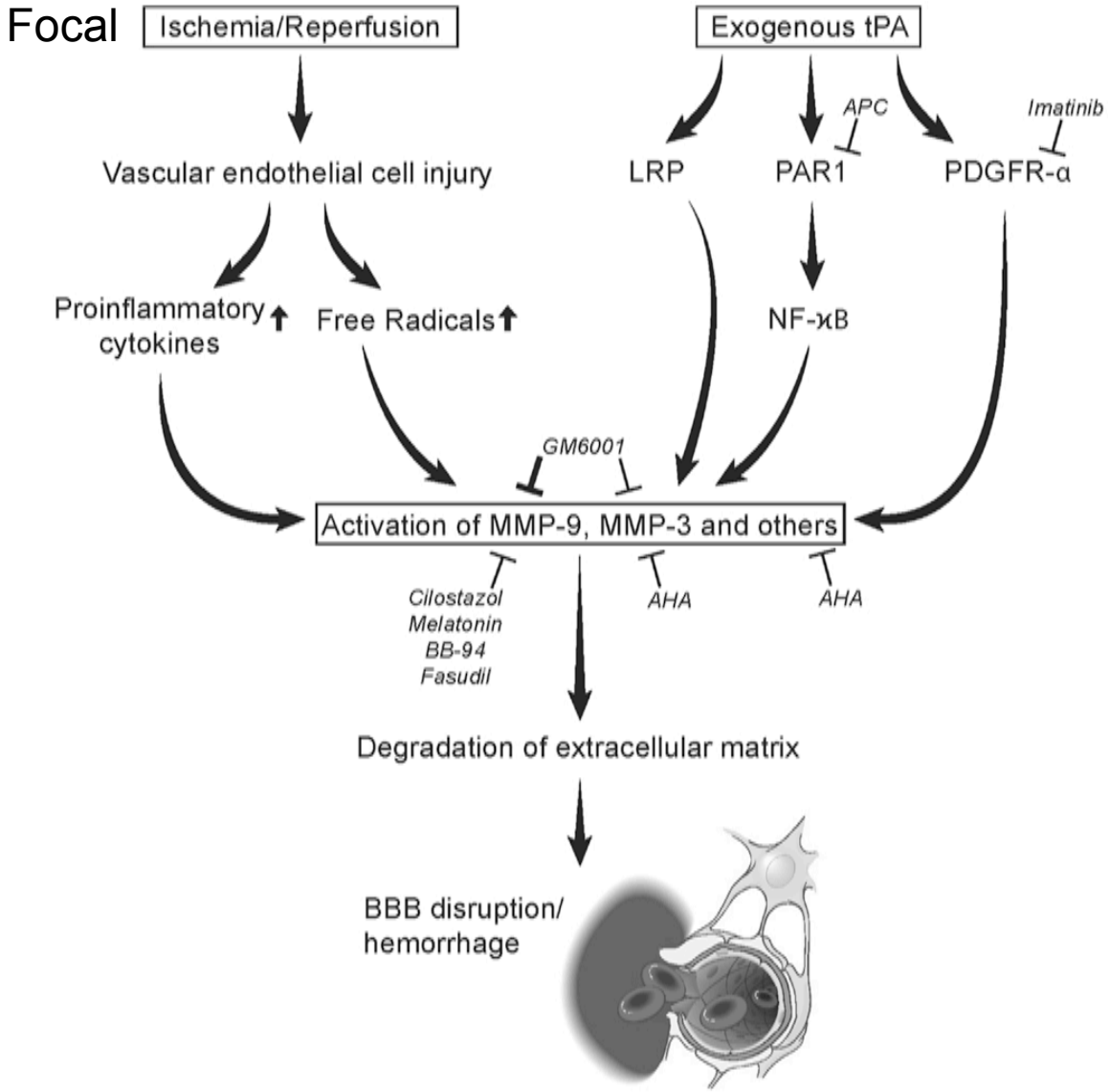
- Cerebral ischemia initiates cascades of pathological events.

- Blood Brain Barrier (BBB) is a dynamic interface between peripheral circulation and the CNS.

Activation of MMPs triggering Blood–Brain Barrier Breakdown in Acute and Chronic Cerebrovascular Disease



Mechanisms in MMP activation leading to degradation of extracellular matrix and BBB disruption/hemorrhage.



Edaravone

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MMP9 Expression

Matrix Metalloproteases in ischemic stroke

These observation collectively suggest that MMPs and its signaling cascades after ischemic stroke may have important diagnostic implications for stroke and represent the potential targets for pharmacological intervention in stroke.