Session Objectives

- Discuss and compare the cellular adaptations of **metaplasia, hyperplasia, hypertrophy, and atrophy**. Give examples of each.
- Discuss and distinguish various causes of **cell injury**.
- Discuss and distinguish the **reversible and irreversible events of cell injury from a cellular, functional, and morphological perspective**.
- Describe and compare the **different types of necrosis** and discuss the **mechanism of apoptosis and its differences from necrosis.**
- Discuss and describe **some cellular accumulations** and their significance.

PATHOLOGY - Introduction

- **Study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease**
- **General Pathology v. Systemic Pathology**
  - **causation *(etiology)***
  - **biochemical and molecular mechanisms *(pathogenesis)***
  - **associated structural *(morphologic changes)* and functional alterations in cells and organs**
  - **resulting clinical consequences *(clinical manifestations)***

Hypertrophy

- Increase in size of cells, results in increased size of organ; **no new cells**

- **Increased production of cellular protein**; results from activation of growth factors and direct effects of mechanical force on pathways which stimulate protein synthesis

  - **Physiologic** – increased functional demands, stimulation by growth factors, hormones
    - examples – uterine growth during pregnancy, skeletal muscle in response to increased demand – e.g body building
  - **Pathologic** – examples – heart in hypertension, aortic stenosis

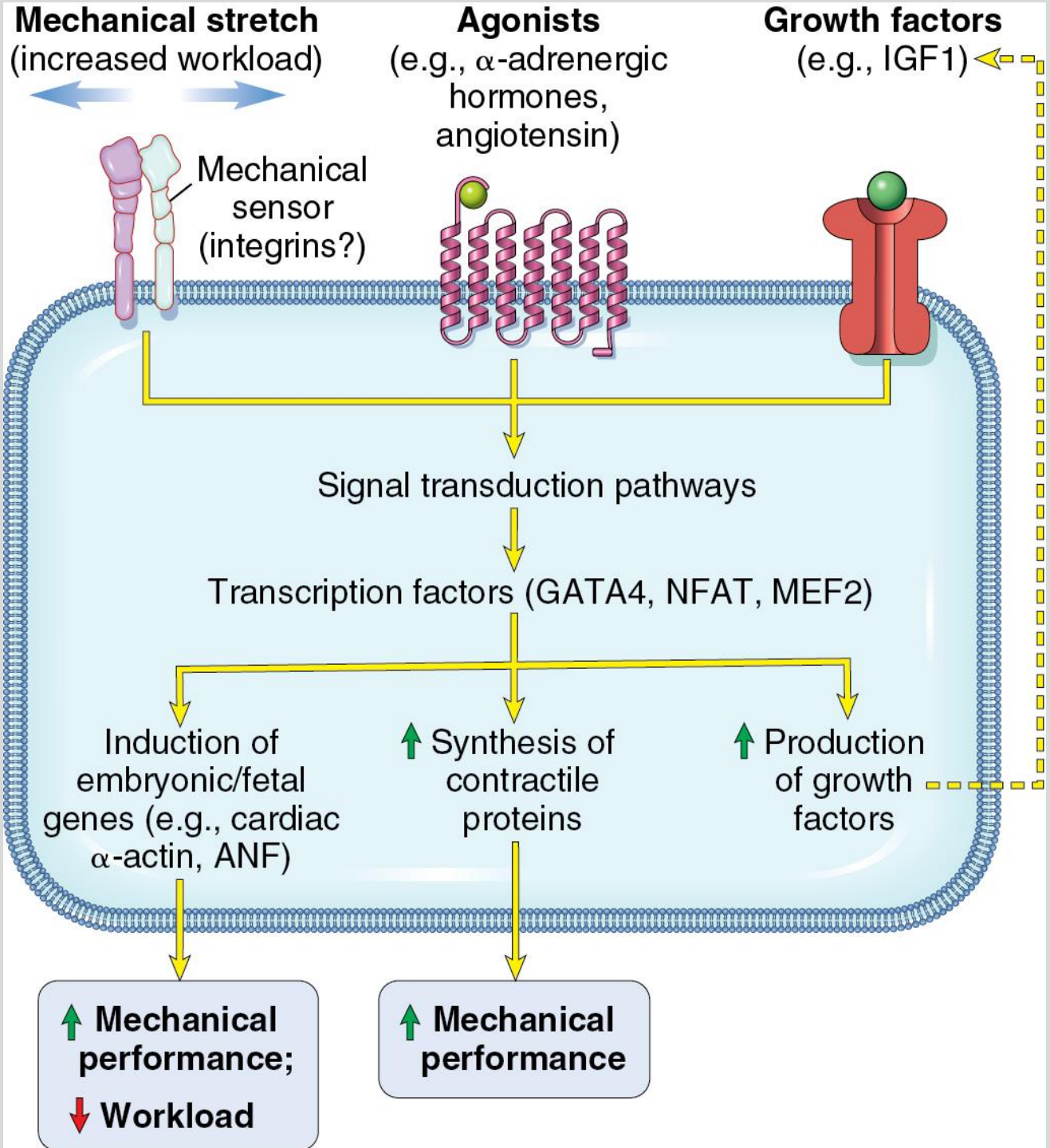

Fig. 2.26 Biochemical mechanisms of myocardial hypertrophy. Mechanical sensors appear to be the major triggers for physiologic hypertrophy, and agonists and growth factors may be more important in pathologic states.

Robbins and Cotran, Pathologic Basis of Disease, 11th ed. 2025

Hyperplasia

- **Increased number** of cells in organ or tissue in response to stimulus
- Can only occur in tissue if cells are **capable of dividing**
- **Hyperplasia and hypertrophy may occur together in some tissue types (not permanent)**
- **Result of growth factor–driven proliferation of mature cells and, in some cases, by increased output of new cells from tissue stem cells**
- **Physiologic –due to hormones or growth factors when needed to increase functional capacity of hormone-sensitive organs, or when there is need for compensatory increase after damage or resection** (breast at puberty/pregnancy, compensatory hyperplasia of liver)
- **Pathological** – e.g, inappropriate or excessive hormonal (endometrial hyperplasia, BPH) or growth factors acting on target cells

Increased cell division associated with hyperplasia increases risk of acquiring genetic aberrations that can drive unrestrained proliferation and give rise to cancer

- **Integrated stress response:** Network of intracellular signaling pathways: modulate gene expression and protein synthesis for cells to adapt to cell injury, respond to stressors

- **Unfolded protein response (ER stress):** Accumulation of misfolded proteins in the ER activates stress adaptive mechanisms; if unchecked, can trigger cell death via apoptosis

- **Autophagy:** Process in which a cell eats its own contents (response to stress in **physiologic** states (e.g., aging and exercise) and in **pathologic** processes (e.g., hypoxia, oxidative stress, organelle, and membrane damage).
    - Nucleation and formation of an isolation membrane, phagophore
    - Formation of a vesicle, the **autophagosome** (regulated by many proteins), from the isolation membrane: intracellular organelles and cytosolic structures sequestered
    - Maturation of autophagosome by fusion with lysosomes, to deliver digestive enzymes that degrade contents of the autophagosome

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- Damage to mitochondria causes decreased oxidative phosphorylation and therefore decreased ATP
- Reduced Na/K pump leads to cell swelling (hydropic change, vacuolar degeneration) – reversible
- Increase in anaerobic glycolysis – decreases glycogen, increases lactic acid, decreases pH (chromatin clumping)
- Decrease in protein synthesis
- Failure of CA pump----Ca enters cell causing membrane and nuclear damage via activation of phospholipases, proteases, endonuclease, and ATPases
- Denaturation of intracellular proteins, enzymatic digestion of cell, contents leak out and elicit inflammation

Robbins and Cotran, Pathologic Basis of Disease, 10th ed., 2020, Ch. 2

- Free radicals: unstable - decay spontaneously
- Cells have multiple nonenzymatic and enzymatic mechanisms to remove free radicals and minimize injury:
  - *Antioxidants* either block free radical formation or inactivate (e.g., scavenge) free radicals, e.g, lipid-soluble vitamins E and A, ascorbic acid and glutathione
  - Free *iron* and *copper* can catalyze formation of ROS. Normally, reactivity of these metals is minimized by binding to storage and transport proteins (e.g., transferrin, ferritin, lactoferrin, and ceruloplasmin)
  - Several *enzymes* act as free radical–scavenging systems and break down H_2O_2 and $O2\bullet^-$:
  - 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 $O2\bullet^-$ to H_2O_2 ($2\ O2\bullet^- + 2H \rightarrow H_2O_2 + O_2$).
  - 3. *Glutathione peroxidase* also protects against injury by catalyzing free radical breakdown ($H_2O_2 + 2GSH \rightarrow$ GSSG [oxidized glutathione] + $2H_2O$).

Apoptosis

- Type of cell death induced by tightly regulated suicide program: **cells destined to die activate intrinsic enzymes (caspases) that degrade cellular DNA and nuclear and cytoplasmic proteins**
- **Regulated mechanism of cell death:** eliminates unwanted and irreparably damaged cells, with least possible host reaction
- Characterized by enzymatic degradation of proteins and DNA, initiated by **caspases**, and recognition and removal of dead cells by phagocytes
- Apoptotic cells break up into plasma membrane–bound fragments (apoptotic bodies), contain parts of cytoplasm and nucleus

Robbins and Cotran, Pathologic Basis of Disease, 11th ed., 2025

Apoptosis: Physiological

- **Normal phenomenon to eliminate cells no longer needed, or mechanism to maintain a constant number of various cell populations in tissues.**

- *Removal of supernumerary cells (excess of required number) during development*
- *Involution of hormone-dependent tissues on hormone withdrawal, (e.g,* endometrial cell breakdown during the menstrual cycle)
- *Cell turnover in proliferating cells populations, e.g.,* epithelial cells in intestinal crypts to maintain constant cell numbers (*homeostasis*).
- *Elimination of lymphocytes that do not produce functional antigens receptors (e.g* immature lymphocytes in the bone marrow and thymus and germinal center B cells)
- *Elimination of potentially harmful self-reactive lymphocytes* to prevent autoimmunity
- Death of host cells that have served their useful purpose, e.g., neutrophils in an *acute inflammatory response,* and lymphocytes at the end of an *immune response* .

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Apoptosis: **pathological**

- **Apoptosis eliminates cells that are injured beyond repair** without eliciting a host reaction, limiting collateral tissue damage

- *DNA damage* - protective by preventing survival of cells with DNA mutations that can lead to malignant transformation
- *Accumulation of misfolded proteins* - cell death triggered by improperly folded intracellular proteins and the subsequent ER stress response
- Certain *infections, esp.* viral infections, because of the virus itself (e.g., adenovirus and HIV infections) or host immune response (as in viral hepatitis)
  - Important host response to viruses: cytotoxic T lymphocytes (CTLs) specific for viral proteins induce apoptosis of infected cells in an attempt to eliminate reservoirs of infection
  - The same CTL-mediated mechanism is responsible for killing tumor cells, cellular rejection of transplants, and tissue damage in graft-versus-host disease.
- May also contribute to *pathologic atrophy in parenchymal organs after duct obstruction, e.g.,* in the pancreas, parotid gland, and kidney

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Apoptosis - Mechanisms

- Results from activation of enzymes called **caspases**
- **Initiation** phase - some caspases become catalytically active and cause cascade of other caspases
- **Execution** phase - terminal caspases trigger cellular fragmentation and demise
- Regulation of caspases depends on finely tuned balance between amount and activity of **pro-apoptotic and anti-apoptotic proteins**

- **Two distinct pathways converge on caspase activation: the mitochondrial pathway and the death receptor pathway**

- Pathways intersect, but generally induced under different conditions, involve different initiating molecules, and serve distinct roles in physiology and disease

- Robbins and Cotran, Pathologic Basis of Disease, 11th ed. 2025

Apoptosis – Extrinsic (Death Receptor Initiated) Pathway

- Initiated by engagement of **plasma membrane death receptors**
- Death receptors = members of TNF receptor family that contain a cytoplasmic domain involved in protein-protein interactions: death domain needed for delivering apoptotic signals

- Best-known death receptors are the type 1 TNF receptor (TNFR1) and related protein called Fas (CD95),

- Extrinsic apoptosis pathway can be inhibited by a protein, FLIP - binds to pro-caspase-8, blocking FADD binding.

Death receptor (extrinsic) pathway eliminates self-reactive lymphocytes and is a mechanism of cell killing by cytotoxic T lymphocytes

Other mechanisms of cell death

- **Necroptosis** resembles necrosis morphologically, but like apoptosis is genetically controlled form of cell death
- Necroptosis is triggered by ligation of TNFR1 and by proteins found in RNA and DNA viruses.
- **Caspase independent** and depends on RIPK1–RIPK3 complex
- RIPK1–RIPK3 signaling leads to phosphorylation of MLKL, which then forms pores in the plasma membrane
- Release of cellular contents evokes an inflammatory reaction like necrosis

- **Pyroptosis** occurs in cells infected by **microbes**.
- Involves activation of caspases, which cleave and activate pore-forming function of GSDMD, resulting in lytic death of infected cell and release of inflammatory mediators

- **Ferroptosis** is an iron-dependent pathway of cell death induced by lipid peroxidation

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Cellular accumulations

Main mechanisms leading to abnormal intracellular accumulations:

•*Inadequate removal* of a normal substance due to defects in production and transport, e.g., fatty change (steatosis) in the liver

•Accumulation of an endogenous substance because of genetic or acquired *defects in its folding, transport, or secretion*

•*Failure to degrade* a metabolite due to inherited enzyme deficiencies, typically lysosomal enzymes.

•Deposition and accumulation of an *abnormal exogenous substance* when the cell has neither the enzymatic machinery to degrade the substance nor the ability to transport it to other sites

- **Lipid** – steatosis – reversible cell injury, especially seen in liver
- **Protein** – normal or abnormal – example of abnormal: amyloid
- **Pigments** - anthracosis, melanin, hemosiderin, lipofuscin
- **Lipofuscin** – "wear and tear" pigment: polymer of lipids and phospholipids in complex with protein may derive from lipid peroxidations, free radical injury