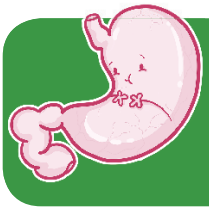

NOTES
CELLULAR PATHOLOGY

NECROSIS & APOPTOSIS

osms.it/necrosis-and-apoptosis

- Two main ways by which cells die

NECROSIS

- Cell death by injury/disease
  - External triggers (e.g. infection, temperature)
  - Internal triggers (e.g. ischemia)

Coagulative necrosis

- Occurs in hypoxic tissue
- Structural proteins bend out of shape
- Lysosomal proteins become ineffective at removing affected proteins
- Cell dies, some structure remains

Gangrenous necrosis

- Also occurs in hypoxic tissue
- *Dry gangrene*: tissue dries up
- *Wet gangrene*: if infection, liquefactive necrosis also occurs

Liquefactive necrosis

- Hydrolytic enzymes digest dead cells into creamy substance

Caseous necrosis

- Occurs in fungal/mycobacterial infections
- Cell disintegrate (not fully) → cottage cheese consistency

Fat necrosis

- Occurs in response to fatty organ trauma
- Adipose cell membranes ruptured
- Fatty acids combine with calcium, causing dystrophic calcifications
- Can occur in pancreas as result of inflammation (AKA pancreatitis)

Fibrinoid necrosis

- Occurs in malignant hypertension/vasculitis
- Fibrin/inflammation damages blood vessel walls

Also includes oncosis

- Toxins/ischemia damage mitochondria
- ATP can no longer be synthesized (e.g. ionic pumps)
- Sodium, water flow into cell → swelling
- Cell bursts, triggers inflammatory process

APOPTOSIS

- Programmed cell death
- Based on caspase cascade
  - Pro-caspases cleaved into caspases, activating caspase 3
  - Caspase 3 causes activation of cascade of caspase proteins
  - Cleaves various integral proteins, degrading cellular components (e.g. nucleus, organelles, cytoskeleton)
  - Cell loses structure, resulting in blebs, which break off, undergo phagocytosis

Intrinsic/mitochondrial pathway

- Induced by stress (e.g. radiation)
- Process
  - Intracellular proteins BAX, BAK pierce mitochondrial membrane
  - This allows SMACS, cytochrome C to flow out of mitochondria
  - SMACS binds to proteins that otherwise inhibit apoptosis
  - Cytochrome C binds to ATP, APAF-1, forming apoptosome
  - Pro-caspase 9 cleaves into caspase 9, activating caspase 3

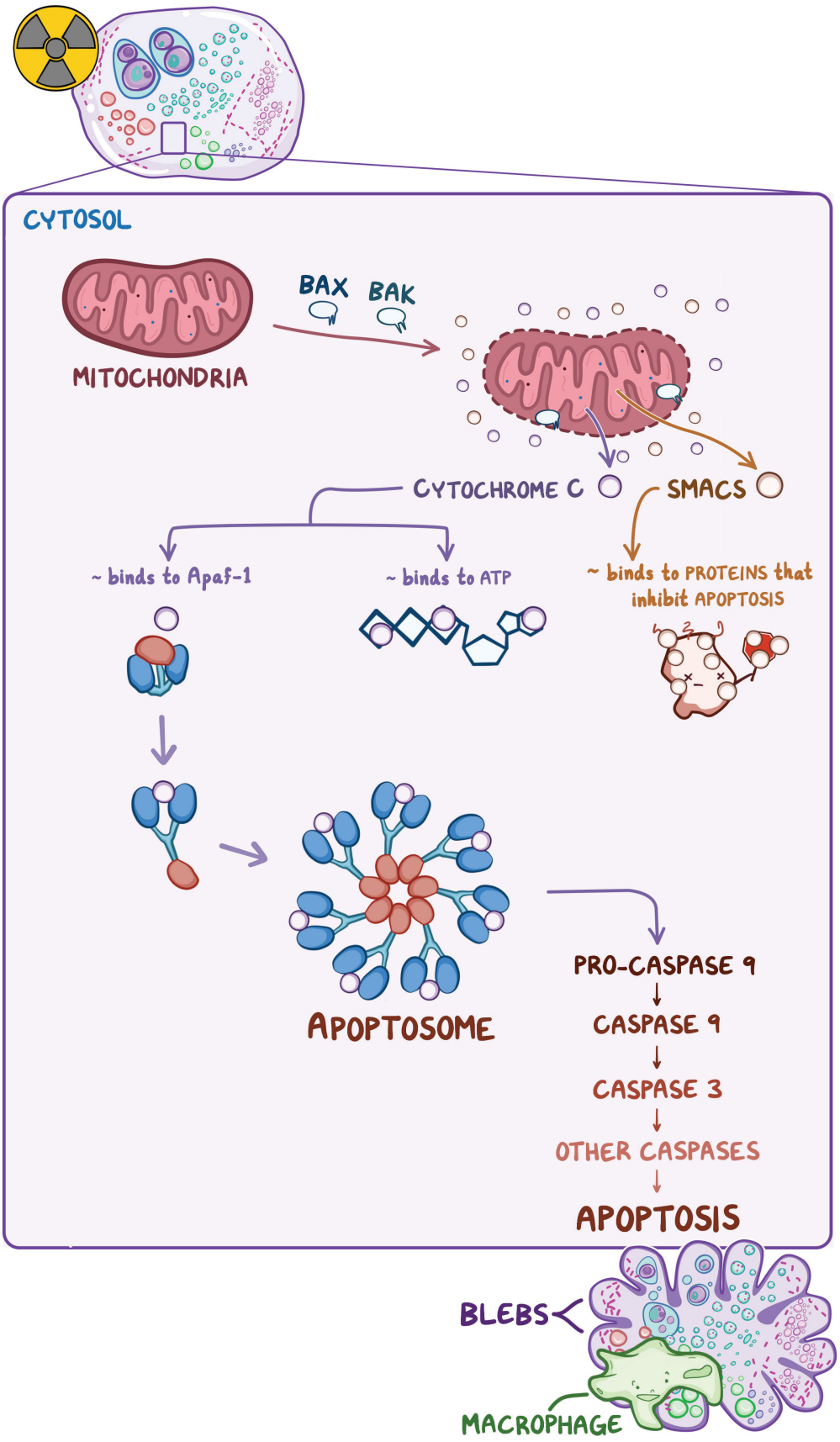

Figure 24.1 The intrinsic/mitochondrial apoptosis pathway.

Extrinsic/death receptor pathway

- Process
  - External cell initiates apoptosis by releasing various signaling proteins
  - Signaling proteins bind to death receptors on cell membrane
  - Cytosolic end of protein dives deep into cell (AKA death domain)
  - Death domain changes shape, binds various proteins to form internal signalling complex
  - Pro-caspase 8 cleaves into caspase 8, activating caspase 3

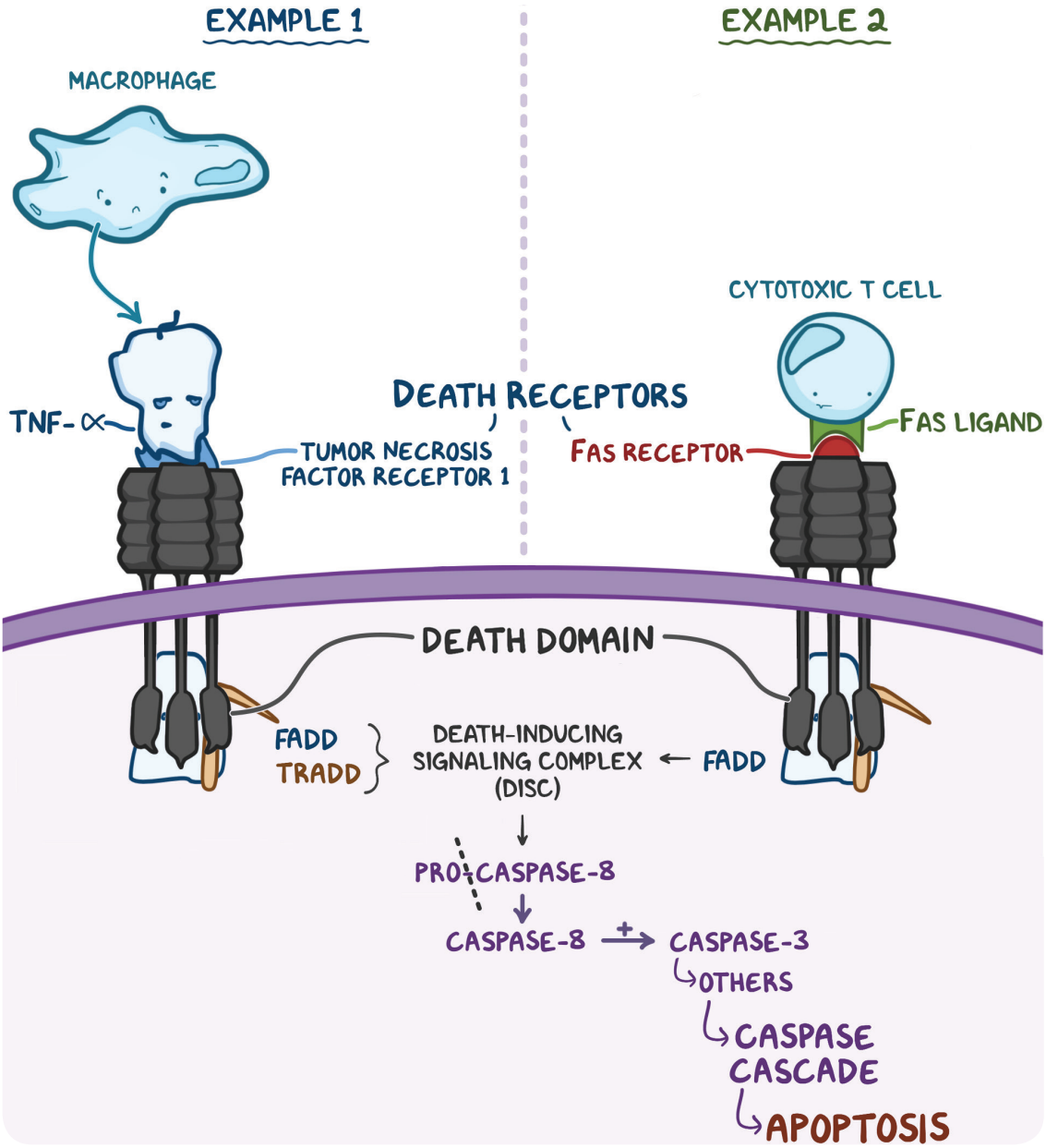

Figure 24.2 Two examples of the extrinsic/death receptor pathway. In *example* 1, a macrophage recognizes an old cell, a pathogenic cell, or a cell that has completed its task. It releases TNF-α, which binds to the death receptor tumor necrosis factor receptor 1. In *example* 2, when a cytotoxic T cell detects that a cell is expressing foreign antigens, the T cell expresses FAS ligand on its membrane. FAS ligand binds to the death receptor called FAS receptor. In both cases, the death domain binds other proteins to form DISC and the caspase cascade leads to apoptosis.

ONCOGENES & TUMOR SUPPRESSOR GENES

osms.it/oncogenes-tumor-suppressor-genes

- Code for proteins involved in progression of cell cycle
  - *Positive regulation:* oncogenes stimulate cell growth, division
  - *Negative regulation:* tumor suppressor genes stop cell cycle progression, promote apoptosis

Proto-oncogenes

- Code for growth factors, growth factor receptors (e.g. receptor tyrosine kinase)
- Signal transduction proteins (e.g. RAS GTPase), transcription factors (e.g. MYC), apoptosis inhibitors (e.g. BCL-2)
- Active when cell needs to grow, divide
- Translocations, amplifications, point mutations turn proto-oncogenes into oncogenes
  - Overexpression
  - E.g. in Burkitt lymphoma, *MYC* moved from chromosome 8 to near IgH promoter on chromosome 14 → overexpression of cyclins, cyclin-dependent kinases
  - E.g. in chronic myeloid leukemia with Philadelphia chromosome

Tumor suppressor genes

- Code for various tumor suppressors, other protein inhibitors
- Active throughout cell cycle
- Various mutations cause uncontrolled cell growth, division

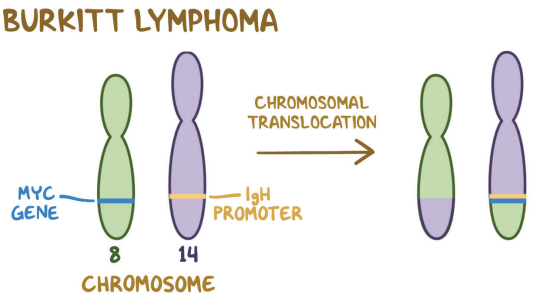

Figure 24.3 Burkitt lymphoma can occur due to translocation between portions of chromosomes 8 and 14, resulting in overexpression of proto-oncogene *MYC*.

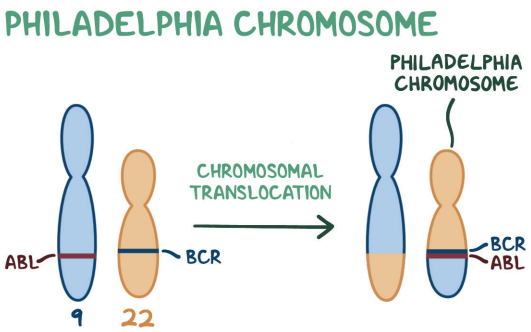

Figure 24.4 When a translocation occurs between the long arms of chromosomes 9 and 22, the resulting chromosome 22 with part of chromosome 9 is called the Philadelphia chromosome. It contains fusion gene *BCR-ABL*, whose protein BCR-ABL has tyrosine kinase activity (on/off switch for cell division). Since it's always on, myeloid cells keep dividing → leukemia.

HYPERPLASIA & HYPERTROPHY

osms.it/hyperplasia-hypertrophy

- Two ways by which cells adapt to stress
- Often happen together in tissues with stem cells

HYPERPLASIA

- Organ/tissue cells ↑ in number
- Only happens in organs with stem cells that can differentiate, mature

Types

- *Compensatory hyperplasia:* in organs that regenerate (e.g. skin)
- *Hormonal hyperplasia:* in organs regulated by hormones (e.g. endocrine)

Causes

- *Physiological processes:* e.g. pregnancy → enlargement of breast
- *Pathological processes:* e.g. excessive hormonal stimulation → excessive endometrial growth
- *Sometimes associated with cancer:* cells mutate → dysplasia

HYPERTROPHY

- Organ/tissue cells ↑ in size

Causes

- *Physiological processes:* e.g. ↑ functional demand → muscle cells produce more myofilaments
- *Pathological processes:* e.g. hypertension → cardiac myocytes produce more myofilaments

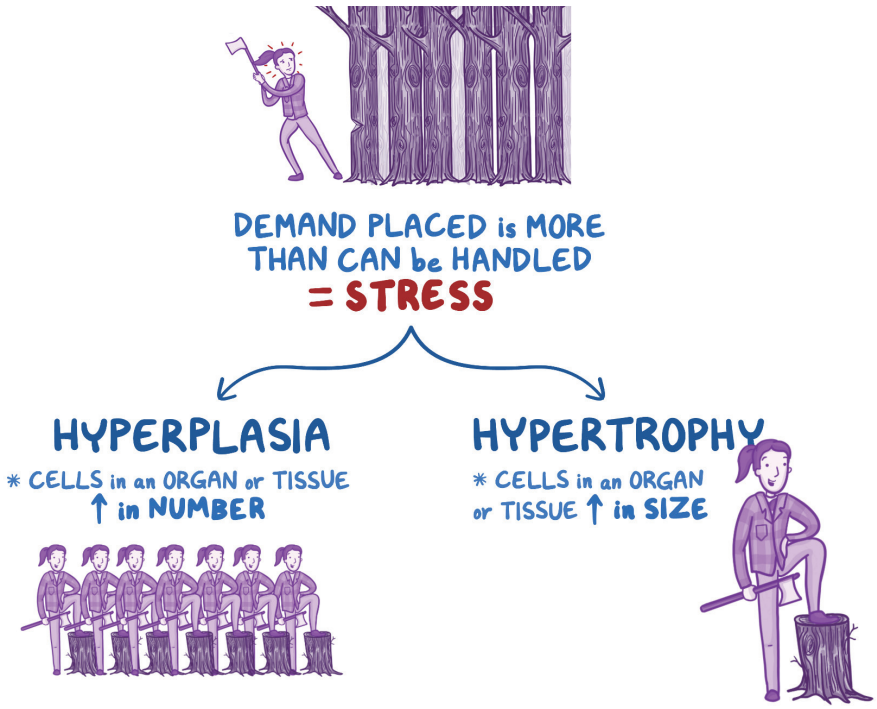

Figure 24.5 An analogy to describe the difference between hyperplasia and hypertrophy. When the workload is bigger than one lumberjack can handle, she gets stressed. Hyperplasia is like hiring more lumberjacks to help; hypertrophy is like the one lumberjack getting bigger and tougher so she can cut down more trees on her own.

METAPLASIA & DYSPLASIA

osms.it/metaplasia-and-dysplasia

METAPLASIA

- Mature differentiated cell transforms into new mature cell type
- Often caused by environmental stressor
  - *E.g. tobacco smoke:* pseudostratified columnar epithelial cells in airways → stratified squamous epithelium
- Reversible if stimulus reverted

DYSPLASIA

- Tissue develops large number of immature cells
- Precancerous state
- Four pathological changes to cell
  - Anisocytosis (AKA unequal cells)
  - Poikilocytosis (AKA abnormally-shaped cells)
  - Hyperchromatism (AKA excessive pigmentation)
  - Increases number of mitotic figures (AKA more mitosis)

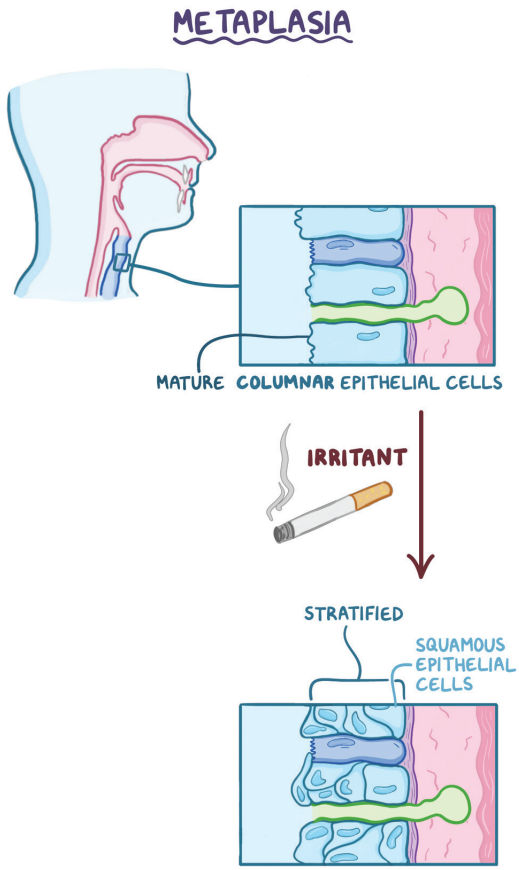

Figure 24.6 Example of metaplasia caused by exposure to tobacco smoke.

ATROPHY, APLASIA, & HYPOPLASIA

osms.it/atrophy-aplasia-hypoplasia

- Three ways by which cellular, bodily growth fails/reverts

ATROPHY

- Cell/organ/tissue size reduction
- Causes include disuse, denervation, ischemia, nutrient starvation, interruption of endocrine signals
- May be associated with ↓ cell number (e.g. apoptosis)
  - E.g. orthopedic casting of an extremity
- May be associated with ↓ cell size
  - Loss of nerve/hormonal supply
  - *Ubiquitin proteasome pathway:* proteasome destroys polyubiquitinated filaments/vacuoles destroy ubiquitin-

tagged organelles (e.g. muscle atrophy)

APLASIA

- Failure of organ/tissue to form properly
- Growth fails during embryogenesis with no precursor cells

HYPOPLASIA

- Reduced size/abnormal shape of organ/tissue
- Growth fails during embryogenesis in some precursor cells

FREE RADICALS & CELLULAR INJURY

osms.it/free-radicals-and-cellular-injury

FREE RADICAL

- Chemical species with unpaired electron in outer orbit
  - *Physiologic causes:* e.g. oxidative phosphorylation, enzyme activity
  - *Pathologic causes:* e.g. ionizing radiation, inflammation, metal interactions, drugs/chemicals)
- May result in cellular injury

FREE RADICAL CELLULAR INJURY MECHANISMS

Lipid peroxidation

- Free radicals "steal" electron from lipids on cell membrane
- Damages cell membrane, entire cell

Protein oxidation

- Free radicals oxidize proteins, including DNA, inside cell
  - DNA oxidation → mutations → cancer

DEFENSE AGAINST FREE RADICALS

Antioxidants

- E.g. vitamins A, C, E
- Eliminate free radicals by donating electrons

Metal carrier proteins

- E.g. transferrin for iron, ceruloplasmin for copper
- Bind, carry metals to prevent free radical production

Enzymes

- Eliminate various free radical species
  - Superoxide dismutase → superoxide
  - Catalase → hydrogen peroxide
  - Glutathione peroxidase → hydroxyl radical

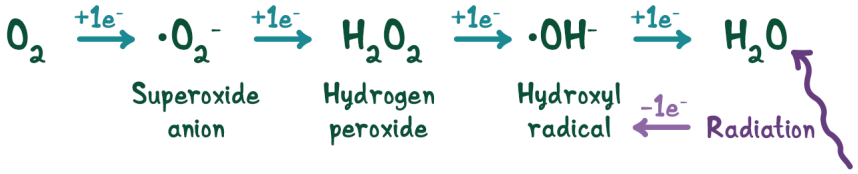

Figure 24.7 Oxygen is an example of a molecule that can become a free radical.

ISCHEMIA

osms.it/ischemia

- Reduction in blood flow to organ/tissue → oxygen shortage
  - Caused by blockage/compression of blood vessel

Arterial ischemia

- ↓ arterial blood flow → ↓ oxygen received
- E.g. *atherosclerosis*: plaque blocks arteries to heart → ischemic heart disease

Venous ischemia

- ↓ venous blood flow → ↓ drainage → ↓ blood flow → ↓ oxygen received
- E.g. *Budd–Chiari syndrome*: clot blocks hepatic vein → liver ischemia → edema/ hepatomegaly

Outcomes

- Sometimes, congestion → ↑↑ pressure → fluid forced out/edema
- ↓↓ oxygen → cell death (e.g. tissue necrosis, infarction)
  - *Ischemic penumbra:* ischemic but still viable tissue
  - *Collateralization:* growth of collateral vessels to serve ischemic tissue
- *Time to reperfusion:* time taken to re-establish perfusion before cells die
  - Short → cells survive → reversible
  - Long → cells die → irreversible

INFLAMMATION

osms.it/inflammation

- Immune response described by four key signs:
  - *Calor*: heat
  - *Dolor*: pain
  - *Rubor*: redness
  - *Tumor*: swelling
- May also involve "functio laesa" (AKA loss of function)
- Triggered by external, internal factors
- External
  - *Non-microbial:* allergens, irritants, toxic compounds
  - *Microbial:* virulence factors, pathogen associated molecular patterns (PAMPs)
- Internal
  - Damage associated molecular patterns (DAMPs)

Example process

- PAMPs, DAMPs recognized by pattern recognition receptors (PRRs) on immune cells
- Activate cells, sparking inflammatory response
- Mast cells contain granules with inflammatory mediators
  - E.g. histamine, serotonin, cytokines, and eicosanoids
- → separate endothelial cells on nearby capillaries
- Macrophages eat any invading pathogens
- Cytokines cause capillaries to enlarge, ↑ vascular permeability
- Endothelial cells release nitric oxide for vasodilation, ↑ vascular permeability
- Leukocytes, especially neutrophils, attracted through capillaries by chemokines, microbial products; squeeze through membrane
  - AKA extravasation
- Leukocyte follows gradient of inflammatory mediators

- Neutrophils phagocytose pathogens immediately before destroying themselves
- Antibodies bound to pathogens activate complement system
  - Aids in opsonization, kills pathogens by lysis
- Dendritic cells phagocytose pathogens, present antigens to T lymphocytes, activating adaptive immune system
- Ends with tissue repair

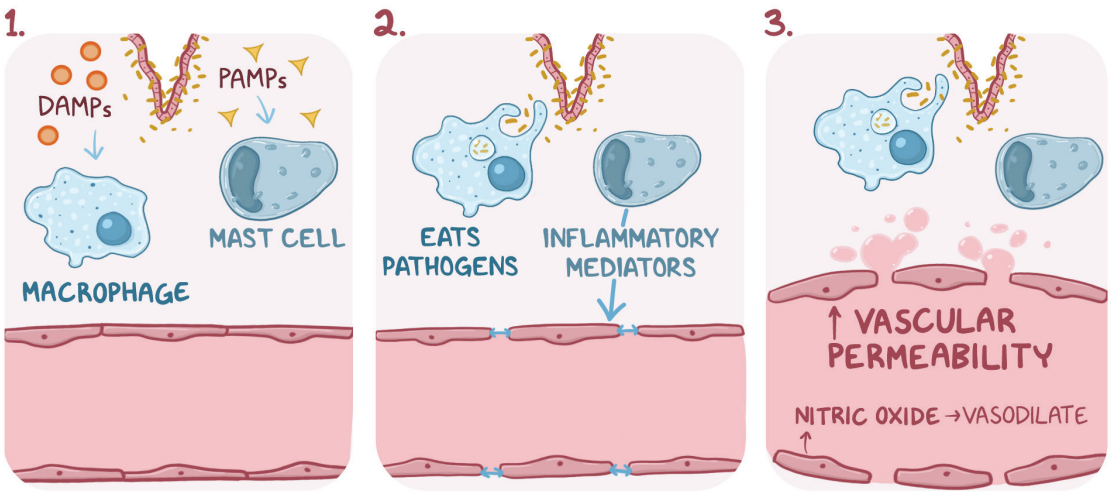

Figure 24.8 *1:* DAMPs and PAMPs activate immune cells. *2:* Macrophages phagocytose pathogens at the site of inflammation. Mast cells release inflammatory mediators that widen the distance between adjacent endothelial cells. *3:* Endothelial cells release nitric oxide → ↑ vasodilation, vascular permeability.

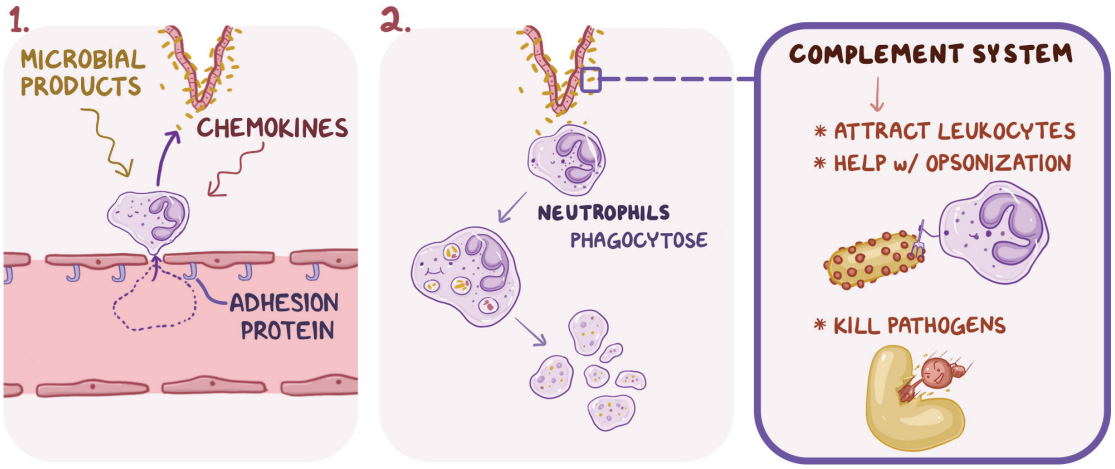

Figure 24.9 *1:* Neutrophils are the first leukocytes recruited during the acute inflammatory process. They squeeze through the gap between endothelial cells (extravasation) and follow the gradient of inflammatory mediators to the site of inflammation. *2:* Neutrophils quickly phagocytose pathogens. While this is happening, complement proteins are activated by the presence of pathogens and help with opsonization (they bind to microbes so leukocytes can more easily eat them). Some can also kill pathogens by forming a channel in their membranes.