Table 2-3 Properties of the Principal Free Radicals Involved in Cell Injury

Properties	$O_2^{\cdot-}$	H_2O_2	$^{\cdot}OH$	$ONOO^-$
Mechanisms of production	Incomplete reduction of O_2 during oxidative phosphorylation; by phagocyte oxidase in leukocytes	Generated by SOD from $O_2^{\cdot-}$ and by oxidases in peroxisomes	Generated from H_2O by hydrolysis, e.g., by radiation; from H_2O_2 by Fenton reaction; from $O_2^{\cdot-}$	Produced by interaction of $O_2^{\cdot-}$ and NO generated by NO synthase in many cell types (endothelial cells, leukocytes, neurons, others)
Mechanisms of inactivation	Conversion to H_2O_2 and O_2 by SOD	Conversion to H_2O and O_2 by catalase (peroxisomes), glutathione peroxidase (cytosol, mitochondria)	Conversion to H_2O by glutathione peroxidase	Conversion to HNO_2 by peroxiredoxins (cytosol, mitochondria)
Pathologic effects	Stimulates production of degradative enzymes in leukocytes and other cells; may directly damage lipids, proteins, DNA; acts close to site of production	Can be converted to $^{\cdot}OH$ and OCl^-, which destroy microbes and cells; can act distant from site of production	Most reactive oxygen-derived free radical; principal ROS responsible for damaging lipids, proteins, and DNA	Damages lipids, proteins, DNA

HNO_2, nitrite; H_2O_2, hydrogen peroxide; NO, nitric oxide; $O_2^{\cdot-}$, superoxide anion; OCl^-, hypochlorite; $^{\cdot}OH$, hydroxyl radical; $ONOO^-$, peroxynitrite; ROS, reactive oxygen species; SOD, superoxide dismutase.

($H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + {}^{\cdot}OH + OH^-$). Because most of the intracellular free iron is in the ferric (Fe^{3+}) state, it must be reduced to the ferrous (Fe^{2+}) form to participate in the Fenton reaction. This reduction can be enhanced by $O_2^{\cdot-}$, and thus sources of iron and $O_2^{\cdot-}$ may cooperate in oxidative cell damage.

- *Nitric oxide (NO)*, an important chemical mediator generated by endothelial cells, macrophages, neurons, and other cell types (Chapter 3), can act as a free radical and can also be converted to highly reactive peroxynitrite anion ($ONOO^-$) as well as NO_2 and NO_3^-.

Removal of Free Radicals. Free radicals are inherently unstable and generally decay spontaneously. $O_2^{\cdot-}$, for example, is unstable and decays (dismutates) spontaneously to O_2 and H_2O_2 in the presence of water. In addition, cells have developed multiple nonenzymatic and enzymatic mechanisms to remove free radicals and thereby minimize injury (Fig. 2-20). These include the following:

- *Antioxidants* either block free radical formation or inactivate (e.g., scavenge) free radicals. Examples are the lipid-soluble vitamins E and A as well as ascorbic acid and glutathione in the cytosol.
- As we have seen, free *iron* and *copper* can catalyze the formation of ROS. Under normal circumstances, the reactivity of these metals is minimized by their binding to storage and transport proteins (e.g., transferrin, ferritin, lactoferrin, and ceruloplasmin), which prevents these metals from participating in reactions that generate ROS.
- A series of *enzymes* acts as free radical-scavenging systems and breaks down H_2O_2 and $O_2^{\cdot-}$. These enzymes are located near the sites of generation of the oxidants and include the following:
  1. *Catalase,* present in peroxisomes, decomposes H_2O_2 ($2H_2O_2 \rightarrow O_2 + 2H_2O$).
  2. *Superoxidase dismutases* (SODs) are found in many cell types and convert $O_2^{\cdot-}$ to H_2O_2 ($2O_2^{\cdot-} + 2H \rightarrow H_2O_2 + O_2$). This group of enzymes includes both manganese-SOD, which is localized in mitochondria, and copper-zinc-SOD, which is found in the cytosol.
  3. *Glutathione peroxidase* also protects against injury by catalyzing free radical breakdown ($H_2O_2 + 2GSH \rightarrow GSSG$ [glutathione homodimer] $+ 2H_2O$, or $2^{\cdot}OH + 2GSH \rightarrow GSSG + 2H_2O$). The intracellular ratio of oxidized glutathione (GSSG) to reduced glutathione (GSH) is a reflection of the oxidative state of the cell and is an important indicator of the cell's ability to detoxify ROS.

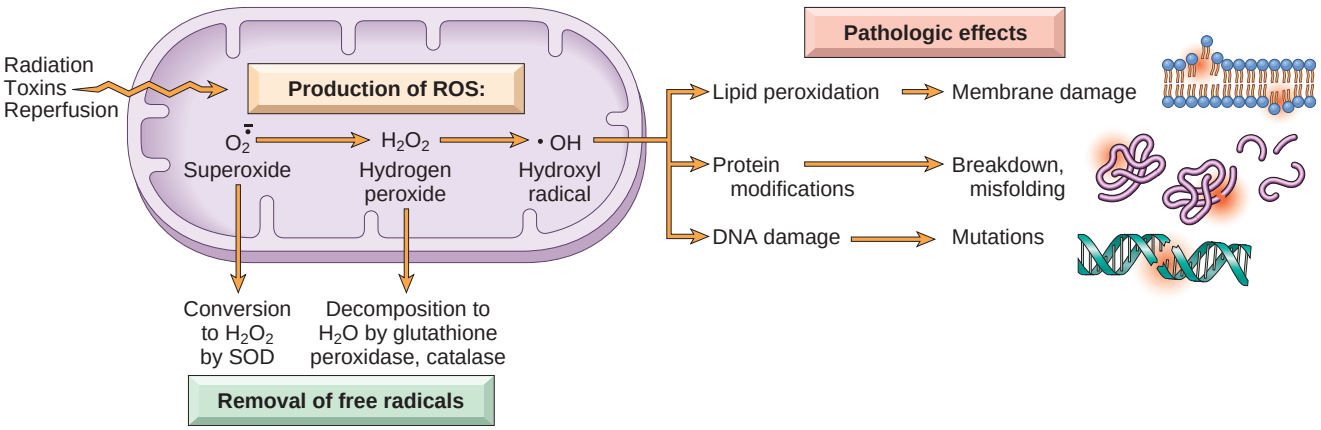

Figure 2-20 The generation, removal, and role of reactive oxygen species (ROS) in cell injury. The production of ROS is increased by many injurious stimuli. These free radicals are removed by spontaneous decay and by specialized enzymatic systems. Excessive production or inadequate removal leads to accumulation of free radicals in cells, which may damage lipids (by peroxidation), proteins, and deoxyribonucleic acid (DNA), resulting in cell injury.