Cellular adaptations, cell injury, and cell death

Monday Feb 7

Terms

- Etiology
- Pathogenesis
- Morphologic changes
- Functional derangements and clinical manifestations

Hypertrophy

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Source: Figure 1.3 in [RC] Kumar, V., A. K. Abbas, and N. Fausto. *Robbins and Cotran Pathologic Basis of Disease*. Philadelphia PA: Elsevier, 2005. ISBN: 0721601871.

Hyperplasia

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Transmissible murine colonic hyperplasia

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Source: CD-ROM in [RC].

- Control colon, H&E 200x
- TMCH colon, H&E 200x
- TMCH colon, BrdU 200x

Hepatic regeneration

- In normal adult liver, only 0.5 to 1.0% of cells are undergoing DNA replication
- After partial hepatectomy, the remaining cells proliferate to replace the lost tissue mass
- Hepatocytes begin to divide by 12 hours, and 1 to 2 days later 10% of the cells are synthesizing DNA
- Once liver mass is restored, some 1 to 2 weeks later, the rate of DNA synthesis decreases

Factors driving compensatory hyperplasia

- HGF from nonparenchymal cells acts via c-Met expressed on hepatoctyes
- TGF-alpha and EGF are also mitogenic for hepatocytes
- IL-6 and TNF-alpha are produced early in hepatic regeneration, and are necessary for the proliferative response
- A priming event is necessary for hepatocytes to respond to these cytokines and growth factors (degradation of ECM, release of norepinephrine, insulin, glucagon, etc.?)

Resolution of compensatory hyperplasia

- TGF-beta is an important inhibitor, which is also produced by nonparenchymal cells in the liver
- The adult stem cells of the liver do not appear to play an important role in hyperplasia following partial hepatectomy

Pathologic hyperplasia

- Hyperplasia constitutes a fertile soil in which neoplasia may develop
- Hyperplasia in certain organs is a risk factor for cancer
- But in tissues with a high turnover rate, hyperplasia may be a beneficial response when mature cells are injured or killed, necessitating compensatory renewal

Metaplasia

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Source: Figure 1.6 in [RC].

Reversible & irreversible injury

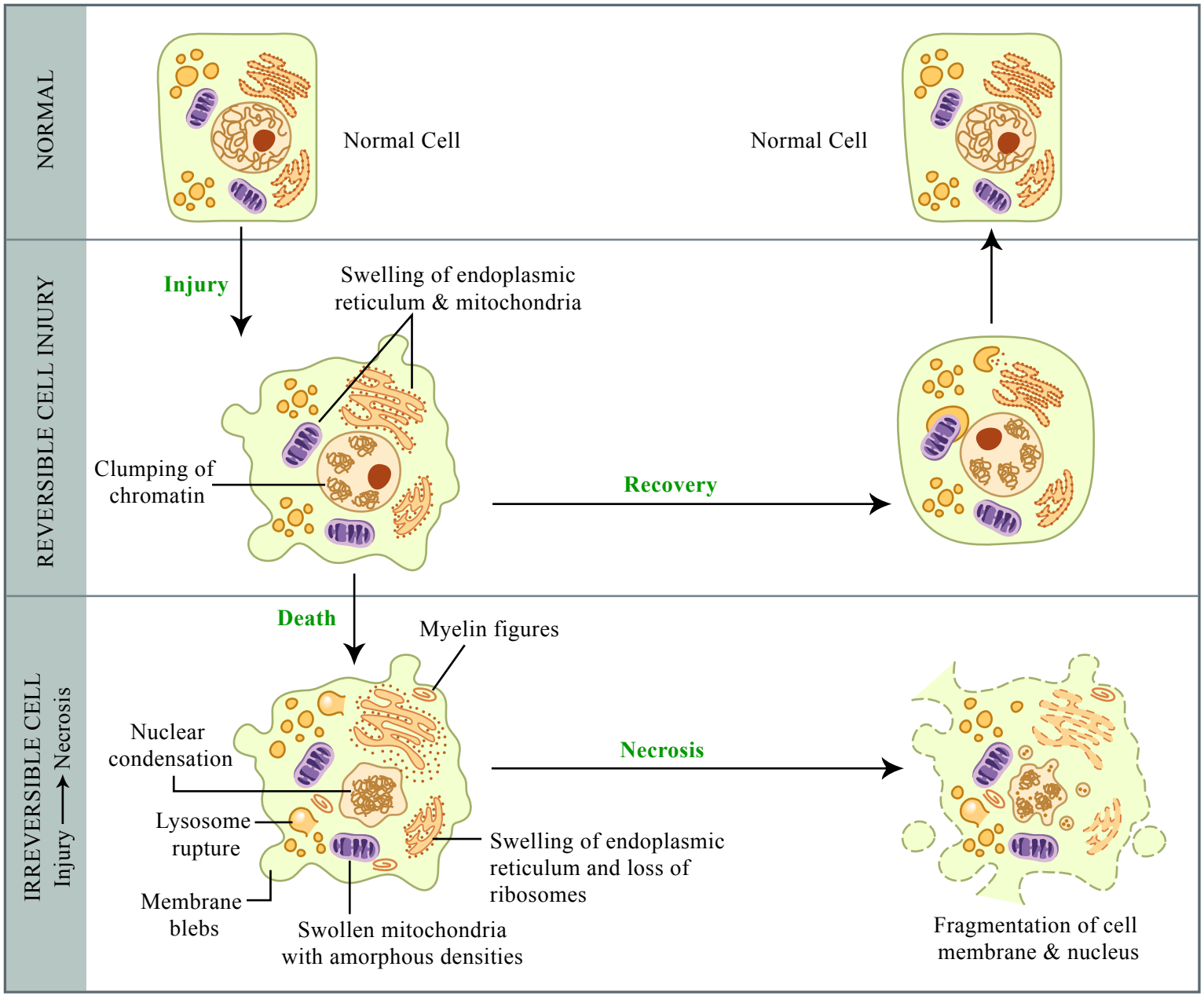


Figure by MIT OCW.

Necrosis and apoptosis

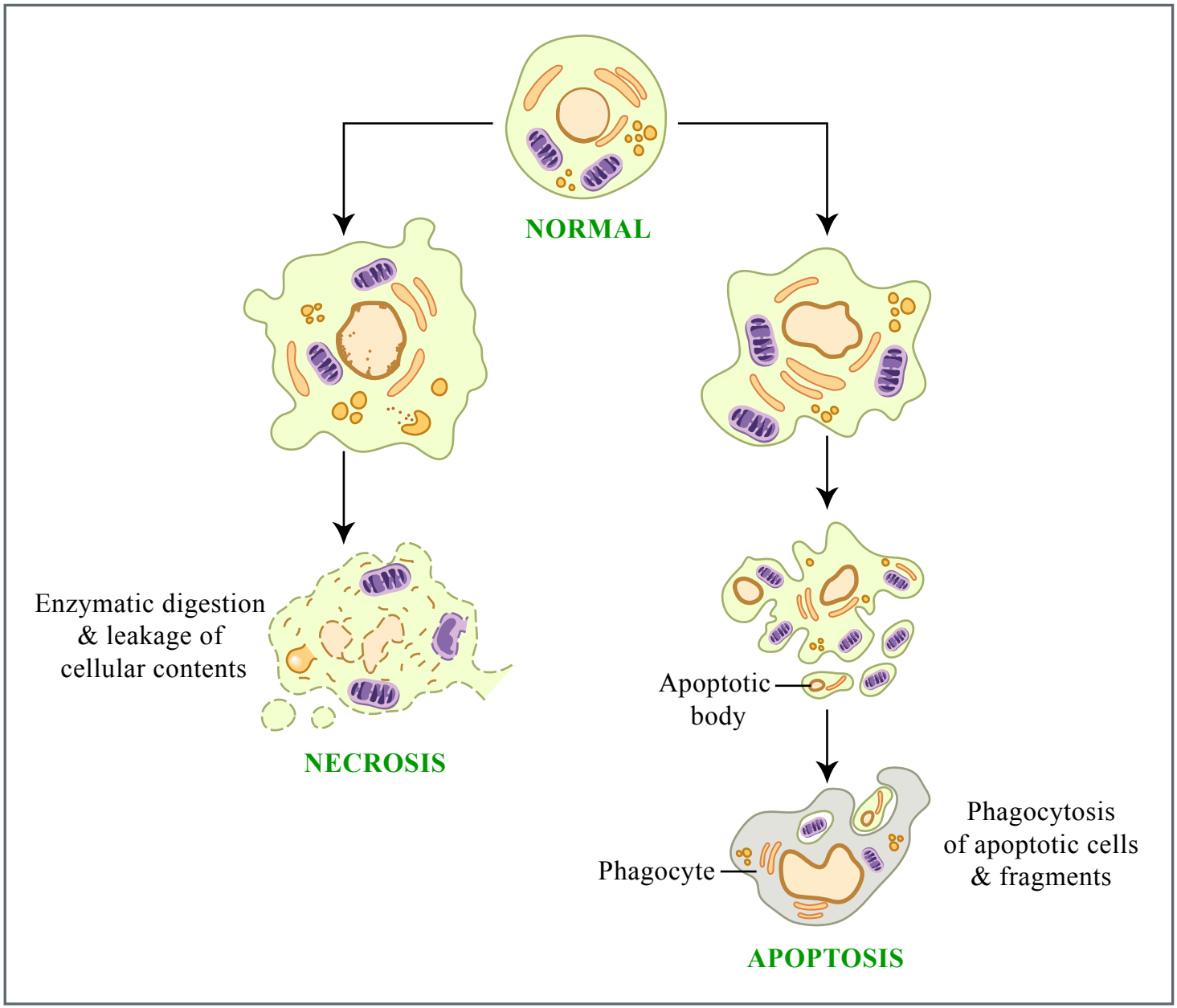
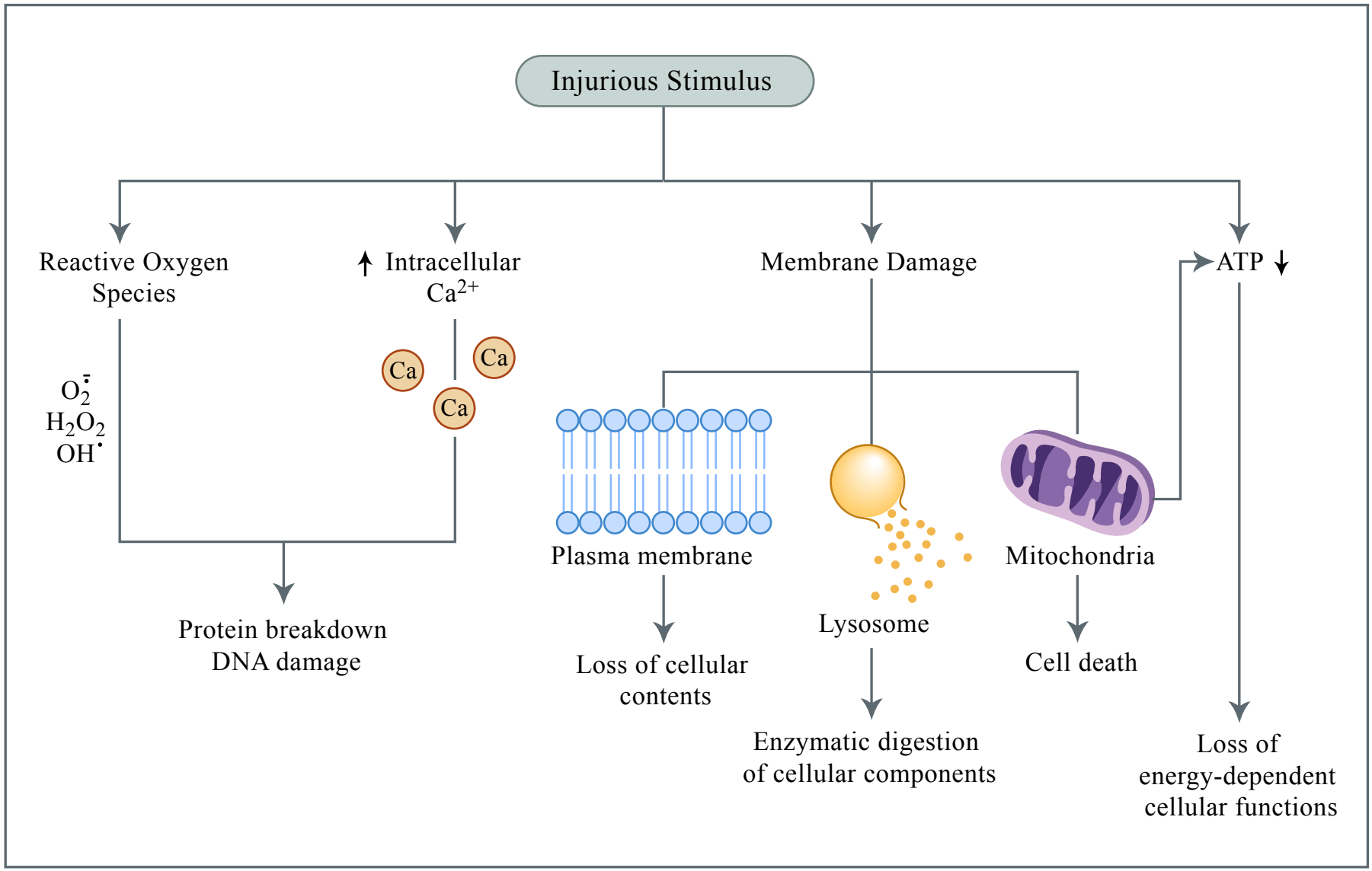


Figure by MIT OCW.

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis, karyorrhexis, karyolysis	Fragmentation into nucleosome size fragments
Plasma membrane	disrupted	Intact, altered structure
Cellular contents	Enzymatic digestion, leakage	Intact, release in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Always pathologic	Often, but not always, physiologic

Cellular and biochemical sites of damage



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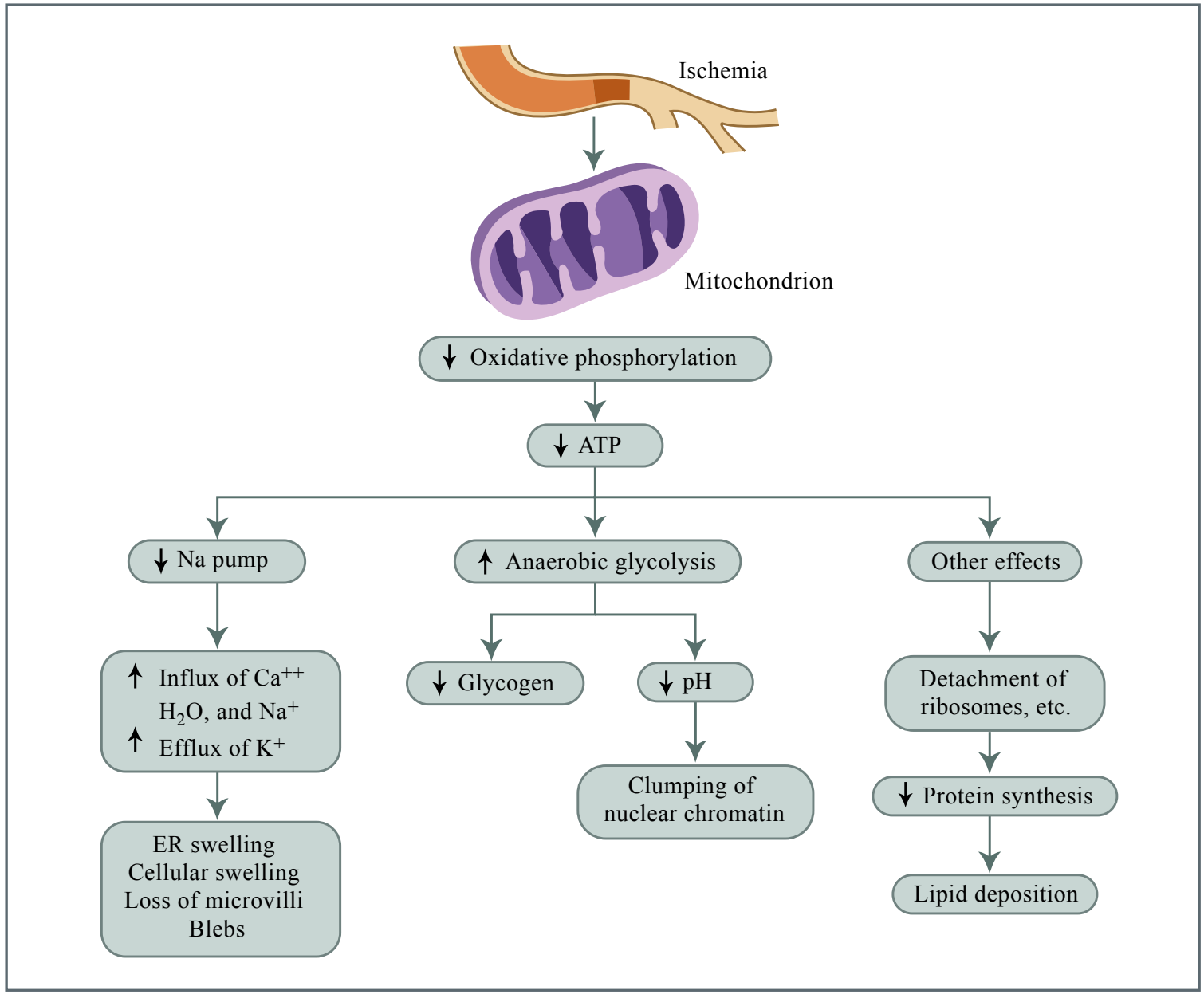
Consequences of ATP depletion



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Mitochondrial dysfunction

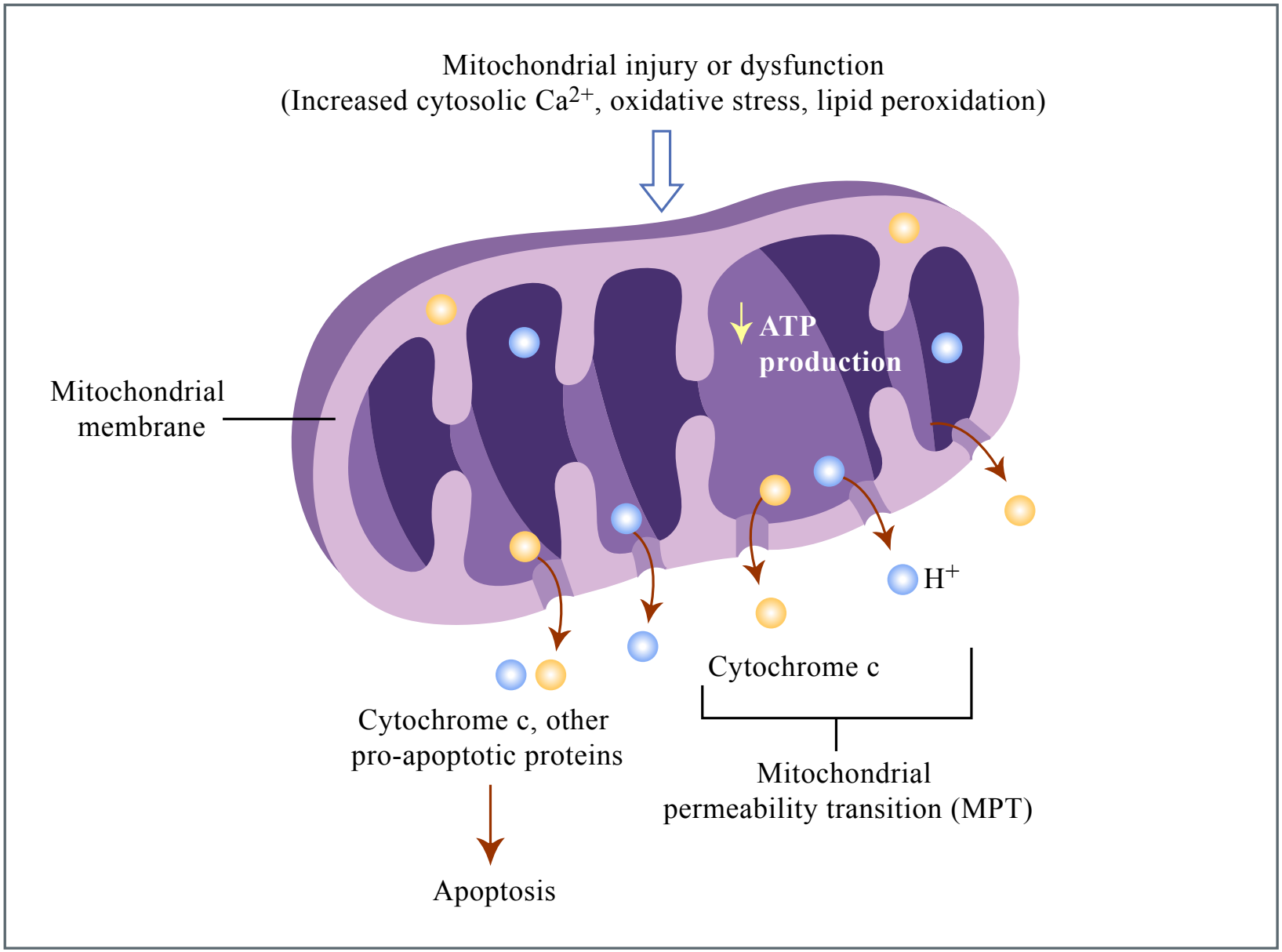

Figure by MIT OCW.

Ca^{2+} in cell injury

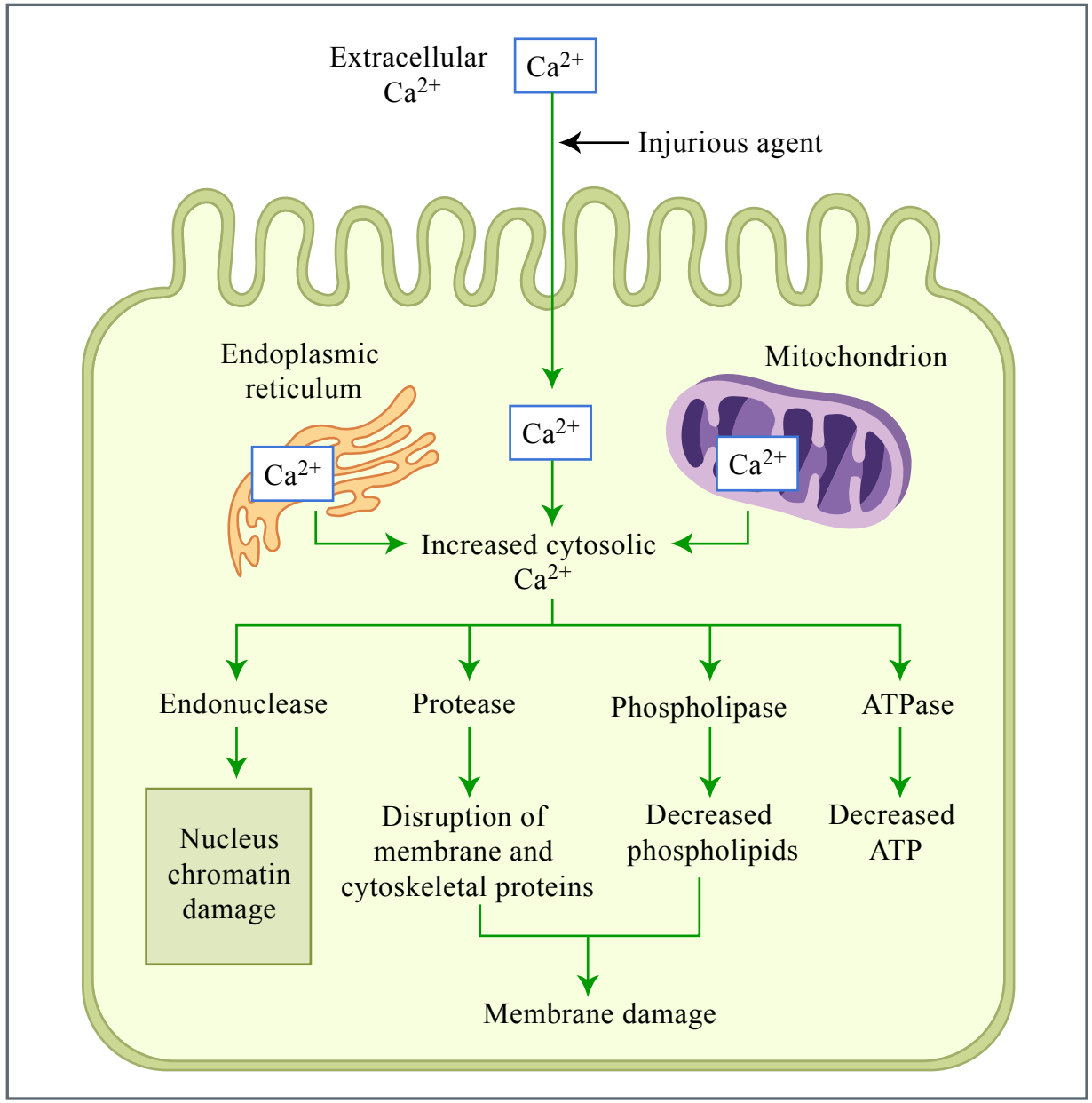

Figure by MIT OCW.

ROS in cell injury

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Source: Figure 1.14 in [RC].

Necrosis

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Source: Figure 1.19 in [RC].

Ischemic cell injury

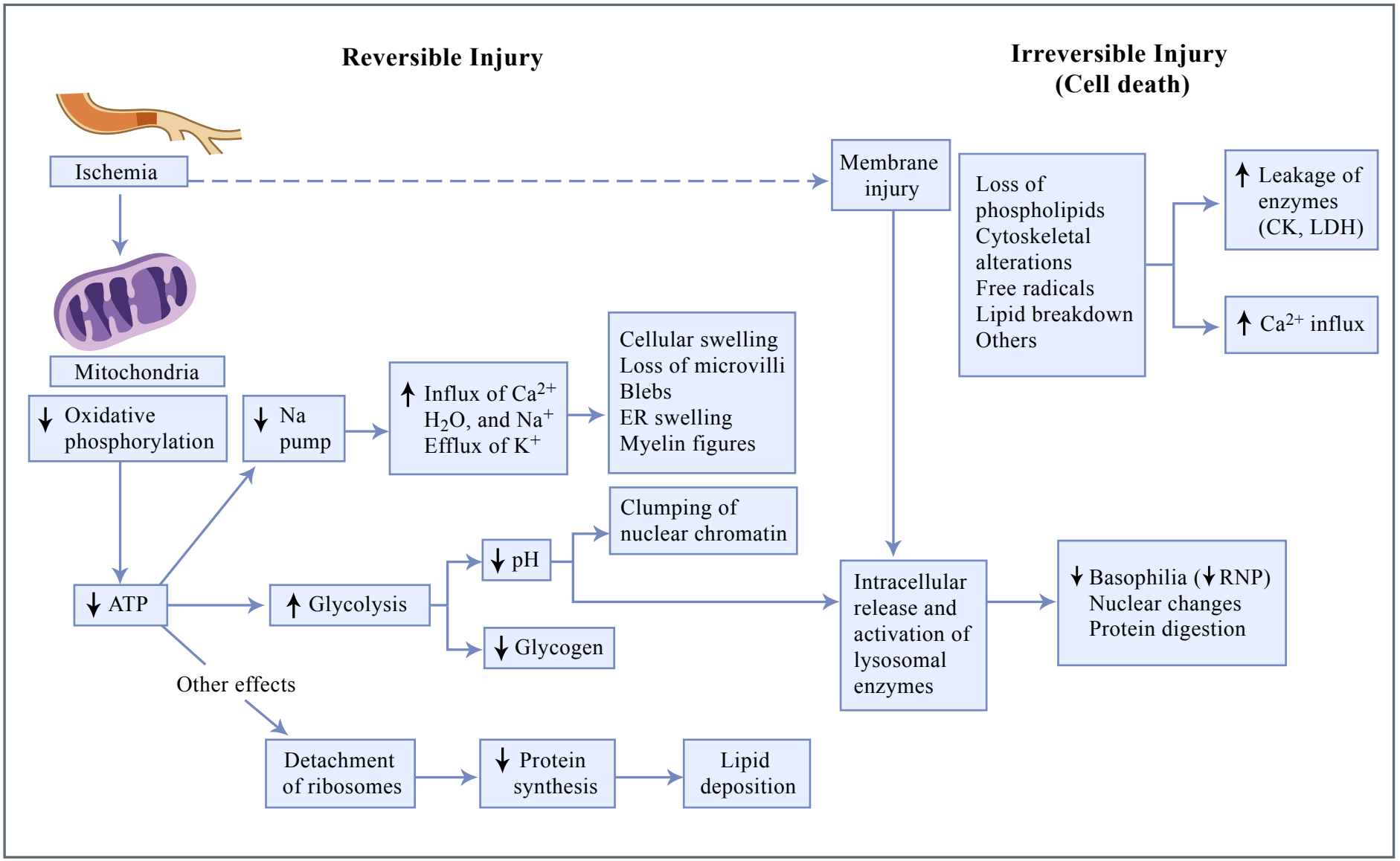
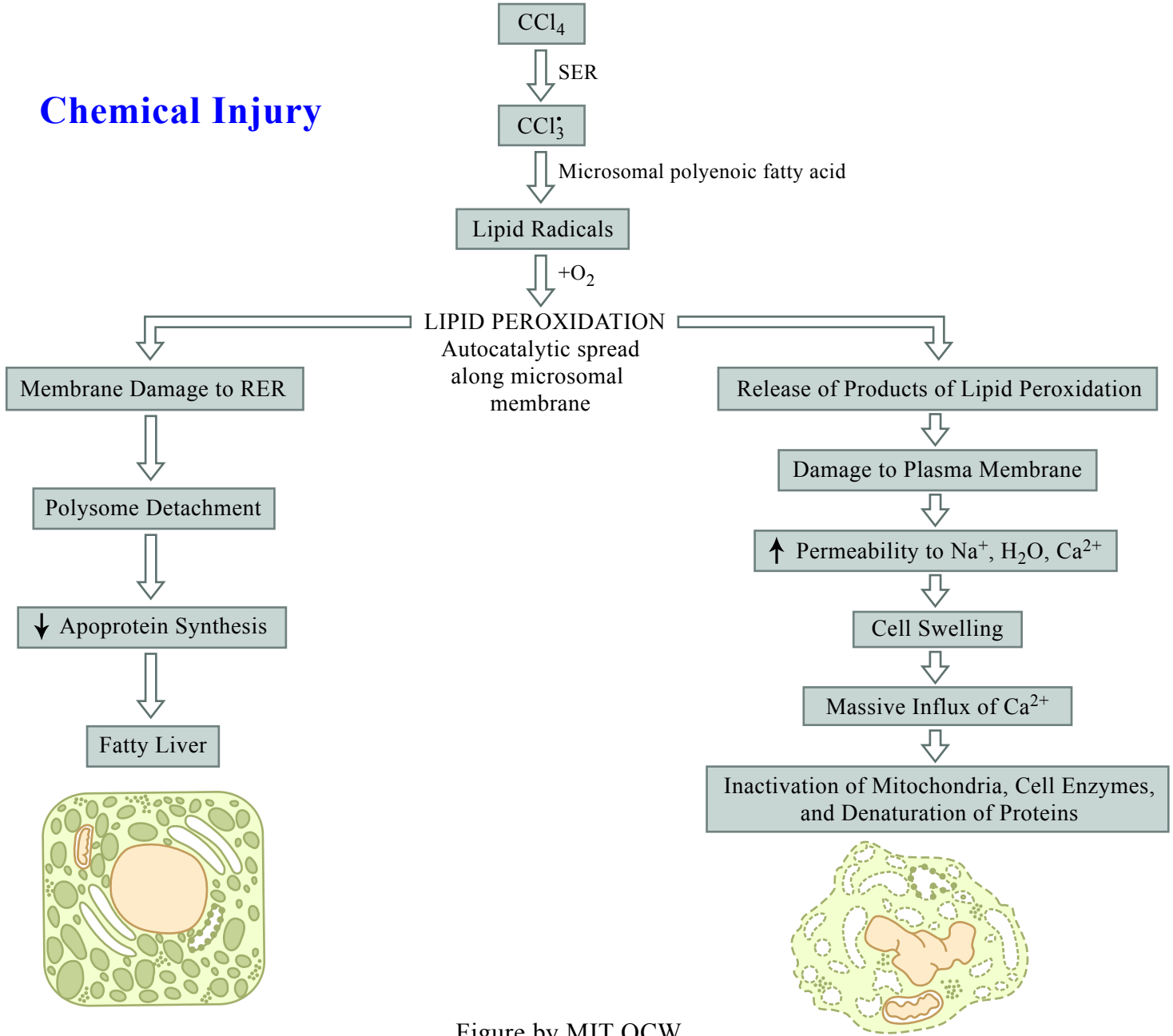


Figure by MIT OCW.

Chemical Injury



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Mechanisms of apoptosis

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Extrinsic pathway of apoptosis

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Intrinsic pathway of apoptosis

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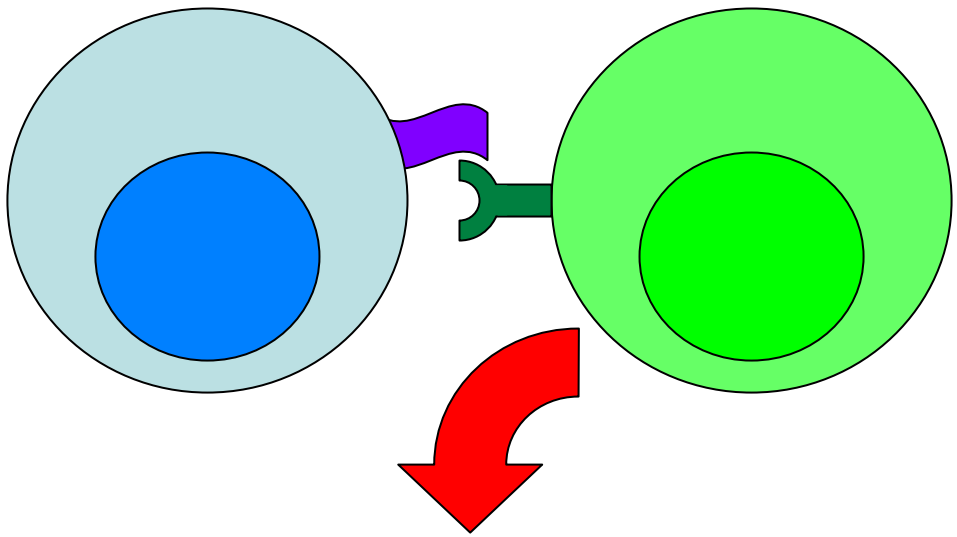
Source: Figure 1.30 in [RC].

Reticulum cell sarcoma model

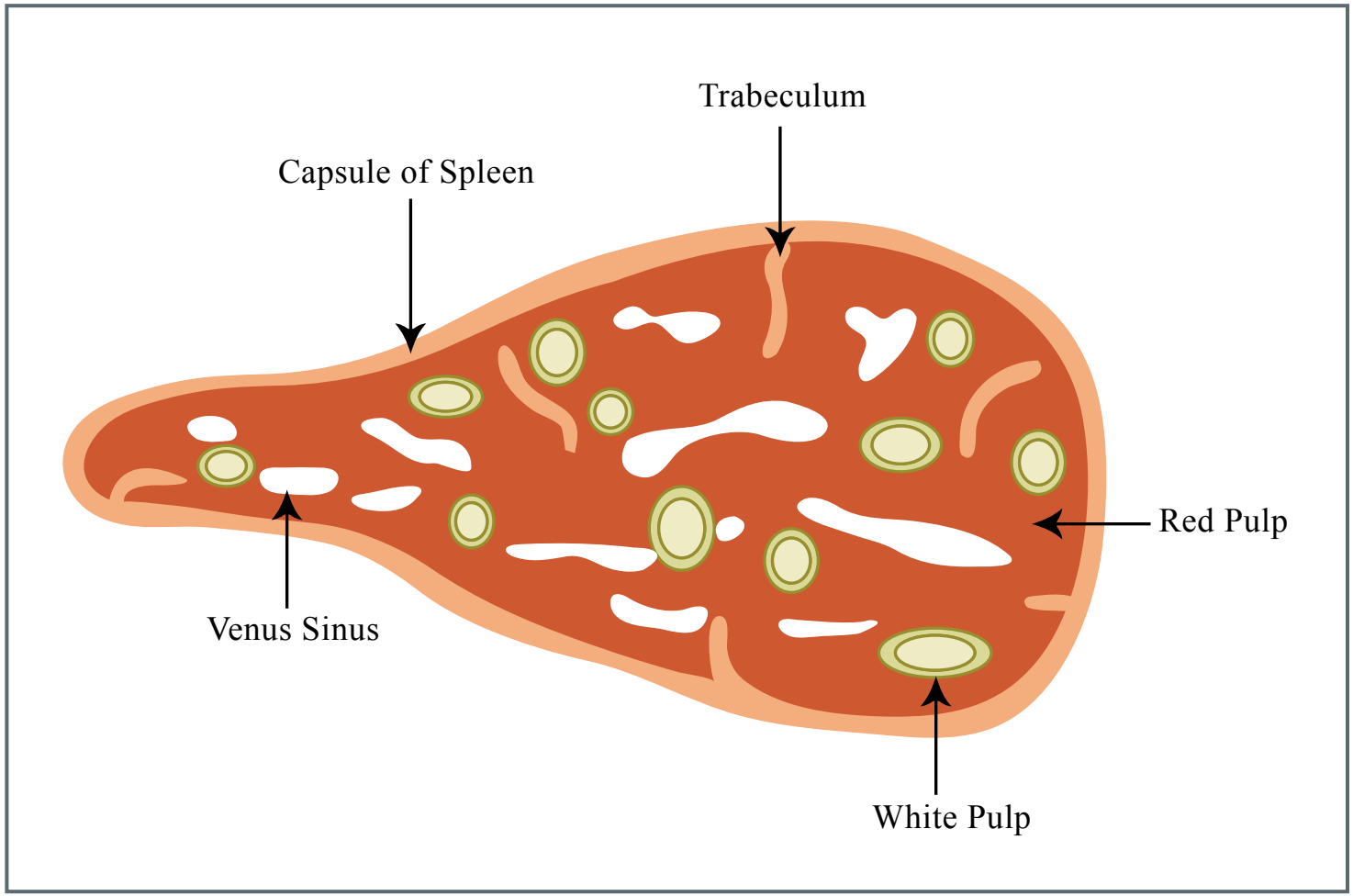
B cell lymphoma
Reticulum cell sarcoma (RCS)
MMTV-encoded superantigen

Syngeneic CD4+ Vb16+ T cells
Produce B cell growth factors
"Reverse immune surveillance"



Th1 cytokines

Normal spleen



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- Normal spleen, H&E 100x
- RcsX spleen, H&E 100x
- Normal spleen, H&E 200x
- RcsX spleen, H&E 200x
- Normal spleen, H&E 400x
- RcsX spleen, H&E 400x
- RcsX spleen, iNOS 400x
- RcsX spleen, activated caspase-3 400x