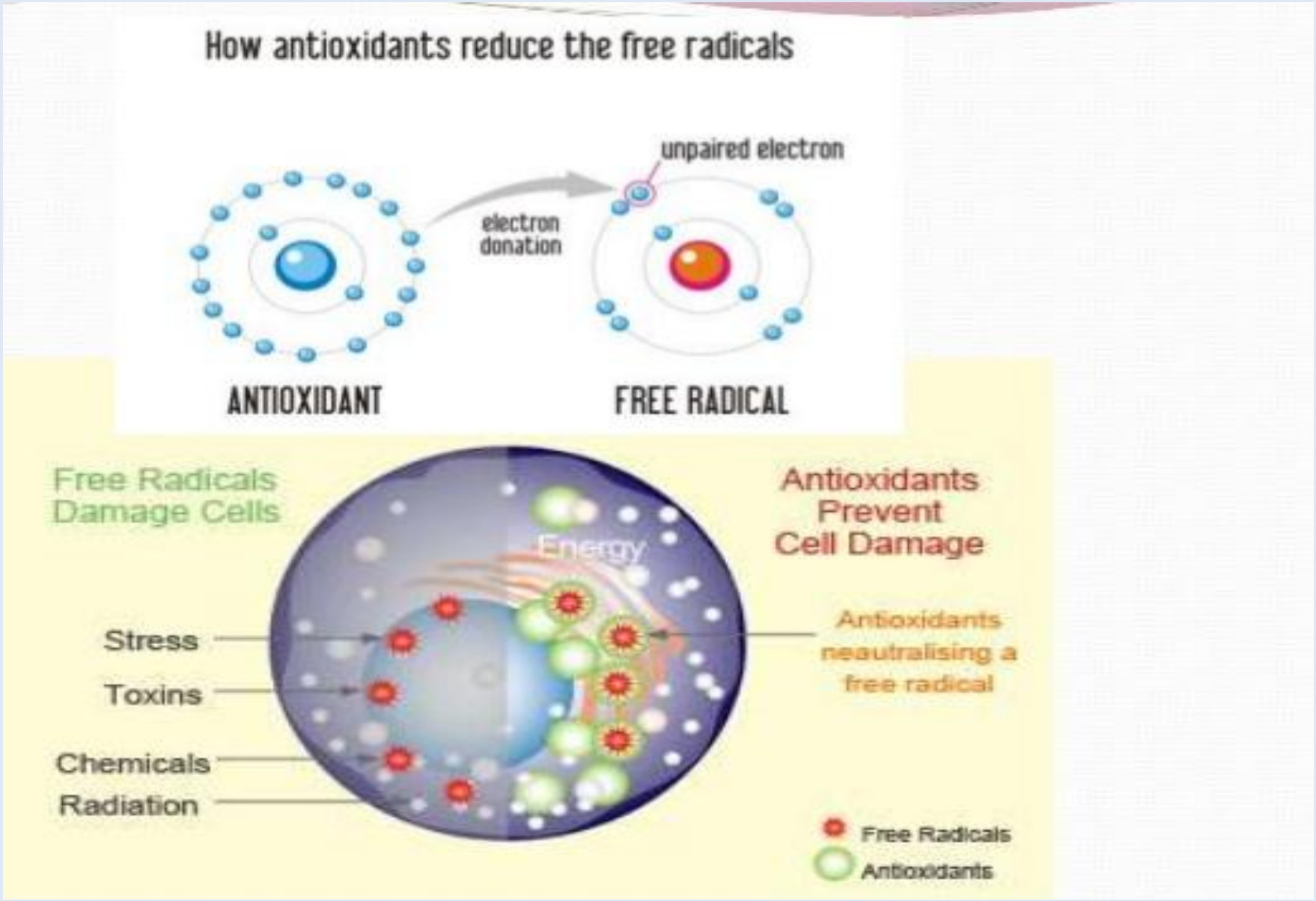
Reactive Oxygen Species (ROS), Antioxidants and Oxidative Stress

Reactive oxygen species (ROS) are usually considered as molecules associated with oxidative stress, they are increasingly shown to take part in normal cellular signaling. This increases the possibilities of ROS to be toxicologically important.

Even at concentrations that do not cause measurable structural alterations, cellular signaling may be disturbed.

Antioxidants can be defined as any substance that significantly delays or prevents the oxidation of a substrate in an organism.


How antioxidants reduce the free radicals
unpaired electron
electron donation
ANTIOXIDANT
FREE RADICAL
Free Radicals Damage Cells
Antioxidants Prevent Cell Damage
Energy
Stress
Toxins
Chemicals
Radiation
Antioxidants neautralising a free radical
Free Radicals
Antioxidants

The antioxidant defenses thus include:

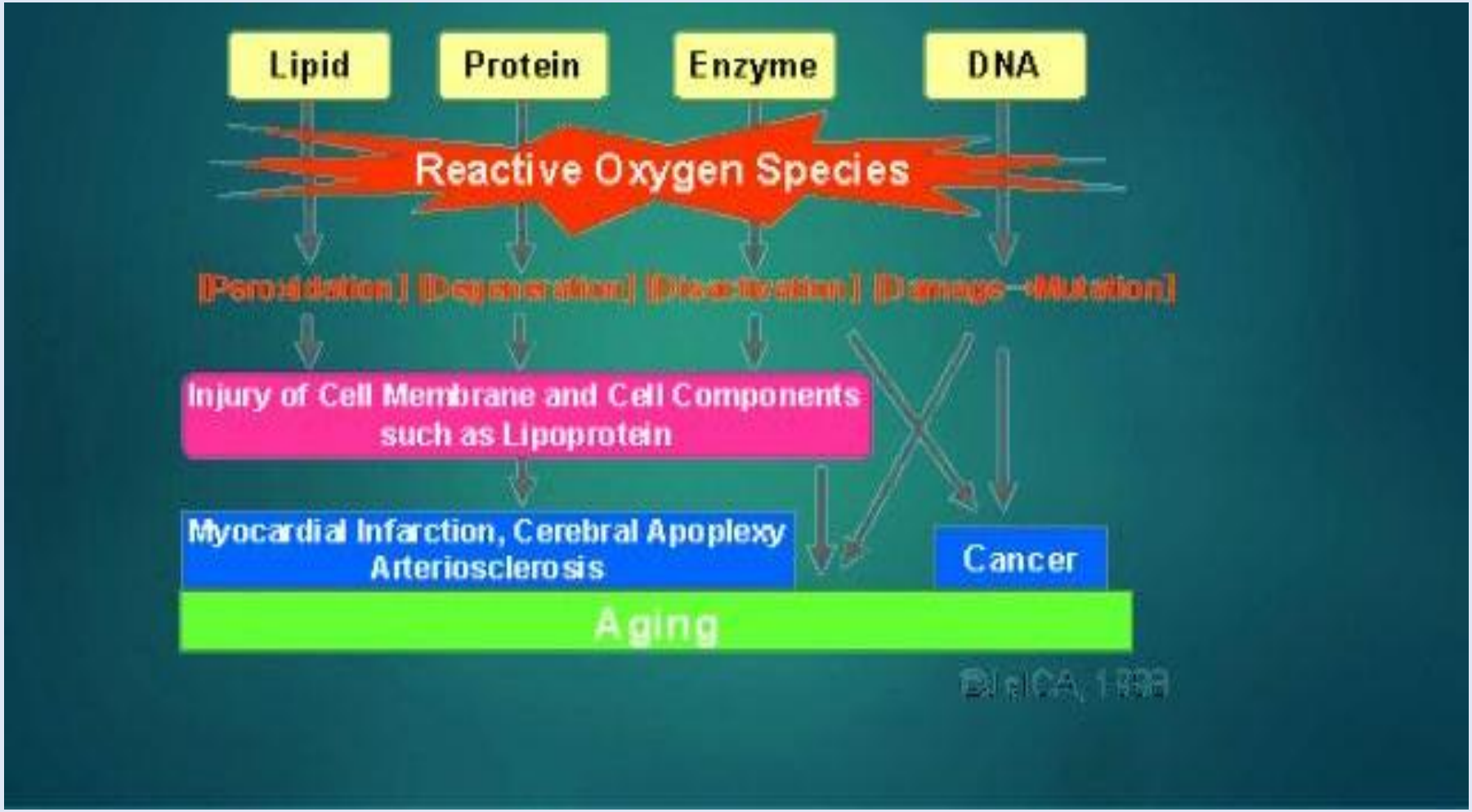
1. Enzymes that directly remove free radicals.

2. Molecules that decrease the formation of radicals (this includes proteins that minimize the availability of pro-oxidants, such as transferrin binding ferrous ions and **metallothionein** binding copper).

3. Molecules that prevent oxidative damage to biomolecules (e.g. histones protecting DNA and chaperones such as heat shock protein 90 **(HSP90)** protecting proteins).

4. Small molecules that either quench pro-oxidants or are preferentially oxidized by them to leave the more complex biomolecules intact (redox buffers).

Cell and Tissue Damage by Reactive Oxygen Species

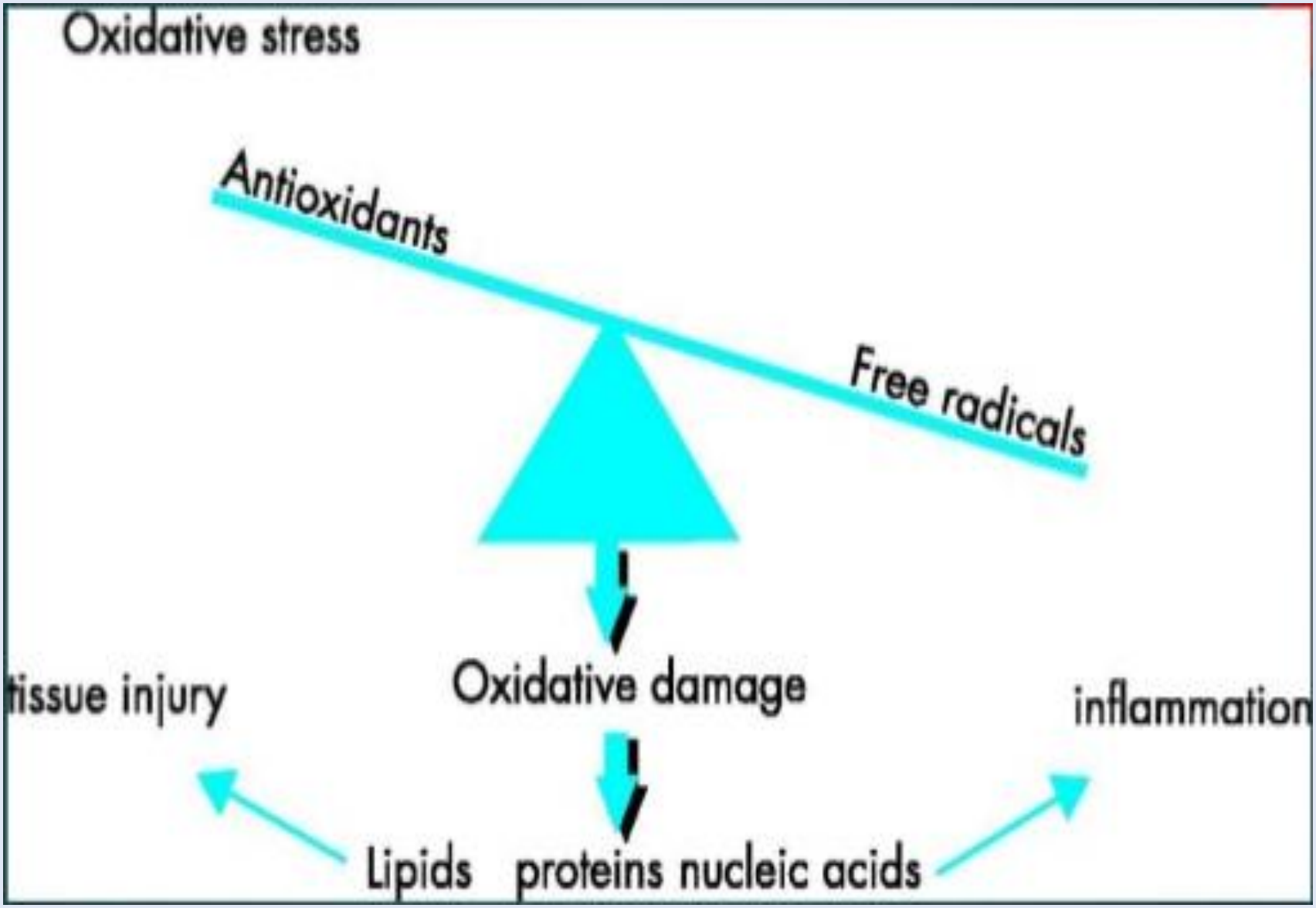


What is oxidative stress?

A disturbance in the balance between reactive species or free radicals and antioxidants.

Under normal conditions, cells are able to balance the production of oxidants and antioxidants.

Oxidative stress occurs when there is imbalance in our cells due to either an *increase* in free radicals or a *decrease* in antioxidants.


Oxidative stress
Antioxidants
Free radicals
Oxidative damage
tissue injury
inflammation
Lipids
proteins
nucleic acids

WHAT ARE FREE RADICALS?

- A free radicals molecules is an oxygen containing molecule that has one or more unpaired electrons making it highly reactive with other molecule.
- Not all reactive oxygen species are harmful to the body some of them are useful in killing invading pathogens or microbes.
- However free radicals can chemically interact with cell components such as DNA protein of lipid and steal their electrons in order to become stabilized.

Example of free radicals

Reactive Oxygen Species (ROS)	Symbol	Reactive Nitrogen Species (RNS)	Symbol
Hydroxyl	$OH\cdot$	Nitric Oxide	$NO\cdot$
Superoxide	$\cdot O_2^-$	Nitric Dioxide	$NO_2\cdot$
Hydrogen Peroxide	H_2O_2	Peroxynitrate	$OONO^-$
Peroxyl	$RO_2\cdot$	Nitroxyl Anion	NO
Singlet Oxygen	$^1O_2$	Dinitrogen Trioxide	N_2O_3
Hypochloric Acid	$HOCl$	Nitrous Acid	HNO_2
Ozone	O_3		

Oxidative stress leads to the structural changes of the cell wall and hamper the process of maturation of cellular structures. Its also lead to the change in the function and death eventually.

There are two types of nonenzymatic redox-sensitive molecules:

1. Endogenous
2. Food-derived.

The most important of all the small molecules is glutathione.

It is present in most cells at millimolar concentrations.

Since glutathione is present in all organisms, it is often measured to indicate the redox state of organisms.

In this context, it is important to note that if glutathione is used to show the redox state of a cell, then the ratio between reduced and oxidized glutathione should be measured.

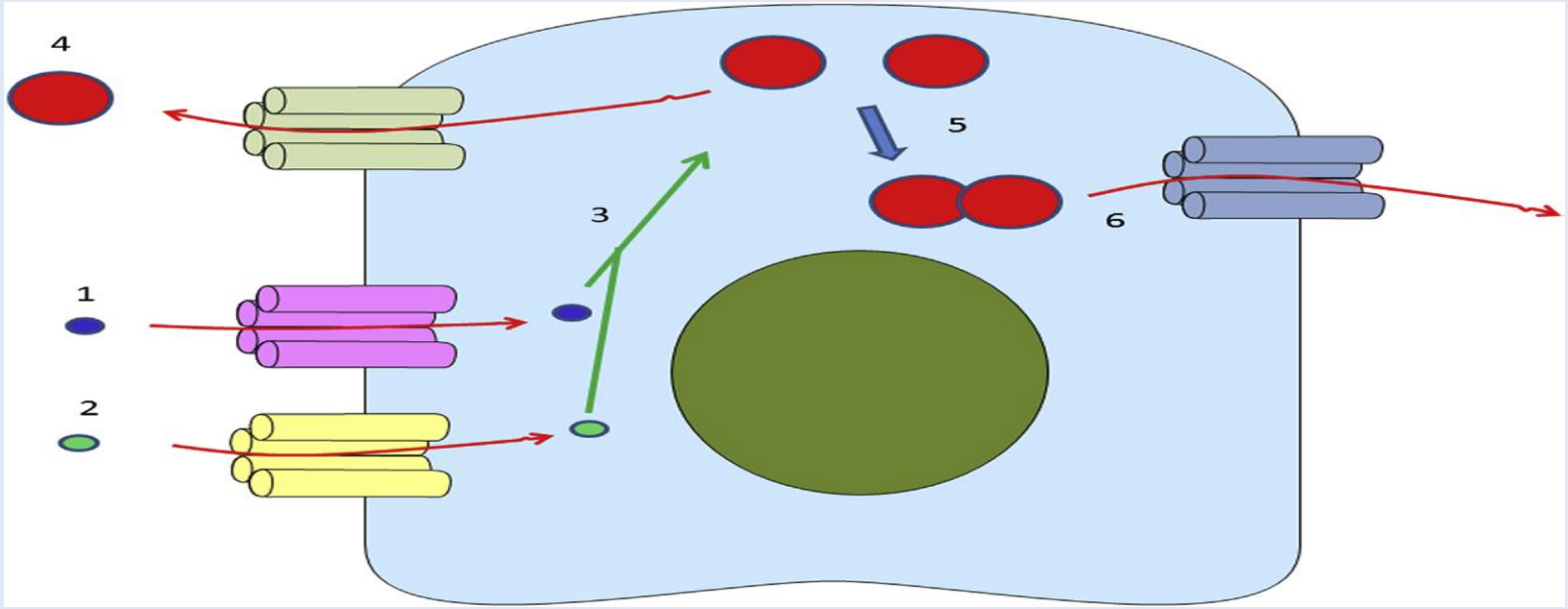


Figure: The glutathione cycle.

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(1, 2) The amino acids glutamate and cysteine are taken up into cells, either as such or as other amino acids subsequently metabolized in the cells into glutamate and cysteine.

(3) Cellular glutathione is mainly formed enzymatically from glutamate and cysteine.

(4) Some of the glutathione produced is excreted in the extracellular compartment or broken down.

(5) In oxidizing conditions, e.g. oxidative stress, reduced glutathione (monomers) is converted to oxidized glutathione (dimers).

Thus, the ratio between oxidized and reduced glutathione can be used as a measure of the redox state of the cells.

(6) Oxidized glutathione dimers can be exported from the cells. Oxidative conditions may affect glutathione synthesis, breakdown, and efflux. The effects observed may depend on the cell type.

Consequently, the total glutathione concentration of cells cannot be used to indicate the redox status of the cells. An increase, no change, and a decrease in total cellular glutathione concentration have all been reported upon oxidative stress.

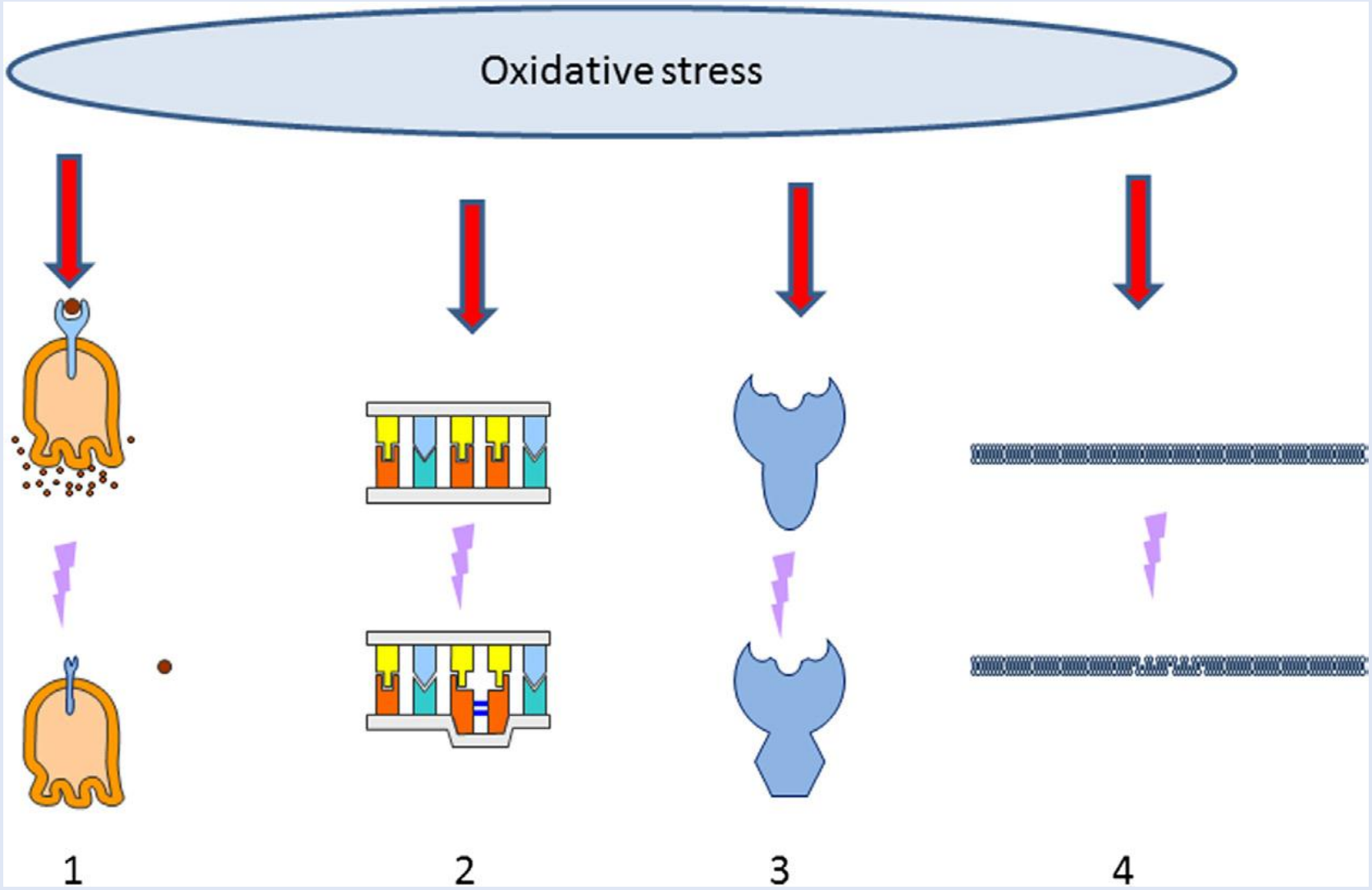
Oxidative stress
1
2
3
4

FIGURE: Principles of oxidative stress effects.

1. Before any structural changes occur, oxidative stress can affect signaling, since ROS appear to be involved in cellular signaling.

2. Oxidative stress can cause effects on DNA; for example, the formation of DNA adducts is increased. When damage to DNA overwhelms the repair capacity, an increased mutation rate is observed.

3. Oxidative stress can affect the three-dimensional structure of proteins, with the consequence that protein activity is altered. (4) Oxidative stress can influence lipids, causing, for example, lipid peroxidation. Such changes can cause alteration in the permeability of cell membranes.

Molecular effects of oxidative stress

- Lipid peroxidation
- DNA damage
- Protein oxidation
- Inactivation of enzymes
- Release of ca ions from intracellular stores
- Cytoskeletal damage
- Chemotaxis

Vascular effects

- altered vascular tone
- increased endothelial permeability