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Cellular Injury and Adaptation: Bridging Basic Mechanisms with Pathological Outcomes

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Abstract- Cell injury and adaptation are key processes that influence a cell's fate when faced with stress and underlie numerous pathological conditions. Long considered crucial in pathology, understanding these mechanisms is increasingly important for addressing human diseases and advancing therapies. Cell injury can be classified as either reversible or irreversible and categorized as acute or chronic, with causes that include ischemia, toxins, infections, and trauma. Key mechanisms involve ATP depletion, mitochondrial dysfunction, oxidative stress, calcium imbalance, endoplasmic reticulum stress, membrane damage, and DNA/protein alterations, leading to specific morphological and biochemical changes such as cellular swelling and enzyme release.The transition from injury to cell death occurs through various mechanisms, such as necrosis, apoptosis, necroptosis, pyroptosis, and ferroptosis. Meanwhile, adaptive responses like hypertrophy, hyperplasia, atrophy, and metaplasia can help cells endure stress but may lead to disease if they become unregulated. This relationship between injury and adaptation is prominent in conditions like myocardial infarction, strokes, chronic liver disease, and cancer. Recent clinical studies have identified biomarkers such as troponins and LDH, and treatments now focus on addressing oxidative stress, maintaining mitochondrial function, and resolving ER stress.Innovative strategies are being developed in gene editing, stem cell treatments, and nanomedicine. Future outlooks highlight the importance of omics profiling, systems biology, and tailored medicine for enhancing diagnosis and treatment. Grasping the equilibrium between cellular damage and adaptation is key to connecting fundamental mechanisms with disease development and new therapies.

Keywords - Cell Injury, Cell Adaptation, Hypertrophy, Hyperplasia, Atrophy, Metaplasia, Endoplasmic Reticulum Stress, Necrosis, Apoptosis, Ferroptosis, Gene Editing, Nano medicine.

I. Introduction

Definations

When a cell cannot cope with heightened stress, it sustains damage. This injury can be reversed up to a specific point, after which it leads to cell death. Cell injury refers to the series of processes that take place when a cell cannot cope with stressors from within or outside its environment [1]. The cell's reaction to such damaging stimuli determines if the injury is reversible, permitting recovery, or irreversible, resulting in cell death.

Adaptation is defined as a lasting alteration in cellular phenotype resulting from internal influences or microenvironmental stimuli. Factors in the microenvironment that contribute to adaptation include modifications in the extracellular matrix (ECM), availability of secretory substances (such as cytokines or hormones), and various electrical or mechanical forces, among others [2].

History

Scientific progress frequently arises from the integration of groundbreaking technologies with established ideas. A prime example of this is the cell theory, which is central to both biology and medicine. Rudolph Virchow and his associates were pivotal in solidifying this theory within biology and pathology. Simultaneously, John F. R. Kerr and his group introduced the concept of apoptosis, which significantly impacted contemporary research on cellular injury. The roots of pathological research can be traced to Giovanni Battista Morgagni, who released "De Sedibus et Causis Morborum per Anatomen Indagatis" in 1761. Influential contributors to the clinical aspects of pathology include French researchers René Laënnec and Marie Francois Xavier Bichet, along with English physician Matthew Baillie.

The discipline thrived particularly in German-speaking countries, primarily due to the pioneering work of Carl von Rokitansky, a leading pathologist who conducted around 30,000 autopsies and founded a renowned Austrian pathology academy. The 19th century saw remarkable advancements in pathology, spurred by technological progress and fresh biological understandings. In 1848, botanist Mathias Jakob Schleiden claimed that all plant tissues are made up of cells or derivatives thereof. The subsequent year, zoologist Theodore Schwann made a comparable assertion regarding animals, detailing that cells comprise nuclei, cytoplasm, membranes, and various organelles. Eventually, advancements clarified the structure of the nervous system, identifying specialized cells such as neurons and glial cells. Rudolf Virchow was crucial in leveraging developments in microscopy and cell theory for medical applications.

As medical knowledge progressed, pathology evolved into the examination of diseases, their origins, and impacts, defining illness as any condition that compromises quality or duration of life. From the 17th to the early 19th centuries, humoral pathology reigned supreme, reflecting adaptations of ancient Galenic theories. By the late 18th and 19th centuries, neural pathology emerged, positing that the nervous system's functionality governs all physiological and pathological processes. As a result, pathology reached a transformative point, adopting a new perspective to engage with ongoing debates.

Revelance to human disease and therapeutic research

Cellular damage and the factors influencing a cell's fate whether it survives, adapts, or dies are central to nearly all major human diseases, making them valuable targets for treatment development. Impaired ATP production, mitochondrial dysfunction, oxidative stress, imbalanced cell death processes (like apoptosis and necroptosis), persistent inflammation, and reduced repair mechanisms contribute to the pathology seen in conditions like cardiovascular disease, neurodegeneration, cancer, liver and kidney failure, as well as various acute injuries (e.g., ischemia-reperfusion). Progress has been made In targeting these mechanisms, leading to potential therapies, including

antioxidants and regenerative approaches, although challenges such as delivery, timing, injury variability, and side effects remain in clinical applications.

II. Classification of CelI injury

Cellular injury, commonly referred to as cell damage, is a key pathological event associated with numerous human diseases. Traditionally, classification was based on morphological characteristics; however, recent progress has leaned towards incorporating biochemical and functional aspects. According to *Mechanisms and Morphology of Cellular Injury, Adaptation, and Death* (PMC), all damaging stimuli ultimately affect four key biochemical mechanisms: depletion of ATP, disruption of membrane integrity, dysregulation of biochemical pathways, and damage to DNA. These disturbances can drive cells toward adaptation, degeneration, or cell death.

Reversible vs irreversible injury
Reversible cell injury refers to a transient and non-fatal reaction to an external stressor, enabling the cell to regain its normal function once the stressor is eliminated. On the other hand, irreversible cell injury results in permanent damage and eventually causes cell death, typically via necrosis or apoptosis, due to the extent or duration of the harm being excessive. The transition from reversible to irreversible injury is commonly known as the ”point of no return,” characterized by significant damage to both mitochondria and cell membranes.

Irreversible cell injury marks the threshold beyond which a cell cannot recover, as intense or extended stress causes lasting damage and ultimately results in cell death. Key indicators of this condition include significant membrane damage and permanent mitochondrial dysfunction. This final outcome arises from multiple concurrent failures that surpass the cell’s ability to repair itself.

Comparison of reversible and irreversible cell injury

Feature	Reversible Cell Injury	Irreversible Cell Injury
Stimulus	It is mild and transient stressor	It is severe and persistent stressor
Reversibilty	Recovery is possible if injurious stimulus is removed	The damage is permanent and it causes cell death
ATP Levels	It is characterized by decreased ATP production due to mitochondrial dysfunction	It involves severe and prolonged ATP depletion that the cell cannot recover from

Morphological Changes	Cellular Swelling: It causes entry of water due to impaired ion pumps is earliest change. Fatty change: Accumulation of lipid vacuoles in cytoplasm, especially in hypoxic injury. Membrane blebbing: Outpouching of the plasma membrane.	Massive swelling: Severe mitochondrial and organelle swelling. Membrane Damage: Influx of calcium and loss of membrane integrity. Nuclear Changes: Pyknosis (shrinkage), karyorrhexis (fragmentation), and karyolysis (dissolution).
Mitochondria	Swelling and small, amorphous densities may form, but it is reversible.	Marked swelling, with large, flocculent (fluffy) densities, and rupture, leading to leakage of enzymes like cytochrome C.
Main Pathways	The cell's adaptive mechanisms are working but are being pushed to their limits	The two primary pathways are necrosis (pathological, with inflammation) and apoptosis (programmed cell death)

Accidental vs regulated cell death

Accidental cell death (ACD) occurs swiftly and uncontrollably due to severe physical or chemical stressors such as injury, high temperatures, osmotic imbalances, or exposure to detergents. This process unfolds without specific signaling pathways and cannot be pharmacologically halted once it begins. The typical morphological characteristics include necrosis, cell swelling, membrane damage, release of cellular contents, and significant inflammation.

Regulated cell death (RCD) refers to a genetically and biochemically regulated mechanism carried out by specific signaling pathways. This process can frequently be postponed or blocked by certain inhibitors or genetic modifications. RCD includes various types, such as apoptosis, necroptosis, pyroptosis, ferroptosis, and parthanatos. Current guidelines and insights are provided by the Nomenclature Committee on Cell Death (NCCD) and recent literature.

Dimension	Accidental cell death (ACD)	Regulated cell death (RCD)

Trigger	Extreme, acute insults (mechanical, heat, toxins at high dose)	Receptor/ligand signals, metabolic stress, pathogens, ROS/lipid peroxidation, DNA damage
Control	No upstream control; execution is biophysical	Driven by signalling cascades; genetically encoded effectors
Drug sensitivity	Not blockable by targeted inhibitors	Often blockable (e.g., casoase, RIPK1/3, GSDMD, lipoxygenase/GPX4 axes)
Kinetics	Very rapid, castaatropi	Ranges from minutes to hours; has definable checkpoints
Morphology	Swelling membrane rupture (necrotic morphology)	Subroutine-specific: apoptotic bodies;MLKL pores; GSDMD pores; shrunken/condensed or swollen mitochondria; lipid peroxide damage
Immunology	Highly pro-inflammatory by passive DAMP release	Varies: apoptosis (often tolerogeniic); necroptosis/pyroptosis (inflammatory); ferroptosis (context-dependent)

Acute vs chronic injury

Acute injury describes a sudden and often intense damage to cells caused by factors like lack of oxygen, blood flow issues, harmful substances, or physical harm. When the damage is significant, it can lead to cell death, typically through necrosis; however, if the injury is less severe or quickly resolved, it may lead to reversible changes, such as swelling in the cells.

Chronic injury develops from ongoing or repeated non-lethal damage, which triggers inappropriate responses, enduring functional deficits, and changes in tissue structure. In the context of tissue, this is frequently seen as fibrosis a characteristic of prolonged injury marked by continuous inflammation and repair processes that lead to an overaccumulation of extracellular matrix and altered tissue architecture.

Comparison of Acute Cell Injury and Chronic Cell Injury

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Aspect	Acute Cell Injury	Chronic Cell Injury
Timeframe	Minutes to days	Weeks to years
Cause	Sudden , severe insults (ischemia toxins)	Prolonged, repeated, or unresolved stress
Key Mechanism	ATP depletion, ionic imbalance, ROS, inflammation	Fibrosis, maladaptive repair, persistent inflammation
Cellular Responses	Reversible change → necrosis	Persistent damage → tissue remodeling / fibrosis
Outcome	Recovery or cell death	Functional Impairment and scarring

III. Mechanisms of cell injury

The processes behind cell injury involve the molecular and biochemical routes by which detrimental factors disturb cellular equilibrium, resulting in either reversible or irreversible harm. Various initiating factors such as lack of oxygen, toxic substances, infections, or physical injuries share several underlying pathogenic mechanisms associated with cell injury. These mechanisms form a complex interplay that often enhances each other's effects, influencing whether a cell survives or succumbs to death. [1]

ATP depletion

A cell's pool of ATP serves as the primary chemical energy source that fuels processes such as ion transport, biosynthetic activities, movement, and cellular repair. When the generation of ATP primarily through mitochondrial oxidative phosphorylation in tissues that require oxygen is insufficient to satisfy cellular demands, due to conditions like hypoxia or ischemia, dysfunction in the respiratory chain, or damage from toxins, a significant energy crisis ensues. This leads to a decrease in ATP levels and an increase in AMP and ADP, resulting in the loss of the energy necessary for essential cellular functions. This energy failure is a key factor contributing to various early and later manifestations of cellular injury. [18,19].

The loss of oxidative phosphorylation (OXPHOS) is a significant contributor to this situation. When oxygen supply is disrupted (ischemia) or when there is harm to the electron transport chain complexes, the proton-

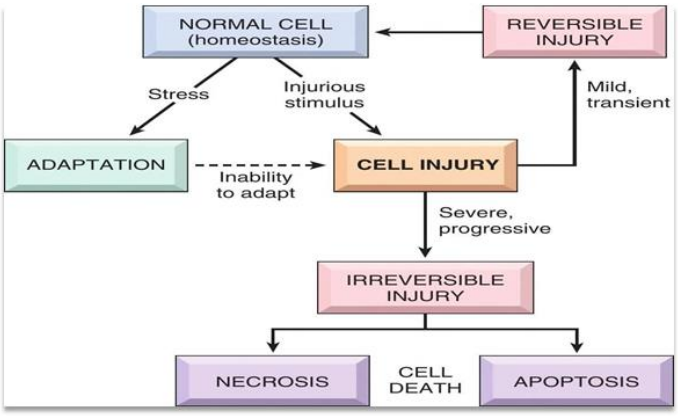

Figure 1: Mechanism of cell injury [Reference: Kumar V, Abbas AK, Aster JC, Debnath J, Das A. Robbins, Cotran & Kumar pathologic basis of disease. 11th ed. Philadelphia: Elsevier; 2025.]

motive force and ATP production diminish. Mitochondrial dysfunction is therefore central to ATP depletion in many clinically significant injuries.[19].

In cases of severe respiratory failure, the F_1F_o-ATP synthase enzyme can operate in reverse, hydrolyzing ATP to pump protons, thereby depleting the already limited ATP supply. Research indicates that blocking this reverse activity of ATP synthase can help preserve ATP levels and maintain cellular health in specific disease models. This backward operation significantly accelerates ATP depletion during mitochondrial dysfunction.[20]

In addition, reactions that consume NAD^+ and ATP, like those involving PARP, can contribute to ATP loss. Severe DNA damage, such as that caused by reactive oxygen species (ROS), activates PARP enzymes that use NAD^+, subsequently disrupting glycolysis and mitochondrial metabolism, which intensifies energetic failure.[19,21]
Cells, particularly in the heart and kidneys, depend on energy buffering systems like creatine kinase/phosphocreatine in muscle and compartmentalized ATP reserves to compensate for energy shortages. However, when these buffering systems are compromised or reduced (as seen during ischemic events or chronic diseases), temporary declines in ATP can evolve into ongoing crises.[18]

Failure of ion pumps, such as Na^+/K^+-ATPase and Ca^{2+}-ATPases, results in the buildup of intracellular sodium and calcium, leading to water influx and consequent cellular swelling, disruption of membrane polarity, and swelling of organelles. These ionic disturbances also depolarize mitochondria, further inhibiting ATP production. [18,19]

In response to compromised OXPHOS, cells may resort to anaerobic glycolysis to generate ATP, which results in lactic acid production. The resulting acidosis alters enzyme function, contributes to chromatin clumping and membrane damage, and hampers recovery following reperfusion. Recent reviews on stroke and brain ischemia

highlight that this shift toward enhanced glycolysis initially serves an adaptive purpose but can eventually become detrimental. [22]

Low ATP levels also impair protein synthesis and membrane repair. A reduction in ATP causes ribosomes to detach from the rough endoplasmic reticulum, leading to decreased protein and phospholipid production necessary for membrane integrity. Consequently, membranes become more vulnerable to attacks by phospholipase and ROS. Excess calcium and enzyme activation occur when ATP is in short supply, leading to further cellular complications.[19]

Oxidative stress and reactive oxygen

Reactive oxygen species (ROS) comprise a diverse group of reactive molecules containing oxygen, including radicals such as the superoxide anion ($O_2^{\bullet -}$) and hydroxyl radical (•OH), along with non-radicals like hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$). These molecules are produced through normal physiological activities, including mitochondrial respiration, NADPH oxidase activity, xanthine oxidase function, nitric oxide synthase activity, and peroxisomal metabolism, occurring within various cellular compartments such as mitochondria, peroxisomes, the endoplasmic reticulum, and the cytosol.[23,24]

At normal physiological levels termed “oxidative eustress” ROS serve as signaling molecules, influencing vital processes such as cell proliferation, differentiation, immune responses, and gene expression. They exert their effects by reversibly oxidizing protein thiols (e.g., through peroxiredoxin-mediated mechanisms), activating several signaling pathways, including MAPK, PI3K/Akt, and transcription factors such as Nrf2, NF-κB, HIF-1α, and AP-1.[23,25]

Nonetheless, when the production of ROS exceeds the capacity of antioxidant defenses, it results in oxidative stress, also known as “oxidative distress,” which can harm essential biomolecules such as lipids, proteins, and DNA leading to cellular dysfunction and damage.[25]

Lipid peroxidation occurs when ROS initiate chain reactions with polyunsaturated fatty acids, producing lipid peroxides that compromise membrane integrity and yield toxic by-products like malondialdehyde and 4-hydroxy-2-nonenal.

In terms of protein oxidation, structural and enzymatic proteins become oxidized, risking misfolding or inactivation and triggering responses associated with unfolded proteins.

Regarding DNA and genomic integrity, ROS can induce base modifications including 8-oxo-guanine and cause strand breaks and cross-links. Such damage can result in mutations, genomic instability, and ineffective repair mechanisms, such as the formation of γ-H2AX foci in response to double-strand breaks.

Oxidative stress arises when there is an imbalance between ROS production and the capacity of antioxidants. While ROS are crucial for physiological signaling at regulated levels, excessive ROS can cause molecular damage, contributing to the development of diseases, aging, and cell death. Understanding the dual nature of ROS alongside how

antioxidant systems and regulatory pathways like Nrf2 manage their effects is essential for developing therapeutic strategies for cancer, neurodegenerative disorders, cardiovascular diseases, and aging.

Disruption of calcium homeostasis

Cells carefully regulate cytosolic calcium (Ca^{2+}) levels, maintaining them at extremely low nanomolar concentrations while allowing higher levels in the extracellular environment and within organelles such as the endoplasmic reticulum (ER) and mitochondria. This significant concentration disparity enables Ca^{2+} to act as a rapid and flexible second messenger. However, disruptions to this gradient or failures in the intricate regulatory mechanisms that control Ca^{2+} which include various channels, pumps, exchangers, and buffering agents can lead to chronic increases in Ca^{2+} within the cytosol and organelles. Such abnormal increases can trigger harmful responses rather than the usual physiological signaling pathways. Recent literature emphasizes the important roles of the ER and mitochondria as major Ca^{2+} stores and as communicators within cellular environments. The release of Ca^{2+} from the ER, facilitated by inositol trisphosphate receptors (IP_3Rs) and ryanodine receptors, alongside mitochondrial uptake through the mitochondrial calcium uniporter (MCU) complex, typically occurs in a coordinated manner to regulate signaling, though this coordination can falter during stressful conditions.[26]

Multiple factors can lead to calcium dysregulation. Injuries to the plasma membrane due to trauma, pore formation, toxin effects, or substantial ATP depletion (such as during ischemic events) can allow extracellular Ca^{2+} to enter cells. Other stressors, including ER stress, oxidative modifications to calcium-regulating proteins, and impaired functionality of Ca^{2+} channels and pumps such as reduced effectiveness of sarcoplasmic reticulum calcium ATPase (SERCA) or plasma membrane calcium ATPase (PMCA), increased activity of store-operated calcium entry, or irregular activation of receptor-operated channels can further prompt the release of Ca^{2+} from the ER into the cytosol. Recent research has pinpointed stress-induced post-translational modifications of proteins like SERCA, IP_3Rs, STIM/Orai, and other regulatory components as critical contributors to the persistent release of Ca^{2+} from the ER.[27,28]

Mitochondria serve a dual purpose in this scenario. While they can take up cytosolic Ca^{2+} for short periods, excessive accumulation can be harmful. High levels of Ca^{2+} in mitochondria, especially in the presence of reactive oxygen species (ROS), can lead to the opening of the mitochondrial permeability transition pore (mPTP). This results in the loss of mitochondrial membrane potential, cessation of ATP production, release of pro-apoptotic factors like cytochrome c, and ultimately cell death, whether through apoptosis or necrosis, depending on the cell's energy status. Recent reviews on the mechanisms and structure of the mPTP highlight its sensitivity to Ca^{2+} and its vital role in the transition from Ca^{2+} overload to irreversible mitochondrial damage. The biochemical effects of prolonged increases in Ca^{2+} levels are extensive.[29,30]

Endoplasmic Reticulum (ER) stress & Unfolded protein response

Endoplasmic reticulum (ER) stress occurs when the ER becomes overwhelmed by an excess of unfolded or misfolded proteins, which may arise from various factors such as genetic mutations, low oxygen levels, oxidative damage, lack of nutrients, or imbalanced calcium storage.

This situation triggers an evolutionary conserved adaptive mechanism known as the unfolded protein response (UPR), which aims to restore balance within the cell. However, if this stress continues, it may lead to inflammation and cell death.[31,32] The UPR involves three ER membrane sensors PERK, IRE1α, and ATF6 that are normally kept inactive by the chaperone BiP/GRP78. When misfolded proteins accumulate, BiP dissociates, allowing PERK to dimerize and phosphorylate eIF2α. This process reduces overall protein translation while promoting the expression of ATF4, which may activate the pro-apoptotic factor CHOP. Additionally, IRE1α undergoes oligomerization, splicing XBP1 mRNA into its active form, XBP1s, which enhances gene expression for chaperones and ER-associated protein degradation (ERAD), and initiates regulated IRE1-dependent decay (RIDD) and inflammatory pathways. ATF6 is also transported to the Golgi for cleavage, resulting in the release of a fragment that boosts folding and the capacity for ERAD.[33,34] Collectively, these mechanisms alleviate the burden on the ER, improve protein folding capabilities, and promote the clearance of misfolded proteins. However, when the stress is intense or prolonged, the protective responses can become overwhelmed and lead to cell death through various pathways involving CHOP, caspase activation, and sustained ATF6 activity, potentially resulting in apoptosis, inflammatory cell death, or cellular senescence depending on the situation.[35,36]

The relationship between ER stress and the UPR Is linked to a variety of human diseases. Chronic activation of the UPR is associated with neurodegenerative diseases (like Alzheimer's and Parkinson's) that lead to neuronal damage due to disrupted proteostasis, metabolic disorders and β-cell dysfunction in diabetes, cancer-related survival and therapy resistance, and chronic inflammation connected to aging through persistent cytokine and inflammasome signaling.[37,38,39] Given that the UPR plays both protective and harmful roles, recent research (2021–2025) has aimed at selectively modulating different branches of the UPR. This includes developing small molecules to inhibit PERK or IRE1 RNase activity, using chemical chaperones to promote protein folding, and strategies to restore ER proteostasis or prevent harmful inflammasome activation. These approaches are viewed as potential therapeutic options though their efficacy is context-dependent, with a focus on timing, specific tissues, and minimizing interference with normal UPR signaling identified as key challenges for translation into clinical applications.[40,41]

Membrane Damage and loss of cellular integrity

Cell membranes, including both plasma and organellar types, face numerous threats from mechanical, chemical, and biochemical factors. One significant biochemical mechanism of membrane damage is lipid peroxidation, which is initiated by reactive oxygen species (ROS) and influenced by iron-mediated Fenton reactions. This process disrupts the physical characteristics of phospholipids, generates harmful aldehydes (such as 4-HNE and MDA), increases the permeability of membranes, and can lead to membrane rupture hallmarks of ferroptosis and other oxidative damage.[42,43]

Mechanical stresses, including trauma, shear forces, elevated temperatures, and agents that form pores (like microbial toxins and the complement membrane attack complex), compromise the integrity of the bilayer and facilitate uncontrolled ion movement.

Additionally, disruption of the cytoskeleton (through the collapse of actin and myosin or loss of connections between the membrane and cytoskeleton) enhances membrane vulnerability, making it more susceptible to rupture under stress. Recent studies have indicated that cytoskeletal breakdown correlates with progressive membrane failure in various regulated cell death processes.[44,45]

Moreover, lysosomal membrane permeabilization (LMP) resulting from lipid peroxidation, iron buildup, or detergent exposure leads to the release of cathepsins and hydrolases into the cytoplasm, exacerbating proteolytic and oxidative harm to membranes and other cellular components. LMP has emerged as a crucial precursor event in certain injury pathways and in the mechanisms of ferroptosis. [46,47]

When the plasma membrane ruptures or even sustains minor defects, it quickly disrupts ionic gradients: sodium (Na^+) and calcium (Ca^{2+}) ions surge into the cell, while potassium (K^+) exits, resulting in cell swelling, osmotic stress, and calcium overload. Increased cytosolic calcium activates phospholipases, calpains, and endonucleases, which further degrade membranes, cytoskeletal elements, and DNA, initiating a cycle of escalating damage. At the same time, the disruption of membrane potential and ion gradients debilitates mitochondria and ATP generation, propelling the cell towards irreversible necrosis from a state of reversible injury.[43,44]

In the context of ferroptosis, extensive lipid peroxidation within membranes alters their structure and permeability, often leading to visible rupture; oxidized phospholipids interfere with ion regulation and the functionality of membrane proteins, ultimately resulting in destabilization of the plasma membrane.[48,49]

The rupture of lysosomes releases hydrolases that break down intracellular components and can instigate additional membrane damage; even minimal or partial LMP may trigger inflammation by releasing damage-associated molecular patterns (DAMPs).[50,51]

Cells have sophisticated and multi-faceted repair mechanisms that can effectively reseal or remodel membrane damage if it is sufficiently limited in duration or extent:
- Calcium-induced lysosomal exocytosis: This process allows for the rapid fusion of lysosomal membranes with the plasma membrane, supplying material to patch up lesions.[52

- ESCRT-III-mediated scission and shedding: The ESCRT machinery can remove sections of damaged membranes and aid in their resealing.[53]
- Involvement of proteins such as annexins, dysferlin, MG53/TRIM72, and synaptotagmins: These proteins play crucial roles in membrane repair processes.[54,55]

DNA and Protein damage

DNA faces constant threats from both internal and external sources, resulting in a variety of damages ranging from minor alterations such as the oxidation of guanine to 8-oxo-G, to more severe issues like single-strand breaks, bulky adduct formations, and the highly detrimental double-strand breaks (DSBs). Oxidative lesions, including 8-oxoguanine, not only act as mutagens (encouraging G→T transversions) but are also

increasingly acknowledged for their non-mutational effects on gene expression and epigenetic regulation.

The specialized base excision repair (BER) enzymes, such as OGG1, are responsible for detecting and removing 8-oxoG to minimize the risk of mutation and prevent disruptions in gene expression. When DNA damage builds up or occurs during cell replication, the DNA damage response (DDR) is triggered, wherein sensor kinases like ATM and ATR activate cell-cycle checkpoints, recruit repair mechanisms, and either restore the integrity of the genome or, if the damage is extensive, initiate processes such as senescence or programmed cell death via downstream effectors like p53. Different repair pathways are responsible for rectifying various types of damage: BER addresses small base lesions, nucleotide excision repair (NER) tackles bulky adducts, mismatch repair (MMR) corrects replication errors, and homologous recombination (HR) or non-homologous end joining (NHEJ) manages DSBs. Disruption or deficiency in these pathways can lead to cancer progression, resistance to treatment, aging, and inflammatory effects from unaddressed DNA damage. Recent literature reviews summarize new therapeutic strategies targeting the DDR, such as the development of next-generation PARP inhibitors, and highlight the influence of DNA repair capabilities and replication stress on cellular outcomes and disease.[56,57,58,59]

In a similar vein, proteins are susceptible to a variety of chemical and physical damage. Processes like oxidation (including carbonylation and the oxidation of methionine/cysteine), glycation, irregular post-translational modifications, truncation, and cross-linking can hinder their proper folding and functionality. Cells combat these challenges with a comprehensive proteostasis system that includes molecular chaperones for assisting folding, the ubiquitin–proteasome system (UPS) and the autophagy-lysosome pathway for removing misfolded or aggregated proteins, as well as mechanisms linked to ribosomal quality control that identify faulty nascent protein chains. When this protective network is overwhelmed a condition referred to as proteotoxic stress there is an accumulation of misfolded proteins that can form oligomers and aggregates, potentially resulting in toxicity, sequestering vital components, and initiating harmful stress responses such as the unfolded protein response (UPR) or cytosolic heat-shock responses. Persistent failure in maintaining proteostasis is a characteristic of neurodegenerative disorders (e.g., accumulation of α-synuclein or β-amyloid), impacts the aging process, and affects how cancer cells respond to proteasome inhibitors. Current reviews outline the intricate regulation of proteasomes, ubiquitin pathways, and selective autophagy as both mechanisms of disease progression and potential therapeutic targets. Crucially, damage to DNA and protein is interconnected; oxidative stress. [60,61,62,63]

IV. Morphologic and biological correlates

Cellular damage initiates a series of biochemical disruptions that occur before any obvious structural changes take place. Early processes, including compromised oxidative phosphorylation, depletion of ATP, disturbed ion balance (specifically Na^+/Ca^{2+} alterations), and heightened levels of reactive oxygen species (ROS), create conditions that lead to subsequent structural changes. Central to this process is mitochondrial dysfunction, where the loss of mitochondrial membrane potential and

reduced ATP production quickly impact ion transporters, particularly the Na^+/K^+-ATPase. This results in intracellular accumulation of Na^+ and water, leading to the typical hydropic swelling observed under light microscopy. Ultrastructurally, this is characterized by an expanded endoplasmic reticulum, detachment of ribosomes, and enlarged mitochondria with a pale matrix that may display occasional amorphous densities. Recent literature highlights that these biochemical changes (declining ATP levels and increasing ROS) can be detected well before overt necrosis occurs, making them vital biomarkers for linking early morphological changes to underlying mechanisms.[64,65]

Cellular swelling

Cellular swelling, also known as hydropic change, is a fundamental and early response to acute metabolic stress that can be potentially reversible. This condition arises from the disruption of energy-dependent ion balance, primarily due to ATP depletion caused by factors such as hypoxia, toxins, or metabolic dysfunction. This depletion affects the functioning of the Na^+/K^+-ATPase and other ion pumps, leading to an increase in intracellular Na^+ and subsequently Ca^{2+} accumulation, which results in osmotic water influx and swelling of organelles. Ultrastructurally, the initial changes include the formation of blebs on the plasma membrane, dilation of the rough endoplasmic reticulum with ribosomal detachment, and swelling of mitochondria accompanied by amorphous densities. Under light microscopy, swollen cells appear pale, distended, and vacuolated. In addition to these morphological changes, cell swelling can modify signaling pathways for instance, it alters GPCR responses in enlarged cardiomyocytes and may lead to irreversible damage if ATP levels are not restored, making it a marker of sublethal injury and a step towards cell death.[66,67]

Fatty change

Fatty change, or steatosis, refers to the buildup of triglyceride-rich lipid droplets within the cytoplasm of parenchymal cells, particularly in hepatocytes. This condition arises when the influx or production of fatty acids surpasses the liver's ability to oxidize them through mitochondrial β-oxidation or export them via very-low-density lipoproteins (VLDL). Recent literature highlights that steatosis is a reversible metabolic adaptation that can arise from factors such as insulin resistance, an excess of free fatty acids, and disrupted lipid management. However, ongoing steatosis may lead to inflammation, programmed cell death, and fibrosis, conditions now referred to as metabolic-associated steatotic liver disease (MASLD). Reviews from 2022 to 2024 explore the mechanisms behind drug-induced steatosis and propose therapeutic interventions to address lipid overload before permanent damage occurs.[68,69]

Hydropic Degeneration

Hydropic degeneration, often referred to as pronounced hydropic change, is characterized by significant intracellular vacuolation due to excessive water accumulation. This condition is observed in various tissues affected by acute toxic insults, ischemic events, viral infections, or degenerative processes within tumors such as hydropic changes in leiomyomas or basal cell carcinoma. Recent literature in pathology associates hydropic degeneration with impaired ion-pump activity, leading

to subsequent lysosomal and proteolytic changes resulting from membrane destabilization. In specific scenarios like brain edema, toxicity from hepatic nanoparticles, or renal ischemia-reperfusion, recent studies show a correlation between hydropic changes and biochemical indicators (such as ATP depletion, oxidative damage, and lysosomal leakage), as well as their impact on cellular function. Therefore, hydropic degeneration can be viewed as a morphological indicator of distinct biochemical disturbances that may either reverse or lead to cell death, influenced by its severity and timing.[70,71,72]

Ultrastructural changes

Mitochondria

Mitochondria undergo significant ultrastructural alterations in the initial stages of cellular stress. Early changes may include swelling of the matrix, deformation or disappearance of cristae, and the development of dense, amorphous inclusions. If the stress escalates or continues, the outer membrane may rupture alongside a collapse of the matrix, which correlates with a decrease in oxidative phosphorylation and eventual bioenergetic failure that cannot be reversed. These structural transformations are largely attributed to calcium overload, oxidative damage to components of the inner membrane, and the extended opening of the mitochondrial permeability transition pore (mPTP), resulting in rapid osmotic swelling and the release of pro-apoptotic factors like cytochrome c. Recent studies using electron microscopy and functional analyses in ischemia-reperfusion and toxicity models have emphasized that changes in mitochondrial dynamics marked by excessive fission mediated by DRP1 and impaired fusion driven by MFN/OPA1 along with persistent mPTP opening, play crucial roles in the ultrastructural alterations and in distinguishing between reversible and irreversible injuries.[73,74,75]

Lysosomes

Lysosomes exhibit a range of ultrastructural responses following injury, including adaptive enlargement and heightened electron density due to increased hydrolases and cargo, as well as severe lysosomal membrane permeabilization (LMP). LMP is identified by the loss of distinct lysosomal boundaries and corresponds functionally to the release of cathepsins and hydrolases into the cytosol. This enzymatic leakage can lead to the degradation of cytoskeletal and nuclear materials, activate inflammasomes, and may cause necrosis or apoptosis, depending on the situation. Recent reviews highlight the existence of lysosomal repair mechanisms and lysophagy that aim to rehabilitate or eliminate damaged lysosomes, influencing cell survival.[76,77]

Endoplasmic reticulum

The endoplasmic reticulum (ER) is characterized by dilation, loss of ribosomes, and interactions with mitochondria. When ER stress occurs, it presents ultrastructurally as an expansion of ER cisternae coupled with ribosomes detaching from the rough ER, leading to the typical “granular loss” observed in damaged secretory cells. If ER disruption persists, it triggers an increase in autophagic vacuoles as cells strive to maintain proteostasis. These structural changes are linked to the biochemical activation of the unfolded protein response (UPR), which includes the phosphorylation of PERK/eIF2α, IRE1 signaling, and CHOP induction. Initially, these processes aim to restore proper protein folding, but if they continue, they can lead to apoptosis. Modern

studies employing electron microscopy and cell biology reveal the significance of mitochondria-associated ER membranes (MAMs); alterations in ER structure can affect ER–mitochondria contact points, impacting calcium transfer and lipid exchange, ultimately contributing to mitochondrial swelling and energy dysfunction. Recent reviews (2021–2025) that integrate electron microscopy findings with molecular UPR and membrane contact biology suggest that changes in ER ultrastructure serve as indicators and active components in cellular injury progression.[78,79,80]

Biochemical markers of cell injury (enzymes, Troponins, LDH, etc.)

Enzyme leakage is a traditional and nonspecific indicator of cellular damage. The primary biochemical effect of compromised plasma membrane integrity is the release of intracellular enzymes into the surrounding fluids. Tests that measure this enzyme leakage, such as lactate dehydrogenase, aminotransferases, and creatine kinase, are fundamental in assessing cytotoxicity in both clinical and experimental settings due to their sensitivity and ease of use. LDH is a commonly utilized marker of necrosis and tissue damage in both cell culture and clinical research. While its kinetics can provide insights into the severity and extent of injury, it lacks specificity to particular tissues, necessitating careful interpretation alongside pattern recognition, isoenzyme analysis, and correlation with organ-specific markers. Recent literature highlights LDH's evolving role as a prognostic indicator in cases of inflammation and organ damage, while also noting its limitations when used in isolation.[81,82]

Cardiac biomarkers, specifically troponins and high-sensitivity assays, are essential in identifying heart tissue damage. Cardiac troponins (cTnI, cTnT) are integral proteins associated with heart muscle contraction and serve as key biochemical markers for myocardial injury, as their release indicates cardiomyocyte death or significant membrane damage. The introduction and widespread use of high-sensitivity troponin (hs-cTn) tests in the past decade have significantly transformed clinical practices. These tests allow for the earlier identification of myocardial damage, assist in risk assessment of non-ischemic conditions (like chemotherapy-related heart toxicity and myocarditis), and contribute to broader prognostic evaluations. However, they also necessitate careful clinical consideration, given that mild, sustained increases in troponin levels may occur in various health issues. Recent multicenter studies and updated guidelines from organizations like the AHA and ACC highlight both the enhanced sensitivity of hs-cTn and the challenges in interpretation it presents.[83,84,85]

Enzymes specific to certain organs, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and creatine kinase (CK), play a crucial role in diagnostics. Elevated levels of ALT and AST typically indicate liver damage, with ALT being more liver-specific and preferred for assessing various forms of liver injury, including those caused by viral infections, metabolic disorders, or medications. In contrast, AST can signal more severe liver damage or mitochondrial damage. CK and its isoenzymes are key indicators of skeletal muscle injury and rhabdomyolysis. Recent reviews from 2021 to 2024 stress that evaluating absolute enzyme levels, their changes over time, and their ratios alongside clinical evaluations and imaging yields the most accurate diagnoses, as single measurements can lead to incorrect conclusions.[86,87]

Pathways of cell death

Cell death is a crucial biological event essential for growth, maintaining tissue balance, and removing damaged or infected cells. Key cell death pathways, such as apoptosis, necroptosis, pyroptosis, ferroptosis, and autophagy-related death, have distinct molecular mechanisms and features but are often linked through common signaling pathways. Recent studies (2021–2025) indicate that disruptions in these processes play a role in various diseases, including neurodegenerative disorders, cancer, heart disease, and infections, underscoring their significance in clinical settings.

Necrosis: Necrosis refers to a type of cell death that generally occurs due to severe and sudden injuries, such as intense ischemia, physical damage, toxins, or infections, which disrupt cellular balance. Biochemically, this process is characterized by a rapid loss of ATP, failure of ion pumps, an influx of sodium (Na^+) and calcium (Ca^{2+}), swelling of the cell, mitochondrial dysfunction, and increased production of reactive oxygen species (ROS), ultimately leading to the breakdown of the plasma membrane and cell rupture. Unlike apoptosis, necrosis triggers a strong inflammatory response due to the release of cellular contents.[88,89,90]

Necrosis types:

Coagulative necrosis

Coagulative necrosis is the most common form encountered in solid organs like the heart, kidneys, and spleen, occurring typically in response to ischemia or infarction. Its hallmark is preservation of tissue architecture for a few days post-cell death, because ischemia denatures structural proteins and lysosomal enzymes, inhibiting proteolytic breakdown. Microscopically, affected cells lack nuclei and stain intensely eosinophilic while retaining their contour, allowing for eventual regeneration or scar formation depending on surrounding cell viability.[89]

Liquefactive necrosis

Liquefactive necrosis involves the transformation of tissue into a thick liquid mass, typically observed in the central nervous system after an infarct or during bacterial infections. Enzymes from white blood cells or the affected tissue lead to the breakdown of dead cells, forming pus or cysts, ultimately resulting in a fluid-filled cavity devoid of structural integrity.[89]

Caseous necrosis

Caseous necrosis, most notably associated with tuberculosis, exhibits a “cheese-like” appearance where tissue architecture is obliterated, replaced by amorphous, granular eosinophilic debris within granulomatous inflammation. It represents a hybrid of coagulative and liquefactive processes, where immune-mediated destruction destroys both pathogen and host tissue, leading to granuloma formation with central necrosis.[89]

Fat necrosis

Fat necrosis results from the enzymatic breakdown of fat tissue, commonly seen in conditions like acute pancreatitis or breast trauma. Pancreatic lipases process triglycerides into fatty acids, which then bond with calcium to create whitish deposits referred to as chalky saponification. Under the microscope, one can identify the faint

shapes of fat cells along with deposits that stain blue due to calcium. (StatPearls, 2021)[89]

Fibrinoid necrosis

Fibrinoid necrosis affects blood vessel walls in immune-mediated conditions (e.g., vasculitis, malignant hypertension) and is characterized by deposition of fibrin and immune complexes within the arterial wall, which stains intensely eosinophilic and amorphous under the microscope. While termed "necrosis," its recognition reflects immunologic injury rather than classical necrotic cell death.[89]

Gangrenous necrosis

Gangrenous necrosis is a clinical rather than purely morphological term, describing extensive necrosis often of the limbs or intestines following prolonged ischemia. Dry gangrene represents coagulative necrosis with mummification, while wet gangrene combines features of coagulative and liquefactive necrosis due to superimposed infection. Gas gangrene, a subtype, involves clostridial infection producing gas within tissues.[89]

Apoptosis (intrinsic and extrinsic pathways)

Apoptosis is a highly conserved, energy-requiring mechanism for programmed cell death that is essential for the removal of unnecessary, damaged, or potentially harmful cells. It is a critical component during

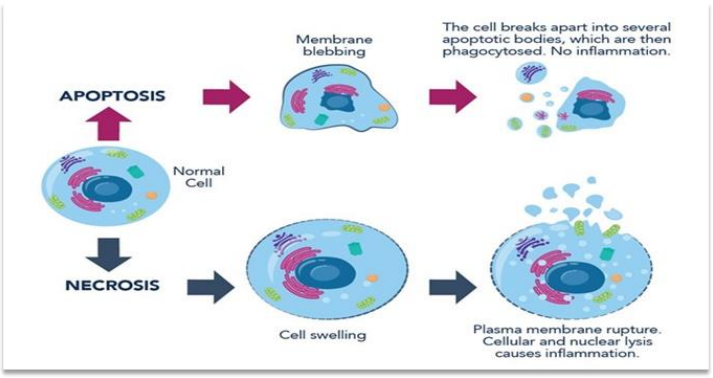

Figure 2: Mechanism of Necrosis and Apoptosis [Reference: Khushi, Rajesh Kumar, Ajeet Pal Singh, Amar Pal Singh, Meenakshi Malhotra. Neoadjuvant Chemotherapy (NACT) in Advanced Epithelial Ovarian Cancer: a Review. Int J Med Phar Drug Res. 2024;8(2):1-7. Doi:10.22161/ijmpd.8.2.5]

developmental processes, aids in maintaining tissue balance, and helps regulate immune responses while avoiding harmful inflammation. Cells undergoing apoptosis display distinct morphological traits, such as shrinkage, condensation of chromatin, fragmentation of DNA at internucleosomal sites, blebbing of the plasma membrane, and the creation of membrane-bound apoptotic bodies. These signs facilitate the prompt recognition and engulfment of apoptotic cells by phagocytes through a process called efferocytosis, which is vital for sustaining tissue health and minimizing inflammation. Recent extensive reviews have highlighted the significance of apoptosis as an essential,

non-inflammatory method of cell death, impacting development, immunity, and various disease mechanisms. [91]

The intrinsic pathway of apoptosis is activated by internal stressors, including DNA damage, oxidative stress, dysfunction of the endoplasmic reticulum, or insufficient growth factors. This pathway is carefully controlled by the BCL-2 family of proteins. Pro-apoptotic members like BAX and BAK congregate at the outer membrane of the mitochondria, leading to its permeabilization. This process allows the release of cytochrome c and other apoptogenic molecules, which aid in the formation of the apoptosome, comprised of Apaf-1 and caspase-9, ultimately triggering the activation of initiator caspase-9. This is followed by the activation of executioner caspases, namely caspase-3 and caspase-7, which are responsible for dismantling the cell. Mechanistic reviews from 2021 to 2024 have shed light on the structural interactions within the BCL-2 protein family, emphasizing the crucial roles of mitochondrial outer membrane permeabilization (MOMP) and the assembly of the apoptosome in the intrinsic pathway of apoptosis.[92]

The extrinsic apoptosis pathway is initiated when external death ligands like FasL and TRAIL bind to specific death receptors on the cell membrane, such as Fas and DR4/5. This interaction leads to the formation of a death-inducing signaling complex (DISC), which brings together FADD and procaspase-8 (or -10). Once activated, caspase-8 can either directly cleave and activate downstream effector caspases or, in certain “type II” cells, initiate the cleavage of the BH3-only protein Bid, converting it into tBid. This connection allows the extrinsic pathway to communicate with the mitochondrial pathway, thereby intensifying the apoptotic signal. Recent reviews highlight how factors like receptor context, the presence of decoy receptors, and various intracellular inhibitors (such as cFLIP and IAPs) can influence the outcome of extrinsic signaling, determining whether it results in apoptosis, cell survival, or alternative death and inflammatory responses. Apoptosis is executed by effector caspases that cleave various substrates.[93]

Other modes

Necroptosis

Necroptosis is a regulated cell death process that integrates aspects of programmed cell death and the inflammatory responses typically linked to necrosis. In contrast to apoptosis, which is mediated by caspases without provoking an immune reaction, necroptosis leads to the breakdown of the plasma membrane and the release of damage-associated molecular patterns (DAMPs), triggering inflammation. The signaling mechanisms are predominantly regulated by receptor-interacting kinases RIPK1 and RIPK3, along with the pseudokinase MLKL, positioning it as a significant component of innate immunity and responses to tissue damage, particularly when apoptosis is insufficient.[94]

Various pathways can activate necroptosis depending on the stimulus and the cellular context. The traditional activation pathway is characterized by death-receptor signaling through TNFR1, especially when caspase-8 activity is inhibited. After TNF engages the receptor, adaptor complexes form, enabling RIPK1 to recruit and activate RIPK3, which subsequently leads to necrosome formation if ubiquitination and caspase checks

fail. Furthermore, alternative pathways (such as certain pattern-recognition receptors via TRIF and ZBP1/DAI targeting viral Z-form nucleic acids) can also independently activate RIPK3. This indicates that necroptosis can be initiated by various upstream signals (death receptor, TLR/TRIF, ZBP1), ultimately converging with the RIPK3-MLKL execution pathway.[95,96]

Pyroptosis

Pyroptosis is an inflammatory, lytic form of regulated cell death initiated in response to pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) and is executed by members of the gasdermin protein family that form membrane pores. Morphologically pyroptotic cells swell and then rupture, releasing cytosolic contents (including IL-1β/IL-18 when inflammasomes are engaged) that act as potent inflammatory signals; functionally pyroptosis serves host-defense roles (eliminating intracellular replication niches and alerting the immune system) but, when excessive or misregulated, contributes to pathological inflammation and tissue injury. [97,98]

The canonical pyroptotic pathway is centered on inflammasome assembly (e.g., NLRP3, AIM2, NLRC4) that activates caspase-1; active caspase-1 cleaves pro-IL-1β/pro-IL-18 to their mature forms and also cleaves gasdermin D (GSDMD) to liberate its N-terminal pore-forming fragment, which inserts into membranes to mediate cell lysis. In contrast, the non-canonical pathway involves direct sensing of cytosolic LPS by caspase-4/5 (human) or caspase-11 (mouse), which cleave GSDMD independently of canonical inflammasome sensors; both canonical and non-canonical routes therefore converge on GSDMD-dependent membrane permeabilization but differ in upstream sensors and caspase usage. [99,100]

Ferroptosis

Ferroptosis is a distinct, regulated form of cell death driven by iron-dependent accumulation of lipid peroxides to lethal levels and by failure of the cellular antioxidant machinery to detoxify those peroxides. Morphologically and biochemically it differs from apoptosis and necrosis: cells undergoing ferroptosis often show smaller, dense mitochondria with reduced cristae and rupture of the outer mitochondrial membrane rather than classic nuclear fragmentation, and death is prevented by iron chelators and lipophilic radical-trapping agents. Ferroptosis was first systematically characterized in the 2010s and has since been refined mechanistically as an intersection of iron metabolism, lipid biochemistry and redox biology. [101,102]

At the molecular core of ferroptosis lies iron-dependent lipid peroxidation. Labile iron (Fe^{2+}) catalyzes Fenton chemistry and lipid radical propagation, and enzymes such as lipoxygenases can enzymatically oxygenate polyunsaturated fatty-acid (PUFA)-containing phospholipids to form phospholipid hydroperoxides (PLOOH). When these lipid peroxides exceed a detoxification threshold they destabilize membranes and trigger cell death. Recent reviews emphasize the roles of PUFA incorporation into membranes (driven by ACSL4/LPCAT3), iron uptake/storage/export balance (transferrin, TFR1, ferritinophagy via NCOA4), and ROS-generating metabolism as central determinants of susceptibility to ferroptosis.[103,104]

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Autophag- related cell death

Autophagy is a conserved, lysosome-dependent catabolic pathway that maintains cellular homeostasis by degrading and recycling cytoplasmic material ranging from soluble proteins to entire organelles within double-membrane vesicles called autophagosomes that fuse with lysosomes for content degradation. It is dynamically regulated by nutrient, energy and stress sensors (for example, mTORC1 and AMPK) and serves dual roles: adaptive survival during transient stress (by supplying metabolites) and, when excessive or dysregulated, contributing to cell death or pathology. Contemporary integrative reviews summarize autophagy as a context-dependent process that is essential for development, quality control of cellular components, and adaptation to metabolic and proteotoxic stress.[105]

The dominant, best-studied form macro autophagy (commonly called "autophagy") begins with nucleation of a phagophore that elongates and engulfs cytoplasmic cargo to form an autophagosome; this process requires the hierarchical action of ATG proteins (ULK1 complex, Beclin-1/VPS34 complex, ATG5–ATG12/ATG16L1 conjugation system and LC3 lipidation) and culminates in autophagosome–lysosome fusion and enzymatic degradation of cargo. Macroautophagy operates as both bulk (non-selective) autophagy during starvation and as selective autophagy when adaptors (p62/SQSTM1, NBR1, NDP52, OPTN) link specific cargoes to LC3. Its central importance for organ physiology especially in the nervous system, heart and liver has been emphasized in recent CNS-focused and mechanistic reviews.[106]

Cellular Adaptations to Stress

Cells encountering environmental stress nutrient deprivation, oxidative insults, or proteotoxic pressure activate the integrated stress response (ISR) to preserve proteostasis and energy balance. Central to this is phosphorylation of eIF2α, which suppresses global protein synthesis while enabling selective translation of adaptive transcripts (e.g., ATF4). This allows cells to conserve energy and prioritize stress-mitigation proteins. A 2024 phosphoproteomic study further pinpointed roles for GCN2 kinase in this translational reprogramming, underlining its adaptation across stress conditions.[107]

A key adaptation to starvation and cellular stress is autophagy, an evolutionarily conserved mechanism that

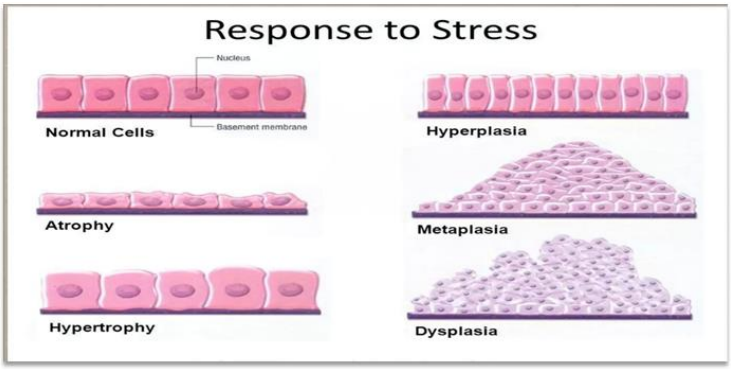

Figure 3: Response to Stress [Reference: Dr. Satyendra Singh, Innate Healing & Health Realisation. SlideShare (pptx). Available at: https://www.slideshare.net/slideshow/innate-healing-health-realisation/248054073]

breaks down intracellular components to preserve nutrients and maintain homeostasis. Mouse models deficient in autophagy genes (e.g., Atg7, Atg5) rapidly succumb to fasting due to failure in maintaining glucose levels, highlighting autophagy's critical survival function. Furthermore, autophagy modulates inflammatory responses by eliminating damaged organelles and protein aggregates; its disruption activates p53-driven stress pathways, while Nrf2 can compensate, demonstrating interconnected protective networks.[108]

Hypertrophy

Hypertrophy is an adaptive increase in cell size (not number) that enlarges an organ to meet heightened functional demand or neurohormonal drive. In the heart and skeletal muscle tissues with limited capacity for hyperplasia hypertrophy helps normalize wall stress or generate more force by expanding contractile apparatus, organelles, and metabolic capacity. Contemporary reviews frame hypertrophy along a spectrum from physiological (exercise, pregnancy) to pathological (pressure overload, endocrine/neurohumoral excess), emphasizing that the stimulus and downstream signaling determine whether growth is beneficial or a prelude to failure.[109]

Core signaling and mechanotransduction. Modern work situates hypertrophy at the intersection of mechanosensing (Z-disc/integrins, stretch-activated channels) and growth-factor pathways (IGF-1, angiotensin II) that converge on PI3K–AKT–mTOR, MAPK/ERK, and stress programs that remodel transcription and translation. These cascades increase protein synthesis, ribosome biogenesis, mitochondrial content, and sarcomere number; they also interface with organelle stress modules (UPR, mitophagy) that tune quality control during growth. Recent reviews detail how mechanosignaling encodes load into biochemical signals controlling myocardial mass, and how pathway balance anabolic mTOR versus stress/inflammatory kinases biases toward adaptive versus maladaptive phenotypes.[110]

Physiological cardiac hypertrophy, seen in athletes and during pregnancy, involves balanced thickening of heart chambers with maintained or improved function, increased capillary density, and metabolic adaptability, shrinking once the triggering factor is removed. In contrast, pathological hypertrophy arises from chronic pressure or neurohumoral stress, leading to myocyte growth linked with fibrosis, reduced capillary presence, altered metabolism, mitochondrial strain, and arrhythmia risk factors increasing chances of heart failure (HFpEF/HFrEF). Recent studies emphasize the role of mitochondrial quality control and endoplasmic reticulum stress in determining whether adaptation or failure occurs, indicating that alleviating stressors can help reverse pathological changes and enhance recovery.[111]

Hyperplasia

Hyperplasia refers to an adaptive increase in tissue mass caused by a rise in cell numbers due to heightened cell proliferation rates. It is distinct from hypertrophy, which involves cell enlargement, and typically occurs in tissues capable of cell division

when responding to greater functional demands, hormonal influences, or chronic injury. At the molecular level, hyperplasia is influenced by mitogenic signals, including growth factors like EGF, PDGF, and IGF, along with cytokines, and is regulated by cell cycle programs (cyclins and CDKs) and the tissue environment, such as extracellular matrix signals, paracrine factors, and immune mediators. Key signaling pathways, including PI3K-AKT-mTOR, MAPK/ERK, and TGF-β, collectively manage cell cycle progression and the balance between proliferation and differentiation. Hyperplasia is generally reversible upon removal of stimuli; however, persistent proliferative signals, especially in the context of genetic or epigenetic factors or chronic inflammation, may set the stage for dysplasia and neoplasia.[112]

Physiologic hyperplasia serves homeostatic and regenerative needs. Classic examples include liver regeneration after partial hepatectomy (compensatory hyperplasia), endometrial proliferation during the menstrual cycle (hormonally driven hyperplasia), and breast glandular expansion in pregnancy and lactation. These forms are tightly coordinated by systemic hormones (estrogen, progesterone, prolactin) and local growth factors, and they normally resolve when the physiological demand ends. Contemporary reviews emphasize that physiologic hyperplasia relies on intact checkpoints (contact inhibition, appropriate growth-factor withdrawal) and effective quality-control processes (autophagy, proteostasis); disruption of these controls is what distinguishes physiologic proliferation from pathologic hyperplasia.[113]

An emerging area of interest in metabolic research is the distinction between adipocyte hypertrophy (enlargement) and adipose hyperplasia (increased adipocyte number) during white adipose tissue expansion. Recent 2021–2024 studies indicate that hyperplastic expansion through recruitment and differentiation of adipocyte precursor cells can be metabolically protective by creating many small insulin-sensitive adipocytes and preventing ectopic lipid deposition, whereas predominant hypertrophy is associated with inflammation, insulin resistance and cardiometabolic risk. Thus, inducing healthy adipose hyperplasia (rather than unchecked hypertrophy) is being explored as a therapeutic angle in obesity and metabolic disease research.[114]

Atropy

Cellular atrophy is a regulated reduction in cell size and function resulting from decreased synthesis and/or increased degradation of cellular components. It occurs across tissues in response to reduced workload (disuse), diminished trophic signals (loss of innervation or hormones), inadequate nutrition, chronic ischemia, or aging. At the tissue level atrophy manifests as decreased organ volume and can be focal (e.g., limb muscle after immobilization), segmental (e.g., renal cortical thinning), or systemic (e.g., cachexia in chronic illness). Clinically important contexts include sarcopenia of aging, disuse atrophy after immobilization or bed rest, denervation atrophy, endocrine-related atrophy (e.g., adrenal atrophy after chronic steroid therapy), and cancer cachexia.[115]

At the molecular level, atrophy is driven by a shift in the balance between anabolic and catabolic programs. Suppression of anabolic signaling (notably the IGF-1 → PI3K → Akt → mTOR axis) reduces protein synthesis and ribosomal biogenesis, while activation of catabolic pathways increases protein degradation. Two muscle-specific E3 ubiquitin ligases Atrogin-1 (MAFbx) and MuRF1 are canonical effectors of the

ubiquitin–proteasome system (UPS), promoted by transcription factors of the FOXO family when Akt signaling is low; their upregulation marks many atrophy programs and mediates selective degradation of myofibrillar proteins. In parallel, autophagy–lysosome pathways (including mitophagy) provide bulk removal of organelles and protein aggregates, and their dysregulation either exacerbates or mitigates atrophy depending on context. Inflammatory cytokines (TNF-α, IL-6) and JAK/STAT signaling also promote catabolism in cachexia and chronic disease states.[116]

Organelle dysfunction is both a cause and consequence of atrophy. Mitochondrial decline reduced biogenesis, impaired oxidative phosphorylation, increased ROS, and defective mitophagy decreases ATP supply and triggers metabolic reprogramming toward proteolysis; several recent reviews link mitochondrial quality-control failure to accelerated muscle loss in aging and disease. Lysosomal function and autophagic flux are essential for removing damaged organelles and maintaining amino-acid pools during fasting or stress; impaired autophagy with age or disease can lead to accumulation of dysfunctional organelles and proteotoxic stress, worsening atrophy. Thus, organelle homeostasis (mitochondria–autophagy–lysosome axis) is central to the atrophy phenotype.[117]

Metaplasia

Metaplasia is a regulated process where one mature, differentiated cell type is replaced by another that is better suited to withstand chronic environmental stress. This adaptive transformation often arises via reprogramming of resident stem or progenitor cells, mediated by altered transcription factor networks and epigenetic changes. While it serves short-term protective purposes, persistent stimuli can push metaplastic tissue toward dysplasia and malignancy. For example, mice and molecular models show that factors like CDX2, SOX2, BMP4, BARX1, and Notch are key orchestrators in epithelial reprogramming particularly in gastrointestinal and airway contexts. Metaplasia thus sits at the crossroads of repair, adaptation, and cancer risk.[118]

Metaplasia is a reversible adaptive process where one type of mature cell is replaced by another that is more capable of handling ongoing or new stressors. This phenomenon highlights cellular flexibility, arising from the transcriptional reprogramming of local stem or progenitor cells, or through the trans-/de-differentiation of mature cells shaped by their surroundings. Recent analyses indicate that metaplasia is a regulated response to chronic injury, such as acid exposure in Barrett's esophagus, tobacco exposure in respiratory and squamous metaplasia, and gastritis from Helicobacter pylori in gastric intestinal metaplasia, involving specific transcription factors and altered signaling pathways that change cellular identity.[119]

Mechanistically, metaplasia commonly proceeds via injury-associated activation of local progenitors or facultative stem cells and by epigenetic and transcriptional reprogramming that establishes a new lineage program. Recent single-cell and bulk-omics studies show that injury/stress creates permissive chromatin states and activates pioneer transcription factors that open lineage-specific enhancers, while DNA methylation and histone modifications lock in new expression patterns that can persist as an "epigenetic memory." These molecular changes explain why metaplastic epithelium can be stable yet potentially reversible if the offending stimulus is removed and the epigenetic program is remodeled.[120]

Molecular mechanisms and signaling Pathways underlying adaptation:
Integrated Stress Response (ISR) and Translational Reprogramming
A cornerstone of cellular adaptation to diverse stressors including nutrient deprivation, proteotoxicity, or mitochondrial dysfunction is the Integrated Stress Response (ISR). Activation of stress-sensing kinases (PERK, GCN2, PKR, HRI) phosphorylates eIF2α, which globally suppresses protein synthesis while selectively enhancing translation of adaptive transcription factors such as ATF4. This shift enables cells to conserve resources and activate stress mitigation gene programs. Recent insights (2024) further elucidate how ISR is finely tuned: feedback dephosphorylation (e.g., via GADD34/PP1) restores proteostasis when stress abates, whereas sustained activation drives maladaptive outcomes such as senescence or apoptosis. In metabolic adaptation, ISR also modulates amino acid biosynthesis and antioxidant responses, linking translational control directly to metabolic reprogramming.[121]

mTOR and PI3K–AKT Pathways in Anabolic Adaptation and Autophagy Control
Growth-promoting adaptation hinges on the PI3K–AKT–mTOR axis, which integrates signals from nutrients, growth factors, and mechanical cues to stimulate protein synthesis, cell growth, and metabolism. mTORC1 activation drives ribosome biogenesis and anabolic processes, whereas its inhibition (e.g., during nutrient stress or lysosomal damage) triggers autophagy as a survival mechanism. Mechanistically, lysosomal membrane damage activates galectin-dependent suppression of mTOR via the GALTOR complex, engaging autophagy machinery through ULK1/Beclin-1 and other Atg components to recycle damaged organelles. These regulatory dynamics allow cells to adapt by balancing growth versus catabolism based on environmental status.[122]

Mechanotransduction and Adaptive Gene Programs
Cells continuously interpret mechanical forces such as shear stress, stretch, or substrate stiffness through mechanosensitive receptors and intracellular pathways, a process known as mechanotransduction. Recent research (2023) highlights the roles of Piezo ion channels and Wnt signaling in translating physical stimuli into biochemical cues that guide adaptation, regeneration, and differentiation. In cardiovascular and musculoskeletal tissues, for example, mechanical loading modulates signaling cascades that regulate cell growth, metabolism, and extracellular matrix remodeling. Additionally, there is emerging recognition that some G protein–coupled receptors (e.g., angiotensin II receptor, β2-adrenergic receptor) can act as bidirectional mechanosensors, integrating both mechanical and chemical stimuli to adaptively modulate cellular responses.[123]

Interplay Between Injury and Adaptation
At the molecular level, adaptation and injury intersect at various points, with a cell's fate hinging on the timing and intensity of signaling in pathways like PI3K–AKT–mTOR, unfolded protein response (UPR), autophagy/mitophagy, and stress-kinase pathways. For instance, short-term suppression of mTOR promotes autophagy, aiding in the removal of damaged organelles and providing cytoprotection. Conversely, chronic mTOR dysregulation disrupts quality control and leads to maladaptive growth or senescence. Similarly, a brief activation of the integrated stress response (ISR) and

eIF2α phosphorylation conserves resources and enhances protective ATF4 targets, while prolonged ISR can trigger apoptosis or senescence through CHOP. Consequently, the duration and intensity with which these pathways are activated ultimately dictate the cell's fate.[124]

Threshold between reversible injury and Irreversible cell death

The idea of a threshold, often referred to as the "point of no return," distinguishes between reversible cellular injury and irreversible cell death. It marks the transition where manageable biochemical and structural alterations escalate into self-perpetuating damage that cannot be reversed, ultimately resulting in cell death. In reality, this threshold isn't defined by a singular molecular trigger, but rather by a series of interconnected processes: prolonged energy failure, severe loss of membrane integrity, and the initiation of programmed cell death. Modern analyses depict this threshold as having biochemical characteristics (maintaining energy and ion balance, redox equilibrium) and being temporally limited (interventions can only effectively restore balance within a certain timeframe).[125]

Mitochondrial dysfunction, particularly the prolonged opening of the mitochondrial permeability transition pore (mPTP), is a key factor in determining cellular irreversibility at the molecular level. This process leads to the loss of membrane potential, significant ATP depletion, and the release of factors that promote cell death. Calcium overload and reactive oxygen species (ROS) initiate the opening of the mPTP, while lysosomal membrane permeabilization and the leakage of proteases further contribute to the breakdown of cellular structures. Once a sufficient number of mitochondria fail catastrophically, or ATP levels dip below a critical threshold for the tissue, the cell can no longer maintain ion gradients or repair its membranes, resulting in a commitment to necrosis or regulated necrotic pathways. Recent mechanistic reviews highlight the significance of mPTP-mediated necrosis and the consequent energy failure as a pivotal moment of no return.[126]

The duration during which an injury can still be reversed differs depending on the type of tissue, the severity of the injury, and the specific circumstances. Research on myocardial ischemia-reperfusion indicates that extremely ischemic heart tissue may only show reversible changes for a brief period, often around 15 minutes in cases of severe ischemia, with irreversible damage taking hold after 20 to 60 minutes. The initial moments of reperfusion are particularly crucial, as this process can introduce reactive oxygen species (ROS) and calcium spikes that may push vulnerable cells beyond the point of no return. Therefore, both the length of the initial insult and the timing and quality of reperfusion, as well as other interventions, play a key role in determining the outcome. Therapeutic approaches like ischemic preconditioning or prompt reperfusion are specifically designed to maintain injured cells in a reversible state.[127]

How adaptive mechanisms can turn Pathological

Adaptive responses are inherently protective, aimed at restoring balance, maintaining viability, or repairing tissue damage. However, they function within specific timeframes and limits. When stress is short or moderate, processes like hypertrophy, enhanced autophagy, activation of the unfolded-protein response (UPR), or temporary increases in cell proliferation successfully restore normal function. Yet, if stressors are chronic, repetitive, or excessive, these same mechanisms may become persistently

activated, leading to further damage and disease progression. The transition from adaptive responses to pathological states is influenced by the intensity, duration, and cellular context, which together transform a beneficial and temporary response into a harmful, self-perpetuating condition.[128]

A notable Illustration is cardiac hypertrophy, where mechanotransduction and neurohormonal signals stimulate the PI3K–AKT–mTOR and MAPK pathways, resulting in increased size and contractile ability of myocytes in response to pressure. While short-term hypertrophy serves a compensatory function, chronic stimulation such as from prolonged hypertension or valve overload leads to maladaptive remodeling. This is marked by interstitial fibrosis, reduced capillary density, metabolic rigidity, and ultimately contractile dysfunction that can result in heart failure. Recent studies have connected ongoing mTOR activation, subpar mitochondrial quality control, and epigenetic changes to this harmful progression, highlighting potential therapeutic targets like mitophagy and mTOR modulation.[129]
Stress-response mechanisms like autophagy and the unfolded protein response (UPR) have complex roles.

Autophagy helps eliminate damaged organelles and protein clumps, aiding survival during nutrient scarcity; however, when it becomes excessive or improperly regulated, it can lead to cell death or enhance cancerous traits by allowing tumor cells to endure metabolic stress and resist treatment. Similarly, while the UPR can initially alleviate protein-folding stress and increase chaperone levels, prolonged UPR activation may induce apoptosis, inflammation, or tumor advancement, depending on the specific situation. Recent literature underscores that the protective or harmful effects of these pathways hinge on how quickly and effectively they respond, as well as their interaction with inflammation and metabolic processes.[130]
Adaptive changes in cell fate, such as metaplasia and cellular senescence, underscore the risks associated with prolonged adaptation. Metaplasia alters epithelial identity to better withstand chronic damage (for instance, Barrett's esophagus due to acid reflux). However, ongoing harmful exposure and entrenched epigenetic changes elevate the likelihood of dysplasia and cancer; recent single-cell and epigenomic research reveals how enduring signals create favorable chromatin that reinforces the metaplastic lineage and enhances the potential for malignancy. Likewise, cellular senescence stops cell proliferation to prevent the division of damaged cells, but the buildup of senescent cells and their secretory phenotype (SASP) leads to chronic inflammation, tissue remodeling, and signals that promote tumor development, contributing to conditions like fibrosis and aging-related diseases. These instances demonstrate how what begins as an adaptive response can ultimately become a catalyst for long-term health issues when mechanisms for clearance or resolution fail.[131]

Pathological outcomes
Cellular damage initiates a series of pathological events, starting with the release of damage-associated molecular patterns (DAMPs) like HMGB1, ATP, and mitochondrial DNA. These molecules activate pattern-recognition receptors on innate immune cells, leading to sterile inflammation marked by cytokine storms, infiltration of leukocytes, and potential systemic inflammatory reactions. Under regulated conditions, this inflammation aids in debris removal and tissue healing through

macrophage polarization, angiogenesis, and remodeling of the extracellular matrix. However, when excessive, persistent, or unresolved, it can lead to pathological fibrosis, characterized by continuous activation of myofibroblasts, excessive collagen production, and compromised tissue structure, ultimately diminishing organ function. The type of cell death whether lytic (e.g., necrosis, ferroptosis, necroptosis) or non-lytic (apoptosis) affects the inflammatory response, with lytic deaths exacerbating inflammation and worsening injury. These processes significantly influence clinical outcomes, such as heart failure following myocardial damage and chronic conditions like pain syndromes and organ failure, as well as increased cancer risk through inflammasome-related mutations, particularly in the elderly.[132,133,134]

Myocardial infraction

Myocardial infarction-induced ischemia occurs when blood flow to a part of the heart muscle significantly decreases or ceases, often due to an atherothrombotic blockage. Within minutes, the diminished oxygen supply halts mitochondrial oxidative phosphorylation in heart cells, leading to a swift reduction in ATP levels. This ATP shortage impairs ion pumps, particularly Na^+/K^+-ATPase and Ca^{2+}-ATPases, resulting in disrupted ionic balances, cell swelling (oncosis), and a gradual collapse of cellular energy. This energetic failure is the key biochemical factor that transforms reversible ischemic stress into permanent cell damage and death.[135]

Mitochondrial dysfunction plays a crucial role in the necrosis of ischemic cardiomyocytes. During ischemia and particularly following reperfusion, there are changes In mitochondrial membrane permeability, such as the opening of the permeability transition pore, leading to an overload of mitochondrial Ca^{2+} and a breakdown in the electron transport chain, which generates excessive reactive oxygen species (ROS). This permeability transition and the resulting ROS escalate membrane damage, reduce ATP production, and trigger the release of pro-apoptotic factors ultimately leading cells towards necrosis, as well as some degree of apoptosis or regulated necrosis.[136]

Reperfusion is critical for rescuing ischemic heart tissue, yet it paradoxically worsens injury. Reoxygenation leads to a surge in reactive oxygen species (ROS), sudden ionic shifts (especially in calcium), and the initiation of inflammation, which can increase the area of irreversible damage. The interplay of ischemia and reperfusion ultimately influences the size of the infarct. Myocardium that has experienced prolonged ischemia beyond a specific timeframe for each cell type will undergo necrosis that cannot be remedied by subsequent reperfusion, although tissue in the ischemic penumbra may recover if blood flow is quickly restored.[137]

When cardiomyocytes experience necrosis, their damaged plasma membranes release various intracellular components, including mitochondrial DNA, HMGB1, ATP, and fragments of sarcomeric proteins. These substances, known as damage-associated molecular patterns (DAMPs), trigger the activation of innate immune receptors (such as TLRs and NLRs) on both resident and recruited immune cells. This activation leads to a robust sterile inflammatory response that helps clear necrotic material but may also result in extracellular matrix remodeling and an exacerbation of injury if not properly

regulated. HMGB1 and other DAMPs are frequently recognized as key mediators that connect necrosis with inflammation following myocardial infarction.[138]

Necrosis in myocardial infarction (MI) progresses through distinct, predictable phases. Initially, within minutes to hours, there is a loss of sarcomeric cross-striations and the appearance of wavy fibers. This is followed by coagulative necrosis characterized by eosinophilic cytoplasm and karyolysis over the course of hours to days. Neutrophils infiltrate next, succeeded by macrophages, leading to granulation tissue and collagen scar development over weeks. This progression from necrosis to inflammation, then granulation, and finally fibrosis plays a crucial role in clinical complications such as ventricular remodeling, aneurysm formation, and heart failure, underscoring the importance of minimizing initial necrosis to enhance patient outcomes.[137]

Necrosis leads to inflammation and negative remodeling, making it crucial to develop therapies that mitigate ischemic necrosis and its subsequent effects. The primary strategy remains timely reperfusion via primary PCI, while complementary approaches under investigation include mitochondrial protective agents, those that manage Ca^{2+} overload and reactive oxygen species, and methods to modulate reperfusion injury signals, such as ischemic conditioning and targeted antioxidants. Additionally, strategies aimed at reducing maladaptive inflammation and DAMP signaling may help limit infarct growth and pathological fibrosis. Recent translational reviews highlight the importance of combining and timing interventions to enhance ATP and mitochondrial function, ultimately improving long-term cardiac outcomes.[137]

Stroke

Ischemic stroke occurs when there is a sudden interruption of blood flow to a specific area of the brain, leading to a lack of oxygen and glucose that quickly disrupts the metabolic processes and ion balance within neurons. This energy deficit (depletion of ATP) hampers the function of ion pumps, resulting in membrane depolarization and excessive release of glutamate. This sets off a biochemical environment characterized by acidification and ionic imbalance, making neurons vulnerable to harmful processes such as excitotoxicity, calcium overload, oxidative stress, mitochondrial dysfunction, and the activation of cell death pathways like apoptosis. The pattern of brain damage, including the irreversible core and the potentially salvageable penumbra, is influenced by the severity and duration of the ischemic event, thus establishing the therapeutic window for neuroprotective interventions.[139]

A key early process leading to neuronal damage is excitotoxicity. This occurs when energy deficits result in excessive glutamate release and inadequate uptake by astrocytes, leading to the overstimulation of AMPA and NMDA receptors on neurons. The influx"of Ca^{2+} through NMDA receptors activates various calcium-dependent enzymes (such as calpains, phospholipases, and endonucleases) that cause both structural and biochemical harm while initiating mitochondrial death pathways. Recent reviews from 2021 to 2024 explore how excitotoxic signaling activates both necrotic and apoptotic pathways, highlighting the significance of disrupting glutamate-receptor signaling or mitigating downstream Ca^{2+} overload as vital, though clinically challenging, neuroprotective approaches.

Mitochondrial processes are interconnected with excitotoxic calcium, oxidative stress, and apoptosis. When mitochondrial calcium uptake becomes excessive, it disrupts the membrane potential, facilitates the opening of the mitochondrial permeability transition pore, elevates reactive oxygen species (ROS) production, and triggers the release of pro-apoptotic factors like cytochrome c and AIF. These changes initiate the intrinsic apoptotic pathway (involving Apaf-1/apoptosome → caspase-9 → caspase-3) and lead to DNA fragmentation through nuclease activation. Recent structural and mechanistic reviews (2021–2025) highlight the role of mitochondria as crucial regulators of neuronal survival versus apoptosis following ischemia and discuss the neuroprotective effects of agents that stabilize mitochondrial function or inhibit mitochondrial-mediated apoptosis.

Chronic liver disease

Chronic Liver Disease (CLD) is a progressive ailment marked by sustained liver damage, starting with fatty liver changes (steatosis) and evolving through inflammation and fibrosis, potentially leading to cirrhosis. Non-alcoholic fatty liver disease (NAFLD), closely tied to obesity, diabetes, and metabolic syndrome, has become the predominant cause of CLD globally, overtaking both alcohol-related and viral factors. The buildup of triglycerides in liver cells triggers steatosis, which can be reversed if the underlying metabolic stressors are eliminated.[140]

The shift from basic steatosis to advanced liver disease is driven by various cellular stress mechanisms, such as endoplasmic reticulum stress, oxidative stress, and altered lipid metabolism. Ongoing stress in liver cells fosters inflammation and fibrosis, primarily by activating Kupffer cells and attracting immune cells. While these responses aim to restore balance within the tissue, their persistence can lead to more serious health issues.[141]

Fibrosis occurs when hepatic stellate cells (HSCs) are activated and produce an excess of extracellular matrix, resulting in the liver's structural distortion. Although fibrosis can be partially reversed by eliminating the cause of injury, ongoing damage can progress to cirrhosis, marked by bridging fibrosis, nodular regeneration, and portal hypertension. Cirrhosis signifies the final stage of chronic liver disease and is closely linked to serious complications like ascites, variceal bleeding, hepatic encephalopathy, and hepatocellular carcinoma.[141]

Recent findings indicate that cirrhosis involves not just structural alterations but also metabolic and immune system dysfunctions. Ongoing inflammation, compromised autophagy, and disrupted metabolic pathways worsen liver cell damage and contribute to the development of hepatocellular carcinoma (HCC). Innovative treatment approaches being researched encompass antifibrotic agents, HSC blockers, metabolic regulators, and immune therapies focused on stopping or reversing liver fibrosis.[142]

Cancer

Cancer develops and advances by shifting the equilibrium from programmed cell death, mainly apoptosis, to enhanced cell survival. In normal tissues, damaged or excessive cells are removed through apoptosis, but cancer cells undergo genetic and epigenetic

changes that impair apoptotic pathways and promote survival mechanisms, allowing them to proliferate even under oncogenic pressure. This imbalance is a fundamental characteristic of cancer and plays a crucial role in both the initiation and advancement of tumors.[143]

Reactivating apoptosis in cancer treatment is a key strategy. The use of clinically approved BH3-mimetics, such as venetoclax, which targets BCL-2, supports this method. Research is underway to investigate combinations that reduce apoptotic thresholds, including MCL-1 inhibitors, IAP antagonists, and TRAIL pathway agonists. Additionally, pairing the reactivation of apoptosis with immunotherapy may turn dying cancer cells into local vaccines. However, tumors often develop resistance by upregulating other BCL-2 family members, increasing autophagy, and altering metabolism. Therefore, contemporary strategies recommend synergistic combinations of apoptosis sensitizers with inhibitors of survival pathways.[145]

Survival signaling pathways play a critical role in enhancing cell viability and invasive capabilities. Pathways such as the oncogenic PI3K–AKT–mTOR and RAS–MAPK promote the expression of anti-apoptotic proteins, support metabolic adaptation, and activate mobility-related programs. The NF-κB signaling pathway, often persistently activated in tumors, facilitates the transcription of genes that promote survival, inflammatory responses, and enzymes involved in matrix remodeling, all of which contribute to invasion. Additionally, autophagy has a role that varies with context: while it may inhibit tumor progression in the early stages of cancer, in established tumors, it aids survival in low-oxygen and nutrient-poor conditions, fostering therapy resistance and increasing metastatic capability.[145]
Resistance to anoikis, the process of apoptosis triggered by detachment, plays a crucial role in facilitating invasion and spread. Epithelial-to-mesenchymal transition (EMT) reduces signals that promote epithelial adhesion while enhancing survival pathways (including integrin signaling, SRC, FAK, and PI3K/AKT), which allows detached cancer cells to withstand circulation and establish growth in distant locations. Additionally, there is a connection between apoptotic signaling and EMT; some apoptotic signals can encourage survival and inflammation, favoring the emergence of more invasive cell variants.[144]

A key therapeutic strategy In cancer treatment involves reactivating apoptosis. The effectiveness of this method is underscored by clinically endorsed BH3-mimetics like venetoclax, which targets BCL-2. Current studies are examining combinations aimed at reducing apoptotic thresholds, such as MCL-1 inhibitors, IAP antagonists, and TRAIL pathway agonists. Additionally, combining apoptosis reactivation with immunotherapy can transform dying cancer cells into in situ vaccines. However, tumors can develop resistance by upregulating other BCL-2 family members, boosting autophagy, and altering metabolism. Consequently, modern strategies favor carefully designed combination therapies that include apoptosis sensitizers alongside inhibitors that target survival pathways.[146]

The tumor microenvironment (TME) plays a crucial role in influencing the balance between apoptosis and survival, which impacts invasion. Factors such as hypoxia, stromal cytokines, cancer-associated fibroblasts, and immune-suppressive cells

enhance survival signals and help select for apoptosis-resistant cell populations. In contrast, treatments aimed at reshaping the TME by normalizing blood vessels and diminishing immune suppression can reduce survival signals and make tumors more susceptible to apoptosis. Therefore, effective anti-metastatic therapies must tackle intrinsic apoptotic deficiencies as well as the external survival signals present in the microenvironment.[147]

Clinical and therapeutic implications

Biomarkers of cell injury and adaptation

Framework for biomarkers and their clinical applications. Biomarkers indicative of cell damage and adaptive responses fulfill various clinical functions: they enable early injury detection, assess severity, track progression or recovery, inform intervention timing, and act as surrogate endpoints in clinical trials. Their development necessitates stringent technical validation (assay accuracy), biological validation (specificity for particular cell types or pathways), and evidence of clinical applicability during relevant phases of injury progression. Contemporary frameworks focus on dynamic sampling (considering kinetics), the use of multimarker panels that reflect interconnected biological processes (such as injury, inflammation, and repair), and the integration of clinical and imaging data to enhance decision-making and trial design. Since 2021, translational efforts have underscored the importance of a phased approach to biomarker qualification (discovery → validation → utility) for effectively translating findings from research to clinical practice.[148]

Biomarkers for cardiac injury: troponins and additional markers. High-sensitivity cardiac troponins (hs-cTnI/T) are the primary standard for identifying myocardial damage due to their exceptional sensitivity and cardiac specificity. Their rise and fall patterns are crucial for diagnosing acute myocardial infarction, assessing risk, and monitoring progress. Recent literature (2021–2024) highlights supplementary markers used in conjunction such as CK-MB (which is less specific), myoglobin (which provides early indication but lacks specificity), heart-type fatty acid binding protein (H-FABP), and innovative panels that integrate troponins with inflammatory or oxidative stress indicators for a more accurate prognosis, particularly in complicated situations like sepsis, cardiotoxicity, and COVID-19. It's critical to ensure assay standardization and consider the clinical context to prevent misinterpretation, such as the chronic elevation of troponins in structural heart diseases.[149]

Biomarkers for Neurological Injury: NfL, GFAP, UCH-L1, and Imaging Integration. Neuronal and glial proteins found in blood and cerebrospinal fluid, including neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), UCH-L1, and S100B, have developed into reliable biomarkers for acute neuronal damage, such as traumatic brain injury and stroke, as well as for tracking chronic neurodegenerative conditions. NfL is indicative of axonal injury and has been linked to outcomes across different scenarios, while GFAP is more specific to astrocyte damage and is useful for assessing acute structural injuries. Recent guidelines highlight the need for standardized testing methods, appropriate timing for sample collection (early versus delayed), and the integration of these fluid biomarkers with imaging techniques to improve prognosis and patient selection in neuroprotective studies. The implementation of these assays in clinical laboratories has rapidly advanced since 2021.[150]

Liver injury indicators: cytokeratin-18, ALT/AST context, and adaptive signaling. Traditional transaminases (ALT, AST) signal liver cell damage but do not specify the type of cell death or prognosis. Circulating fragments of cytokeratin-18 (M30/M65) indicate caspase-mediated (apoptotic) versus overall epithelial cell death and have shown potential in assessing NASH severity and predicting outcomes. Additional markers (CK18, miRNAs, keratin fragments, extracellular vesicle profiles) help differentiate adaptive steatosis from harmful NASH. Recent clinical research (2021–2024) endorses the use of panels (CK-18 plus fibrosis biomarkers and imaging) to minimize liver biopsy requirements and track therapeutic responses in antifibrotic studies.[151]

Biomarkers for kidney and acute organ damage: NGAL, KIM-1, and TIMP-2·IGFBP7. In cases of acute kidney injury (AKI), the delayed response of creatinine has led to the identification of early tubular injury indicators such as neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), and the stress markers TIMP-2·IGFBP7, which are utilized in the NephroCheck test. Recent reviews since 2021 underscore that integrating injury biomarkers with functional assessments enhances the ability to predict the need for renal replacement therapy, facilitating earlier supportive or nephroprotective measures. Nonetheless, there are ongoing challenges related to specificity (such as in sepsis and chronic kidney disease) and the clinical validation of action thresholds.[152]

Pan-tissue indicators: DAMPs, oxidative stress indicators, and death pathway profiles. Damage-associated molecular patterns (DAMPs), including HMGB1, cell-free mitochondrial DNA, and extracellular histones, indicate uncontrolled cell membrane damage or immunogenic cell death, while also linking to inflammation and poorer outcomes in sepsis, trauma, and organ preservation. Measurements of oxidative stress (such as 8-oxo-dG, isoprostanes, and antioxidant capacity tests) alongside lipid-peroxidation products reveal underlying mechanisms (e.g., susceptibility to ferroptosis). Recent literature suggests that integrating DAMPs with regulated death pathway markers (like necroptosis/ferroptosis signatures) could enhance prognostication and inform targeted therapies (e.g., antioxidants, ferroptosis inhibitors, DAMP antagonists) in critical care and transplantation.[153]

Clinical Translation, Therapeutic Implications, and Future Directions. For biomarkers to be clinically useful, they must correlate with an intervention that leads to a positive change in outcomes; otherwise, they serve only as prognostic tools. The most significant biomarkers are those that pinpoint treatable moments (for instance, troponin levels for timing of reperfusion, brain biomarkers for identifying candidates for neuroprotection, and markers for acute kidney injury that activate nephroprotective strategies). Emerging therapeutic uses involve: (a) utilizing biomarkers to enhance clinical trial participation by selecting patients who are likely to gain the most benefit, (b) applying serial biomarker trends as early surrogate endpoints to expedite drug development, and (c) creating companion diagnostics that align a biomarker profile with a specific therapy (such as a ferroptosis signature paired with GPX4/FSP1-targeting treatments). Current hurdles include standardizing assays, ensuring biological

specificity, conducting cost-effectiveness analyses, and executing prospective trials to demonstrate that biomarker-guided interventions lead to improved outcomes.[153]

Therapeutic targets: Clinical and Therapeutic Considerations: Targets for Treatment

Antioxidants play a crucial role in addressing oxidative stress, which is linked to conditions such as ischemia-reperfusion injury, neurodegeneration, chronic inflammation, and cancer. This has led to their exploration as potential therapies. Strategies include: (a) small-molecule scavengers and chain-breaking antioxidants (e.g., vitamin E derivatives), (b) enzyme-mimicking compounds (e.g., SOD mimetics), and (c) methods that enhance natural defenses (e.g., NRF2 and GSH activators). While preclinical studies suggest that targeted antioxidants can mitigate damage and enhance function, larger clinical trials often yield inconclusive results. Current literature stresses the importance of tailored antioxidant delivery, optimal timing, and patient stratification based on oxidative stress markers.[154,155]

Mitochondrial protectants (mechanisms, examples, and current status). Given the crucial roles mitochondria play in ATP synthesis, calcium management, and reactive oxygen species (ROS) production, safeguarding their structure and function presents a compelling therapeutic avenue. Various mechanistic strategies have been proposed, including (1) the stabilization of cardiolipin and the architecture of cristae (such as with elamipretide/SS-31), (2) the selective delivery of antioxidants to the mitochondrial matrix (e.g., MitoQ, SkQ), (3) the modulation of mitochondrial dynamics and mitophagy (utilizing Drp1 and PINK1/Parkin modulators), and (4) the inhibition of maladaptive permeability transition through mPTP inhibitors. Elamipretide, a tetrapeptide that targets mitochondria by binding to cardiolipin, along with other small molecules aimed at mitochondria, has demonstrated reliable protective effects in preclinical studies related to heart failure, ischemia-reperfusion injury, and mitochondrial myopathies. Additionally, encouraging results have emerged from early-phase clinical trials, though ongoing larger pivotal studies are needed to establish clear clinical outcomes. Recent reviews emphasize that mitochondrial therapies should show effective tissue delivery, engage targets (enhancing bioenergetics and reducing mitochondrial ROS), and achieve clinically relevant results. Strategies combining mitochondrial stabilizers with upstream reperfusion or anti-inflammatory treatments seem particularly promising.[156,157]

Modulating ER stress (targets, agents, and clinical potential). The unfolded protein response (UPR) and endoplasmic reticulum (ER) stress play significant roles in various diseases, including metabolic disorders, neurodegenerative conditions, ischemia, and cancer, making the ER stress pathway an attractive target for drug development. Therapeutic approaches encompass the use of chemical chaperones to aid in protein folding (such as tauroursodeoxycholic acid, TUDCA, and 4-phenylbutyrate, 4-PBA), small-molecule inhibitors or modulators of UPR sensors (including PERK inhibitors, IRE1 RNase inhibitors, and ATF6 modulators), as well as agents aimed at restoring Ca^{2+} homeostasis between the ER and mitochondria or improving ER proteostasis (like HSP modulators and ERAD enhancers). Preliminary and early clinical findings indicate that chemical chaperones and targeted UPR modulators can lower markers of ER stress, reduce cell death, and enhance organ function across various models (such as liver

regeneration, neuroprotection, and metabolic diseases). However, UPR responses are highly context-sensitive: while transient activation is beneficial, persistent inhibition may have adverse effects. Consequently, recent reviews emphasize the importance of selective modulation of pathways (e.g., partial inhibition of PERK instead of complete shutdown), appropriate timing, and biomarker-driven patient selection to ensure the safe application of ER-stress-targeted therapies.[158,159]

Emerging intervention

Gene editing techniques, especially the CRISPR/Cas system, have transformed therapeutic methods for cell damage by enabling targeted alterations in genetic pathways related to cell survival and death. Recent developments reveal that CRISPR-based techniques can rectify mutations associated with apoptosis imbalance, adjust necroptosis regulators, and improve resilience against oxidative stress in laboratory models. Moreover, preclinical research is advancing toward clinical applications, showcasing the potential of gene editing for ischemic injuries, neurodegenerative diseases, and hereditary metabolic conditions.[160]

Stem cell therapy is an emerging field that not only shows promise for regeneration but also provides paracrine signaling advantages that reduce apoptosis, necrosis, and fibrosis. For instance, mesenchymal stem cells (MSCs) release extracellular vesicles loaded with anti-apoptotic and pro-angiogenic factors, enhancing tissue repair after ischemic injury. Additionally, advancements in genetic modification have improved stem cell survival in challenging environments, while scaffold engineering optimizes their integration and performance. These approaches highlight the potential of stem cell therapies to support both structural repair and the modulation of harmful stress responses.[161]

Nanomedicine has developed into a dynamic therapeutic approach that facilitates the precise delivery of medications, antioxidants, and genetic materials to damaged tissues with exceptional accuracy. These nanoformulations can help alleviate oxidative stress, stabilize mitochondrial membranes, and reduce endoplasmic reticulum (ER) stress by transporting protective agents directly into the affected cells. For instance, specially designed nanoparticles aimed at ischemic heart tissue have demonstrated considerable effectiveness in minimizing cell death and enhancing recovery. Likewise, nanocarriers created to introduce antioxidants or iron chelators are showing promise in influencing ferroptosis and other regulated cell death mechanisms.[162]

Combination therapies are increasingly seen as essential for effectively tackling complex diseases characterized by various types of cell death. Research has demonstrated the synergistic potential of merging gene editing with stem cell therapy or combining nanomedicine with CRISPR-based approaches in preclinical trials. These methods underscore the need to address not only the genetic factors at play but also the environmental stresses that lead to cell damage. Nevertheless, implementing these strategies in clinical practice necessitates thorough assessment of long-term safety, ethical implications, and the ability to scale manufacturing.[163]

Future perspective

Innovations aimed at enhancing organelle quality, particularly in mitochondria, will be a key focus in the next 5 to 10 years. Mitochondrial issues are central to energy depletion, reactive oxygen species (ROS) production, and the activation of programmed cell death. Increasing preclinical and early clinical investigations emphasize improving mitochondrial health through techniques like mitophagy manipulation, promoting mitochondrial biogenesis via PGC-1α pathways, utilizing mitochondria-targeted antioxidants, and even considering mitochondrial transplantation to swiftly restore cellular energy post-injury. These methods hold the potential for organ-level recovery (in the heart, brain, and kidneys), but require advancements in delivery methods, longevity, and safety data in human studies.[164]

Systems biology and omics approaches to Cell injury

Systems biology shifts the focus of cell injury from the traditional single-gene/single-pathway perspective to a more integrated view of interconnected, multi-level processes. Rather than pinpointing a sole failing molecule, this approach examines how various molecular module such as metabolism, protein maintenance, immune response, and organelle quality control interact over time and among different cell types to influence outcomes, whether repair or cell death. This viewpoint is crucial in injury contexts, as both adaptive and harmful responses intersect at common points (e.g., mTOR, UPR, mitophagy), where the specifics of timing, intensity, and interactions can determine a cell's fate. Recent reviews and system analyses compile methodologies that facilitate these complex, multi-node deductions.[165]

Multi-omics, encompassing genomics, transcriptomics, proteomics, phosphoproteomics, metabolomics, and lipidomics, offers complementary insights into the molecular condition of damaged cells. Transcriptomic analysis uncovers changes in gene expression and shifts in cell states, while proteomic studies reveal signaling activities and post-translational modifications that may not align with RNA levels. Additionally, metabolomic and lipidomic analyses highlight the functional outcomes of disrupted pathways, such as ATP depletion and lipid peroxidation, influencing cell fate processes like ferroptosis. Reviews on methodologies stress the importance of meticulous experimental design, including time-series sampling and standardized processing, as well as statistical integration techniques, to effectively interpret multi-omics data.[166]

Novel imaging and diagnostic tools

Molecular and targeted PET imaging is advancing rapidly beyond FDG, offering pathway-specific insights into disease biology with new tracers for conditions like hypoxia, amino acid metabolism (glutamine), fibroblast activation protein (FAP), and various receptor targets (e.g., GRPR, integrins). These advanced radiotracers empower clinicians and researchers to pinpoint not just the presence of injury or disease but also the active biochemical processes, enhancing early detection of pathological changes and allowing for better-targeted therapies. Recent reviews from 2023–2025 highlight these emerging agents and demonstrate how pathway-selective PET can improve early treatment response assessments compared to anatomical imaging alone.[167]

Hyperpolarized (HP) MRI, particularly ^13C-pyruvate imaging, offers a unique noninvasive approach to monitor tissue metabolism, distinguishing between glycolysis and oxidative processes. Its temporal resolution enables the detection of early metabolic

changes following injury or treatment. Unlike standard MRI, HP-MRI provides real-time data on substrate conversion (e.g., pyruvate transforming into lactate), showing potential in cancer, cardiometabolic disorders, and ischemia models to identify metabolic dysfunction or recovery before any structural changes occur. Recent reviews highlight clinical pilot studies and advancements that are advancing HP-MRI from experimental contexts to targeted clinical use.[168]

Photoacoustic imaging (PAI) and similar optoacoustic techniques merge the benefits of optical contrast with the deep penetration capabilities of ultrasound, allowing for detailed imaging of hemoglobin oxygenation, blood vessel structures, and specific optical markers at depths exceeding that of conventional optical microscopy. PAI is particularly effective for imaging functional blood vessels, mapping inflammation, and defining tumour boundaries. Recent advancements noted in literature from 2022 to 2025 emphasize enhancements in signal clarity, the development of portable clinical systems, and the use of machine-learning for image reconstruction, making PAI increasingly practical for use in clinical settings or during surgery. The technique is particularly valuable when integrating anatomical and functional data such as oxygen levels, blood flow, and specific contrast agents to inform immediate medical interventions, including wound evaluations, assessments of tumor blood supply, and the characterization of inflammatory lesions.[169]

Personalized medicine approaches

Modern personalized medicine is built on the foundations of genomic and molecular analysis. Techniques such as diagnostic sequencing (including whole-exome and genome sequencing, as well as targeted panels) uncover actionable mutations, pharmacogenomic variations, and Mendelian conditions that can significantly influence treatment decisions (like targeted therapies, enzyme replacement, or personalized drug choices). This approach has revolutionized cancer treatment (through tumor sequencing leading to targeted inhibitors and tumor-agnostic approvals) and care for rare diseases (with swift genetic diagnostics informing gene therapies and tailored supportive care). Recent large-scale reviews highlight how next-generation sequencing and clinical genomics have become standard diagnostic tools, enabling customized therapies.[170]

Digital technologies and artificial intelligence have enhanced personalization efforts by merging intricate datasets (such as imaging, multi-omics, and electronic health records) to forecast patient outcomes, medication effectiveness, and potential side effects. Generative and predictive AI techniques facilitate the discovery of biomarkers, simulation of in-silico trials, and the development of tailored treatment plans. However, recent evaluations highlight the urgent need for thorough validation, transparency, regulatory oversight, and bias reduction prior to their standard application in clinical settings. In addition to laboratory assays, high-sensitivity liquid biopsies (including cfDNA, methylation, and extracellular vesicle content) and sophisticated proteomics utilizing mass spectrometry are providing non-invasive, real-time assessments that support flexible and responsive treatment strategies.[171]

In conclusion, effectively implementing personalized strategies necessitates a focus on validating biomarkers, regulatory measures, equity, and clinical execution. While regulatory systems are adapting to allow biomarker-based approvals and flexible trial

methodologies, challenges such as standardized analysis processes, consistent assay results across different sites, reimbursement structures, and healthcare system preparedness still exist. Recent reviews from 2022 to 2024 highlight practical actions such as sharing data before competition, creating prospective validation groups, integrating companion diagnostics, and training clinicians to transition precision healthcare from theoretical research to equitable, evidence-driven medical practice. Collectively, this shift signifies a move from the concept of "precision promise" to the actualization of scalable personalized medicine, particularly at the intersection of molecular targets, validated biomarkers, and effective treatments.[172]

V. Conclusion

Cell injury is a fundamental concept in pathology, connecting environmental factors, genetic vulnerabilities, and adaptive mechanisms to the development and advancement of diseases in humans. Research across various domains morphological, biochemical, molecular, and systems-level demonstrates that injury exists on a continuum rather than as a simple yes or no condition. This range spans from reversible adaptations to severe, irreversible cell death. Key indicators like cellular swelling, fatty changes, and damage to organelles continue to be crucial for diagnosis. However, recent advancements in biochemistry and imaging techniques, such as the identification of enzyme leakage, troponins, and high-resolution imaging, facilitate earlier and more accurate assessments of injury progression. Additionally, adaptive responses, including hypertrophy, hyperplasia, atrophy, and metaplasia, illustrate the flexibility of cells when faced with stress. Nonetheless, numerous studies indicate that these adaptive mechanisms can shift from being compensatory to pathological, contributing to the development of chronic conditions such as fibrosis, cancer, and neurodegeneration.

Recent breakthroughs in molecular biology and omics technologies have yielded remarkable insights into the signaling pathways and regulatory mechanisms that dictate a cell's fate whether it will adapt, recover, or undergo regulated cell death. The combination of multi-omics with spatial and single-cell analysis is uncovering the diverse responses to injury within tissues, while systems biology approaches are pinpointing critical "decision points" that could be targeted for therapy. Additionally, emerging concepts such as ferroptosis, necroptosis, and pyroptosis demonstrate how these programmed cell death processes not only play a role in disease but also offer potential avenues for therapeutic intervention, particularly in cancer treatment and immune system modulation.

In the realm of translational medicine, innovative diagnostic technologies such as liquid biopsies, photoacoustic imaging, hyperpolarized MRI, and advanced PET tracer are elevating diagnostics from mere structural assessments to insights into function and molecular characteristics. When integrated with AI-powered analytics and interpretable radiomics, these advancements facilitate earlier detection, improved prognostic accuracy, and individualized tracking of treatment effectiveness. Additionally, personalized medicine approaches, rooted in genomics and multi-omics integration, along with organoid-based assays, are transitioning from theory to practice, allowing treatments to be customized not only to the disease but also to the unique molecular profile of each patient.

The exploration of cell Injury has significantly evolved, blending traditional pathology with modern advancements. While classical pathology serves as the core framework, the integration of omics, imaging, and computational technologies provides unprecedented mechanistic insights and practical applications that were unimaginable just ten years ago. The path forward involves merging these area combining morphological and biochemical characteristics with systems-level and personalized insights to develop strategies that not only avert irreversible damage but also leverage adaptive responses for therapeutic benefits. By reconceptualizing cell injury through the perspectives of precision pathology and systems medicine, both researchers and clinicians can transition from reactive disease treatments to proactive strategies aimed at maintaining cellular health.

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