Reactive nitrogen species (RNS)

Reactive nitrogen species (**RNS**) are a family of antimicrobial molecules derived from nitric oxide (•NO) and superoxide ($O_2^{\bullet-}$) produced via the enzymatic activity of inducible nitric oxide synthase 2 (NOS2) and NADPH oxidase respectively. NOS2 is expressed primarily in macrophages after induction by cytokines and microbial products, notably interferon-gamma (IFN-γ) and lipopolysaccharide (LPS).

Reactive nitrogen species act together with reactive oxygen species (ROS) to damage cells, causing **nitrosative stress**. Therefore, these two species are often collectively referred to as ROS/RNS.

Reactive nitrogen species are also continuously produced in plants as by-products of aerobic metabolism or in response to stress.

Types

RNS are produced in animals starting with the reaction of nitric oxide (•NO) with superoxide ($O_2^{\bullet-}$) to form peroxynitrite ($ONOO^-$).

- •NO (nitric oxide) + $O_2^{\bullet-}$ (superoxide) → $ONOO^-$ (peroxynitrite)

Superoxide anion (O_2^-) is a reactive oxygen species that reacts quickly with nitric oxide (NO) in the vasculature. The reaction produces peroxynitrite and depletes the bioactivity of NO. This is important because NO is a key mediator in many important vascular functions including regulation of smooth muscle tone and blood pressure, platelet activation, and vascular cell signaling.

Peroxynitrite itself is a highly reactive species which can directly react with various biological targets and components of the cell including lipids, thiols, amino acid residues, DNA bases, and low-molecular weight antioxidants.However, these reactions happen at a relatively slow rate. This slow reaction rate allows it to react more selectively throughout the cell. Peroxynitrite is able to get across cell membranes to some extent through anion channels[5]Additionally peroxynitrite can react with other molecules to form additional types of

RNS including nitrogen dioxide ($\bullet NO_2$) and dinitrogen trioxide (N_2O_3) as well as other types of chemically reactive free radicals. Important reactions involving RNS include:

- $ONOO^- + H^+ \rightarrow$ ONOOH (peroxynitrous acid) $\rightarrow \bullet NO_2$ (nitrogen dioxide) + •OH (hydroxyl radical)
- $ONOO^- + CO_2$ (carbon dioxide) $\rightarrow ONOOCO_2^-$ (nitrosoperoxycarbonate)
- $ONOOCO_2^- \rightarrow \bullet NO_2$ (nitrogen dioxide) + $O=C(O\bullet)O^-$ (carbonate radical)
- $\bullet NO + \bullet NO_2 \rightleftharpoons N_2O_3$ (dinitrogen trioxide)

Biological targets

Peroxynitrite can react directly with proteins that contain transition metal centers. Therefore, it can modify proteins such as hemoglobin, myoglobin, and cytochrome c by oxidizing ferrous heme into its corresponding ferric forms. Peroxynitrite may also be able to change protein structure through the reaction with various amino acids in the peptide chain. The most common reaction with amino acids is cysteine oxidation. Another reaction is tyrosine nitration; however peroxynitrite does not react directly with tyrosine. Tyrosine reacts with other RNS that are produced by peroxynitrite. All of these reactions affect protein structure and function and thus have the potential to cause changes in the catalytic activity of enzymes, altered cytoskeletal organization, and impaired cell signal transduction.

Diseases related to reactive nitrogen species

Reactive nitrogen species (RNS) that are overproduced or undereliminated cause nitrosative stress, and the consequences of nitrosative stress can include mitochondrial dysfunction, altered structure and function of critical protein mediators, and cell injury or death. Nitric oxide, peroxynitrite, nitrotyrosine, and nitrosothiols are the principal RNS, and they can coexist and interact with ROS.ROS and reactive nitrogen species (RNS) are thought to play important roles in diverse nervous system disorders such as stroke, spinal cord injury, Parkinson's disease, Alzheimer's disease, Huntington's disease, Freidrich's ataxia, and amyotrophic lateral sclerosis (ALS).

Peroxynitrite is the most reactive and potentially injurious RNS, and it has powerful oxidizing and nitrating actions. The wide spectrum of substrates (lipids, thiols, amino acids, DNA) targeted by peroxynitrite can result in the lipid peroxidation of membranes, mitochondrial damage, posttranslational modifications of proteins, disturbances in cell

signalling, apoptosis, and cell necrosis. Peroxynitrite can also generate other RNS, including nitrogen dioxide and dinitrogen trioxide.

Reactive Oxygen Species (ROS)

Radicals:

$O_2^{\cdot -}$	Superoxide
$OH^{\cdot}$	Hydroxyl
$RO_2^{\cdot}$	Peroxyl
$RO^{\cdot}$	Alkoxyl
$HO_2^{\cdot}$	Hydroperoxyl

Non-Radicals:

H_2O_2	Hydrogen peroxide
$HOCl^-$	Hypochlorous acid
O_3	Ozone
$^1O_2$	Singlet oxygen
$ONOO^-$	Peroxynitrite

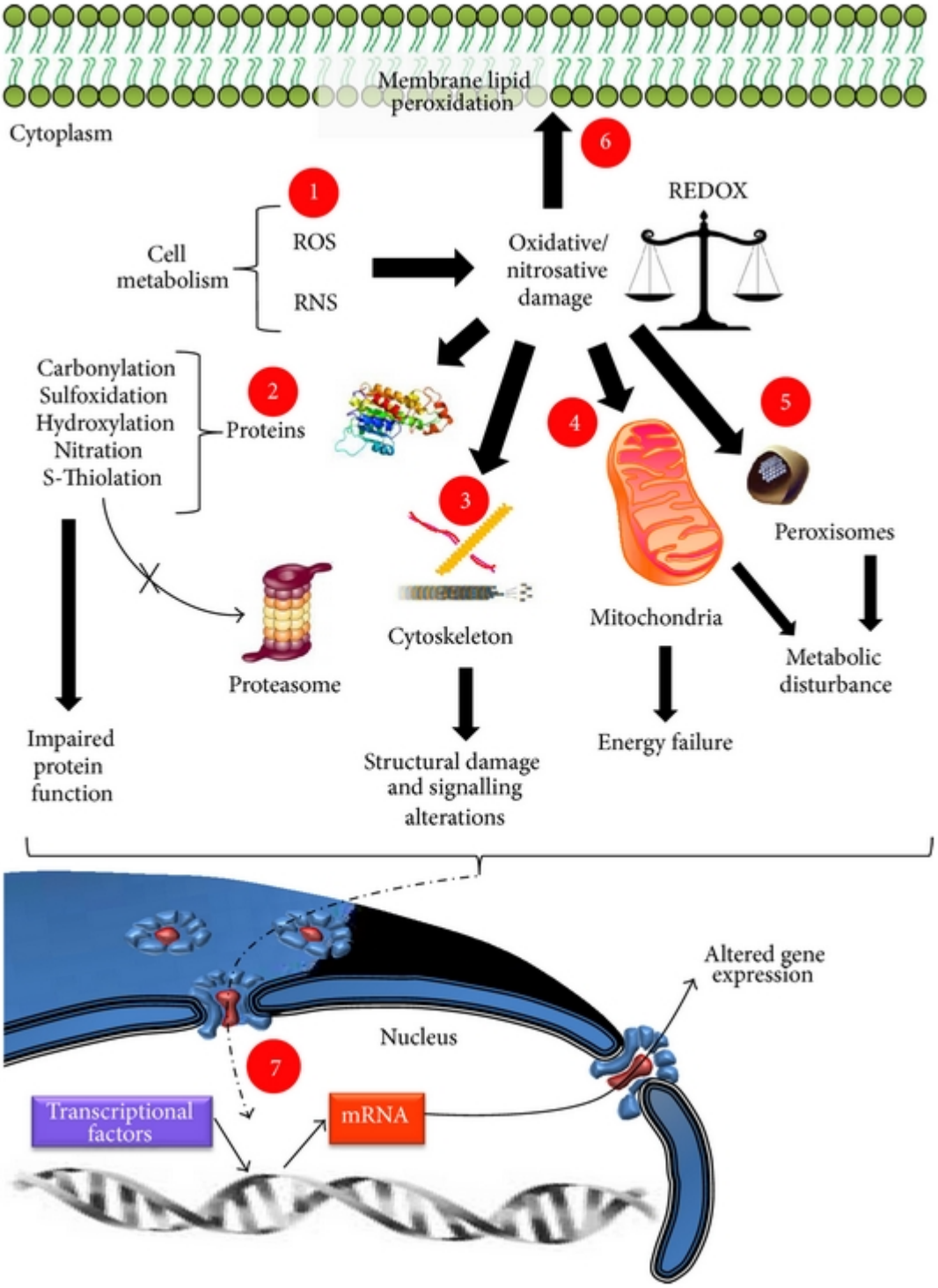
Reactive Nitrogen Species (RNS)

Radicals:

$NO^{\cdot}$	Nitric Oxide
$NO_2^{\cdot}$	Nitrogen dioxide

Non-Radicals:

$ONOO^-$	Peroxynitrite
ROONO	Alkyl peroxynitrites
N_2O_3	Dinitrogen trioxide
N_2O_4	Dinitrogen tetroxide
HNO_2	Nitrous acid
NO_2^+	Nitronium anion
NO^-	Nitroxyl anion
NO^+	Nitrosyl cation
NO_2Cl	Nitryl chloride


Membrane lipid peroxidation
Cytoplasm
6
1
ROS
Cell metabolism
RNS
Oxidative/ nitrosative damage
REDOX
Carbonylation
Sulfoxidation
Hydroxylation
Nitration
S-Thiolation
2
Proteins
3
4
5
Peroxisomes
Proteasome
Cytoskeleton
Mitochondria
Metabolic disturbance
Impaired protein function
Structural damage and signalling alterations
Energy failure
Altered gene expression
Nucleus
7
Transcriptional factors
mRNA