Review Article

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Life inside the cell: A modern review of cellular physiology and molecular regulation

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ABSTRACT

Cell physiology is fundamental to all life processes, as every biological function depends on molecular regulation and organelle dynamics within cells. Advances in technology, such as high-resolution microscopy, multi-omic approaches, and genome engineering, have revealed new complexities in how cells process information, maintain homeostasis, and respond to stress. This review aimed to summarize recent developments in the understanding of cell physiology, molecular regulation, and their implications for health and disease. Cell architecture, including eukaryotic compartmentalization and cytoskeletal dynamics, determines the coordination of signal transduction, metabolism, and adaptive responses. Major pathways such as MAPK, PI3K/AKT, NF-κB, and mTOR integrate environmental signals to regulate cell proliferation, differentiation, and survival. Genetic and epigenetic regulation, including transcription factor activity, histone modifications, and ncRNA, provides layered control that ensures precise gene expression. At the protein level, the proteostasis system involving chaperones, proteasomes, and autophagy maintains protein quality and prevents toxic aggregation. The dynamics of organelles, mitochondria, ER, and lysosomes regulate energy, protein folding, and metabolism through complex cross-organelle interactions. Stress responses such as the heat shock response, unfolded protein response, and the NRF2 antioxidant pathway enable cells to adapt to disturbances in homeostasis. The integration of molecular signaling, genetic regulation, proteostasis, and organelle dynamics demonstrates that cell physiology is a highly coordinated regulatory network. Although much progress has been made, the spatio-temporal relationships between pathways and the long-term effects of environmental stress remain important gaps in our knowledge. This understanding opens new avenues for basic research and cell-based therapy development.

Introduction

Cell physiology is the foundation of all life processes because every biological function at the organism level is rooted in the dynamics that occur within cells (Rosslenbroich, 2016). In the era of modern biology, understanding of how cells process information, maintain homeostasis, and respond to environmental changes has rapidly advanced thanks to technological advances such as high-resolution microscopy, next-generation sequencing, and multi-omic approaches (Ruprecht *et al*., 2024). Cells are no longer viewed as passive structural units, but as dynamic entities with complex regulatory capabilities through organized molecular interactions (Beck *et al*., 2024). These developments have placed cell physiology at the center of explaining disease pathogenesis, therapeutic innovation, and biological adaptation in various organismal systems (Lindsey and Douglas, 2025).

Within cells, biological information flow is controlled through signal transduction mechanisms involving surface receptors, adapter proteins, and enzymatic networks such as kinases and phosphatases (Zhang *et al*., 2025). Classic pathways such as Mitogen-Activated Protein Kinase (MAPK), Phosphoinositide 3-Kinase / Protein Kinase B (PI3K/AKT), and Janus Kinase / Signal Transducer and Activator of Transcription (JAK/STAT) play an important role in integrating external signals to regulate proliferation, apoptosis, and metabolism (Hu *et al*., 2021). These regulatory mechanisms are spatial-temporal in nature, meaning that molecular activity can change according to subcellular location or cell cycle phase (Erenpreisa *et al*., 2023). Additionally, positive and negative feedback systems ensure that cellular responses remain controlled and do not develop into pathological conditions, such as hyperproliferation in cancer or inflammatory dysregulation in degenerative diseases (Chavez-Dominguez *et al*., 2021). Thus, molecular regulation not only determines basic physiological functions but also determines the direction of cellular adaptive responses to stress (Haykin and Rolls, 2021).

In addition to signaling systems, cellular homeostasis is greatly influenced by the dynamics of organelles such as mitochondria, endoplasmic reticulum (ER), and lysosomes (Zhang *et al*., 2023a). Mitochondria act as bioenergetic centers that regulate energy production, but also as stress sensors through the release of Reactive Oxygen Species (ROS) and pro-apoptotic proteins (Casanova *et al*., 2023). The ER plays a key role in protein synthesis and detoxification, where the activation of the unfolded protein response (UPR) becomes a compensatory mechanism when misfolded proteins accumulate (Yap *et al*., 2021). Lysosomes, previously understood only as degradation compartments, are now known to have metabolic regulatory functions through the mechanistic Target of Rapamycin Complex 1 (mTORC1) pathway (Settembre and Perera, 2024). These inter-organelle relationships form a physiological network that ensures cell survival under both physiological and pathological conditions (Genovese *et al*., 2022). An imbalance in any one component can trigger a chain reaction leading to cellular dysfunction (Liu *et al*., 2022a).

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In addition, gene expression regulation plays a fundamental role in determining cell phenotype (Carthew, 2021). This process depends not only on transcription factor activity but also involves epigenetic mechanisms such as Deoxyribonucleic Acid (DNA) methylation, histone modification, and non-coding Ribonucleic Acid (RNA) regulation (Bure *et al*., 2022). Recent technologies show that small RNAs such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have the ability to finely but significantly regulate mRNA stability and protein activity (Chen and Kim, 2024). This complexity provides cells with flexibility in adapting to environmental stimuli, including nutrition, oxidative stress, and inflammatory mediators (Iakovou and Kourti, 2022). Disruption of epigenetic mechanisms has been shown to contribute to various chronic diseases such as cancer, neurodegenerative disorders, and metabolic dysfunction (Farsetti *et al*., 2023).

Despite rapid progress, there are still gaps in knowledge regarding intermolecular integration and how specific environmental factors modulate cell physiology in the long term (Tan *et al*., 2022). Cross-organelle interactions, biomolecular liquid-liquid phase separation dynamics, and cellular responses to metabolic stress are areas that are not yet fully understood (Lin *et al*., 2025). This complexity highlights the need for comprehensive information synthesis to integrate the latest findings within a broader biological context. Therefore, this review was compiled to summarize recent developments in cell physiology and molecular regulation, while highlighting existing knowledge gaps and future research directions.

Overview of cellular architecture

Cell architecture is fundamental to understanding the physiology and molecular regulation that govern life at the microscopic level (Harold, 2005). Although all organisms are composed of cells, the diversity of their internal structures reflects different levels of biological complexity among life groups (Antifeeva *et al*., 2022). In general, cells can be categorized into two main forms, prokaryotes and eukaryotes, which exhibit fundamental differences in their organization and compartmentalization (Lamża, 2023). Prokaryotic cells, such as bacteria and archaea, have a relatively simple architecture with no membrane-bound organelles (Murat *et al*., 2010). Genetic material is located in a membrane-less nucleoid region, while transcription and translation occur simultaneously in the cytoplasm (Fefilova *et al*., 2022). Despite their simplicity, prokaryotic cells are not entirely "structurally minimal"; they possess primitive cytoskeletal elements such as Filamenting temperature-sensitive mutant Z (FtsZ) and Morphogenesis protein B (MreB) that regulate cell division and morphology, confirming that structural complexity emerged long before the evolution of eukaryotic cells (Irastortza-Olaziregi and Amster-Choder, 2021).

In contrast, eukaryotic cells exhibit a much higher level of internal organization through the presence of membrane-bound compartments that enable the separation of biochemical functions (Zhukov and Popov, 2023). The nucleus protects genetic information and serves as the center of gene expression regulation, while organelles such as mitochondria, endoplasmic reticulum, Golgi apparatus, lysosomes, and peroxisomes regulate different but interconnected metabolic pathways (Sengupta and Levy, 2024). This compartmentalization provides significant functional advantages, including metabolic efficiency, tighter regulatory capabilities, and coordination of complex processes such as protein synthesis, signal transduction, and ionic homeostasis (Bar-Peled and Kory, 2022). Furthermore, physical connections between organelles via membrane contacts, for example, between the endoplasmic reticulum and mitochondria, indicate that cellular communication relies not only on vesicular trafficking but also on direct integration between compartments (Zhang *et al*., 2023b).

The modern understanding of cell organization emphasizes that subcellular structures are highly dynamic (Beck *et al*., 2024). The cell membrane system and its organelles not only form physical boundaries but also function as active platforms for signal transduction, metabolic regulation, and adaptation to environmental changes (Picard and Shirihai, 2022). Mechanisms such as membrane fusion and fission, endocytic and exocytic vesicle formation, and lipid domain reorganization enable cells to respond to stimuli quickly and specifically (Cui *et al*., 2022). On the other hand, the cytoskeletal network, which includes actin microfilaments, microtubules, and intermediate filaments, acts as a dynamic framework that maintains cell shape, regulates organelle distribution, and drives intracellular transport via motor proteins (He *et al*., 2022). Close interactions between the cytoskeleton and plasma membrane also enable mechanotransduction, which is the ability of cells to convert mechanical signals into biochemical responses (Uray and Uray, 2021). The overall differences in cellular organization between prokaryotic and eukaryotic cells are summarized in Figure 1.

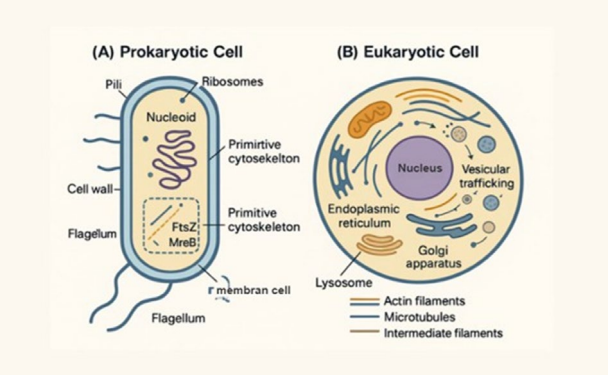

Figure 1. Comparative schematic of prokaryotic (A) and eukaryotic (B) cell architecture.

Molecular basis of cellular regulation

Molecular-level cellular regulation is the main foundation that ensures cells are able to maintain homeostasis, respond to environmental stimuli, and perform physiological functions in a coordinated manner (Lennicke and Cochemé, 2021).

Genetic and epigenetic regulation

Gene activity regulation is an essential process that ensures each cell can perform its biological functions properly (Carthew, 2021). At the genetic level, gene expression is controlled through a series of mechanisms that include transcription initiation, messenger RNA (mRNA) processing, translation, and protein degradation (Buccitelli and Selbach, 2020). Transcription factors play a role in recognizing promoter and enhancer sequences, while chromatin structure dynamics determine DNA accessibility to the transcription machinery (Ito *et al*., 2022). This combination of interactions allows cells to respond to physiological changes, maintain homeostasis, and undergo specific differentiation (Van Neerven and Vermeulen, 2023).

In addition to genetic regulation, epigenetic mechanisms provide an additional layer of control without altering the DNA sequence (Fitz-James and Cavalli, 2022). Epigenetic modifications such as DNA methylation, histone modifications, and non-coding RNA (ncRNA) activity play a major role in determining long-term gene expression patterns (Kan *et al*., 2022). DNA methylation, especially at Cytosine-phosphate-Guanine (CpG) dinucleotides, is typically repressive of transcription (Adetunji *et al*., 2025). Conversely, histone acetylation reduces histone–DNA interactions, thereby opening the chromatin structure and increasing gene expression (Shvedunova and Akhtar, 2022). Other types of histone modifications can stimulate or inhibit transcription depending on the enzymes and residues involved (Millán-Zambrano *et al*., 2022). Meanwhile, ncRNAs such as microRNAs and lncRNAs regulate gene expression at the post-transcriptional level through translation inhibition or accelerated mRNA degradation (Sebastian-delaCruz *et al*., 2021).

Protein homeostasis (Proteostasis)

Proteostasis or protein homeostasis is an integrated system that ensures the quality, stability, and availability of proteins necessary for cell function (Shukla and Narayan, 2025). Since proteins are the main working molecules in almost all biological processes, cells must maintain a balance between synthesis, folding, assembly, and degradation (Wen *et al*., 2023). Disruption of this mechanism not only reduces the functional capacity of cells but also contributes to various degenerative, inflammatory, and even cancerous diseases (Chaudhary *et al*., 2023).

The proteostasis process begins at the early stages of protein synthesis, when new polypeptide chains emerging from the ribosome must be folded correctly to obtain a stable three-dimensional structure (Shukla and Narayan, 2025). This folding is aided by chaperone proteins, such as Heat shock protein 70 (Hsp70) and Heat shock protein 90 (Hsp90), which prevent polypeptide aggregation through an Adenosine triphosphate (ATP)-dependent binding–release cycle mechanism [Rutledge *et al*., 2022]. Chaperonins, such as the TCP-1 Ring Complex / Chaperonin Containing TCP-1 (TRiC/CCT) complex, provide an isolated environment that allows large polypeptides or complexes to fold properly (Shen and Willardson, 2025). Changes in cellular conditions—including heat stress, accumulation of oxidative species, or metabolic disturbances can increase the burden of misfolded proteins, which then triggers a heat shock response as an adaptive effort to increase chaperone expression (Que *et al*., 2024).

When proteins fail to fold correctly or undergo irreparable structural damage, cells divert them to the degradation pathway to prevent the formation of toxic aggregates (Wen *et al*., 2023). The main system involved is the ubiquitin-proteasome pathway, in which proteins tagged with ubiquitin are recognized and degraded by the 26S proteasome (Li *et al*., 2022). This process is crucial in regulating the cell cycle, degrading regulatory proteins, and clearing proteins susceptible to damage (Zou and Lin, 2021). However, proteasome capacity can become limited when there is a large accumulation of abnormal proteins, especially under conditions of chronic stress or aging (Frankowska *et al*., 2022).

As a complementary mechanism, cells also use the autophagy pathway to eliminate damaged proteins, protein aggregates, or even dysfunctional organelles (Wen *et al*., 2023). Macroautophagy occurs through the formation of autophagosomes that engulf cytoplasmic cargo and then fuse with lysosomes for degradation (Wang *et al*., 2023). This pathway is crucial for maintaining long-term homeostasis, especially in tissues with low cell turnover rates such as neurons and muscle (Banjac *et al*., 2023). Additionally, chaperone-mediated autophagy (CMA) provides specific control over proteins containing specific degradation motifs, thereby offering an additional layer of regulation (Pan *et al*., 2025).

Signal transduction pathways

Signal transduction is a fundamental mechanism that enables cells to maintain homeostasis, respond to environmental changes, and regulate physiological processes such as proliferation, differentiation, metabolism, and survival (Picard and Shirihai, 2022). This system involves a series of coordinated interactions between cell surface receptors, adapter proteins, signal-converting enzymes, and transcription factors that collectively convert extracellular signals into targeted intracellular responses (Chandel, 2021). Signal transduction pathways are dynamic, overlapping, and mutually modulating, creating a complex regulatory network that ensures precise cellular reactions (Gao *et al*., 2023). Table 1 summarizes the major signal transduction pathways involved in regulating proliferation, differentiation, metabolism, immunity, stress responses, and cellular homeostasis.

One of the main pathways in cell regulation is the MAPK pathway, which consists of the ERK, c-Jun N-terminal Kinase (JNK), and p38 modules (García-Hernández *et al*., 2021). The MAPK pathway controls proliferation, differentiation, and stress responses (Whitaker and Cook, 2021). MAPK activation occurs through a sequential phosphorylation cascade that begins with Rat sarcoma–Rapidly accelerated fibrosarcoma–Mitogen-activated protein kinase kinase–Extracellular signal-regulated kinase (Ras–Raf–MEK–ERK), which then stimulates the expression of target genes in the nucleus (Pua *et al*., 2022). This pathway is highly sensitive to growth and environmental stress, making it an important regulatory center in development and tumorigenesis (Li *et al*., 2024).

The PI3K/AKT pathway is a major regulator of cellular metabolism, growth, survival, and stress response (Tian *et al*., 2023). Phosphoinositide 3-Kinase (PI3K) activation triggers Phosphatidylinositol (3,4,5)-trisphosphate (PIP3) production in the plasma membrane, which recruits and activates Protein Kinase B (AKT) (Glaviano *et al*., 2023). The AKT protein then modulates various downstream effectors, including mTOR, Glycogen Synthase Kinase 3 beta (GSK3β), and Forkhead box O (FOXO) (He *et al*., 2021). Disruption of the PI3K/AKT pathway, whether due to somatic mutations or excessive growth receptor activation, is a common feature in various cancers and metabolic diseases (Stefani *et al*., 2021).

Table 1. Main signal transduction pathways and their functions.

Signal path	Primary function	Activation mechanism	Pathological relevance	References
MAPK (ERK, JNK, and p38)	Regulates proliferation, differentiation, and stress response	Tiered activation through the cascade Ras → Raf → MEK → ERK	Tumorigenesis, inflammatory response, and developmental disorders	(Pua *et al*., 2022)
PI3K/AKT	Controls metabolism, cell growth, survival, and metabolic stress	PI3K activation produces PIP3, which recruits AKT; AKT regulates mTOR, GSK3β, and FOXO.	Cancer, diabetes, insulin resistance, and metabolic dysfunction	(Glaviano *et al*., 2023)
NF-κB	Regulates inflammation, immunity, and oxidative stress response	Degradation of IκB due to TNF-α/IL-1 signaling allows NF-κB to enter the nucleus.	Autoimmune diseases, chronic inflammation, and cancer	(Guo *et al*., 2024)
mTOR (mTORC1 and mTORC2)	Nutrient/energy sensor regulates growth, biosynthesis, and autophagy	Integration of signals from AKT, AMPK, and cellular nutritional status	Obesity, type 2 diabetes, cancer, and metabolic disorders	(Szwed *et al*., 2021)
Wnt/β-catenin	Regulating cell identity, embryonic development, and tissue homeostasis	β-catenin stability is enhanced by Wnt signaling, thereby activating gene transcription.	Colorectal cancer, developmental disorders, and stem cell dysregulation	(Liu *et al*., 2022b)
Notch	Controlling cell differentiation, maintaining the stem cell niche	Ligand–receptor interactions between cells trigger proteolytic processing and activation of the Notch intracellular domain (NICD).	Leukemia, solid cancer, and developmental abnormalities	(Zhou *et al*., 2022)

The Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway plays an important role in inflammation, immunity, and oxidative stress regulation (Capece *et al*., 2022). Under basal conditions, NF-κB is bound by the Inhibitor of kappa B (IκB) in the cytoplasm (Prescott *et al*., 2021). Activation through proinflammatory signals such as Tumor Necrosis Factor alpha (TNF-α) or Interleukin-1 (IL-1) triggers phosphorylation and degradation of IκB, allowing NF-κB to translocate to the nucleus to induce the expression of inflammatory, anti-apoptotic, and immune response genes (Guo *et al*., 2024). Uncontrolled NF-κB activity is known to contribute to autoimmune diseases, chronic inflammation, and cancer (Mao *et al*., 2025).

The mTOR complex is a cellular nutrient and energy sensor that coordinates cell growth, metabolism, and ribosome biogenesis (Goul *et al*., 2023). mTOR functions through two main complexes, mechanistic Target of Rapamycin Complex 1 (mTORC1) and mechanistic Target of Rapamycin Complex 2 (mTORC2), which respond to nutritional status, growth signals, and metabolic stress (Szwed *et al*., 2021). mTORC1 integrates signals from AKT, AMP-activated protein kinase (AMPK), and environmental stress factors to regulate translation, autophagy, and cellular anabolism (Chun and Kim, 2021). Dysregulation of mTOR is frequently observed in obesity, type 2 diabetes, and various malignancies (Stanciu *et al*., 2024).

In addition to kinase-based pathways, signal transduction also involves developmental pathways such as Wnt and Notch, which regulate cell identity, embryonic development patterns, and adult tissue homeostasis (Whiteley *et al*., 2021). Wnt signaling regulates the stability of β-catenin, which acts as a transcription factor, while the Notch pathway relies on cell-neighbor interactions to control differentiation decisions through proteolytic processing of the Notch receptor (Liu *et al*., 2022b; Zhou *et al*., 2022). Both pathways are crucial for maintaining the stem cell niche and are often implicated in cancer when their activity is disrupted (Ju *et al*., 2022).

Cellular physiology

The physiological system of cells works through a series of integrated mechanisms that ensure each cell is able to produce energy, maintain homeostasis, regulate growth, and adapt to various forms of stress (Alzeer, 2024).

Cellular metabolism and energy regulation

Cellular metabolism is the main foundation that supports cell function and survival, with mitochondria acting as the energy-producing center (Liu *et al*., 2023a). The glycolysis process in the cytoplasm converts glucose into pyruvate and produces a small amount of ATP and Nicotinamide Adenine Dinucleotide (NADH) (Stein and Imai, 2012). Pyruvate can then be further oxidized through Oxidative Phosphorylation (OXPHOS) in the mitochondria (Adant *et al*., 2022). At this stage, electrons from NADH and Flavin Adenine Dinucleotide ($FADH_2$) are transferred through the electron transport chain to generate a proton gradient that drives ATP synthesis by ATP synthase (Bao *et al*., 2025). OXPHOS is the primary source of energy in eukaryotic cells and is highly sensitive to environmental changes, including oxygen availability, nutrients, and oxidative stress (Garcia-Caparros *et al*., 2021).

Metabolic regulation occurs strictly through interactions between biochemical pathways, cellular energy status, and molecular signals that regulate enzyme activity and organelle dynamics (Carthew, 2021). AMPK acts as an energy sensor that activates catabolic pathways to increase ATP production when cellular energy decreases, while suppressing anabolic processes that require high energy (Min *et al*., 2024). Conversely, mTOR regulates cell growth and biosynthesis when nutrients and energy are sufficient (Liu *et al*., 2025). The balance between AMPK and mTOR activity is a key determinant of the cell's response to physiological environmental fluctuations (Chun and Kim, 2021).

Under conditions of cellular stress, infection, or neoplastic transformation, cells can undergo metabolic reprogramming, which is the readjustment of metabolic patterns to meet specific physiological or pathological needs (Xia *et al*., 2021). In cancer cells, this phenomenon is evident in the Warburg effect, where cells rely more on aerobic glycolysis even when oxygen is available, in order to provide biosynthetic precursors for rapid proliferation (Alberghina, 2023). On the other hand, activated immune cells, fibroblasts in wounds, and cells in hypoxic conditions also exhibit similar changes to support their specific activities (Mahjoor *et al*., 2023). This metabolic reprogramming is influenced by various molecular regulators such as Hypoxia-Inducible Factor 1 alpha (HIF-1α), Myelocytomatosis oncogene (MYC), and inflammatory signals (Darweesh *et al*., 2025).

Membrane transport and ion homeostasis

Membrane transport is a fundamental process that maintains the intracellular environment optimal for biochemical activity (Levental and Lyman, 2023). The plasma membrane is selective and dynamic, regulating the movement of molecules and ions through various mechanisms, including passive diffusion, facilitated transport, and active transport that requires energy (Tomkins *et al*., 2021). Ion channels, ion pumps, and membrane transporters work in coordination to maintain electrochemical stability and enable cells to respond appropriately to physiological signals (Mei *et al*., 2022).

Ion pumps, such as Sodium-Potassium Adenosine Triphosphatase (Na^+/K^+-ATPase), are key components of primary active transport. These pumps use energy from ATP hydrolysis to maintain the Sodium (Na^+) and Potassium (K^+) gradients essential for membrane potential, nerve impulses, and cell volume regulation (Contreras *et al*., 2024). Additionally, Calcium Adenosine Triphosphatase (Ca^{2+}-ATPase) in the plasma membrane and endoplasmic reticulum plays a crucial role in maintaining very low cytosolic Calcium (Ca^{2+}) concentrations, as Ca^{2+} is a universal signaling molecule that regulates muscle contraction, neurotransmitter exocytosis, enzyme activation, and other signal transduction pathways (Zhao and Sheng, 2025).

Ion channels work on the principle of selectivity and high conduction speed. K^+, Na^+, and Ca^{2+} channels can be activated by voltage, ligands, or mechanical changes, enabling cells to respond to electrical and chemical stimuli (Dixon *et al*., 2022). For example, voltage-gated Na^+ channels mediate rapid depolarization in neurons, while K^+ channels contribute to repolarization and the return of the membrane potential to its resting state (Aman and Raman, 2024). Transporters such as symporters and antiporters also play a role in coordinated ion transfer, for example, the Na^+/Ca^{2+} exchanger (NCX), which functions to remove excess Ca^{2+} from the cytosol as part of the recovery mechanism after cell activation (Al-Khannaq and Lytton, 2022).

Ionic homeostasis, particularly of Ca^{2+}, Na^+, and K^+, is key to maintaining stable cellular function (Bernal *et al*., 2023). Ca^{2+} acts as a critical "second messenger" that must be tightly controlled to prevent cellular toxicity, while the balance of Na^+ and K^+ determines osmoregulation, electrical excitability, and ion pump activity that supports energy metabolism (Pikor *et al*., 2024). Ionic imbalance can trigger various physiological dysfunctions, including cardiac arrhythmia, neuromuscular disorders, oxidative stress, and activation of the apoptosis pathway (Rafaqat *et al*., 2022).

Cell growth, division, and death

Cell growth, division, and death are a series of fundamental processes that maintain a dynamic balance between tissue regeneration and the elimination of damaged or unnecessary cells (Kopeina *et al*., 2025). Strict regulation of these three processes is vital for maintaining biological homeostasis and preventing the development of pathologies such as can-

cer, tissue degeneration, and chronic inflammatory disorders (Meizlish *et al*., 2021).

The cell cycle proceeds through four phases: G_1 (cell growth), S (DNA replication), G_2 (mitosis preparation), and M (mitosis). Transitions between phases are controlled by coordinated interactions between cyclins and cyclin-dependent kinases (CDKs) (Wang, 2022). Activation of the cyclin–CDK complex drives cell cycle progression, while CDK inhibitors (CKIs) such as p21^Cip1 and p27^Kip1 can halt the rate of proliferation in response to genotoxic stress (Kciuk *et al*., 2022). This regulation is reinforced by checkpoints at the G_1/S and G_2/M phases and the spindle checkpoint during mitosis. Checkpoints function as surveillance systems that ensure DNA has been replicated correctly, genetic damage has been repaired, and the spindle apparatus is perfectly assembled before chromosome separation (McAinsh and Kops, 2025). Key proteins such as p53, Ataxia Telangiectasia Mutated/ATM- and Rad3-Related (ATM/ATR), and Checkpoint Kinase 1/Checkpoint Kinase 2 (CHK1/CHK2) initiate cell cycle arrest and activate DNA repair mechanisms. Failure of checkpoints leads to genomic instability, a key feature of cancer cell transformation (Zannini *et al*. 2014; Kciuk *et al*., 2025).

In addition to proliferation mechanisms, cells also have programmed cell death pathways to regulate cell quality and quantity (Loftus *et al*., 2022). Apoptosis is the most dominant form of programmed cell death, characterized by cell shrinkage, chromatin condensation, DNA fragmentation, and the formation of apoptotic bodies that are then phagocytosed without triggering inflammation (Hajibabaie *et al*., 2023). The intrinsic apoptosis pathway begins with mitochondrial dysfunction regulated by the balance of pro-apoptotic proteins (Bcl-2-associated X protein (BAX) and Bcl-2 homologous antagonist/killer (BAK)) and anti-apoptotic proteins (B-cell lymphoma 2 (Bcl-2) and B-cell lymphoma-extra large (Bcl-XL)) (Chota *et al*., 2021). Meanwhile, the extrinsic pathway is mediated by the activation of death receptors such as First apoptosis signal (Fas) and Tumor Necrosis Factor Receptor (TNFR), which activate initiator and executor caspases to irreversibly degrade cellular components (Green, 2022).

In addition to apoptosis, cells can undergo other forms of cell death, such as autophagy-dependent cell death and necroptosis (Liu *et al*., 2023b). Autophagy is essentially a protective mechanism in which cells recycle organelles and macromolecules through the formation of autophagosomes that fuse with lysosomes (Reggiori and Molinari, 2022). However, prolonged or uncontrolled activation of autophagy can cause massive cellular degradation, leading to death. Unlike apoptosis, necroptosis is a form of programmed cell death that is proinflammatory (Zhao *et al*., 2021). This pathway is regulated by the activation of Receptor-Interacting Protein Kinase 1 (RIPK1) and Receptor-Interacting Protein Kinase 3 (RIPK3) kinases, which then phosphorylate Mixed Lineage Kinase Domain-Like protein (MLKL), triggering plasma membrane disruption and the release of damage-associated molecular patterns (DAMPs) (Wegner *et al*., 2017). Necroptosis emerges as an alternative pathway when apoptosis is inhibited, for example, in viral infections or certain inflammatory conditions (Bertheloot *et al*., 2021).

Stress responses and cellular adaptation

The cellular stress response is an adaptive mechanism that allows cells to maintain viability and function when faced with adverse environmental changes (Singh *et al*., 2022). Various forms of stress, including excessive heat, accumulation of misfolded proteins, oxidative stress, hypoxia, and calcium homeostasis disruption, trigger the activation of specific molecular pathways that serve to stabilize cell structure and prevent further damage (Nandakumar *et al*., 2025). This mechanism involves the integration of stress sensors, signal transduction, and the expression of protective genes aimed at restoring homeostasis (Chen *et al*., 2023).

One of the most conserved adaptive mechanisms is the heat shock response (HSR) (Lang *et al*., 2021). When cells experience increased temperature or other conditions that cause protein denaturation, the transcription factor heat shock factor 1 (HSF1) is activated and induces the expression of heat shock proteins (HSPs) (Kmiecik and Mayer, 2022). HSPs act as molecular chaperones that assist in protein refolding, prevent aggregation, and facilitate the degradation of damaged proteins through the ubiquitin–proteasome pathway (Tedesco *et al*., 2023). HSR activation is essential for maintaining proteostasis integrity, especially in tissues with high metabolic activity or repeated stress exposure (van Oosten-Hawle, 2023).

In addition to HSR, cells also rely on defense mechanisms against oxidative stress, which occurs due to the accumulation of ROS (Sachdev *et al*., 2021). Physiological levels of ROS function as signaling molecules, but excessive increases can damage proteins, lipids, and DNA (Juan *et al*., 2021). Under these conditions, the transcription factor Nuclear Factor Erythroid 2–Related Factor 2 (NRF2) is released from its Kelch-like ECH-Associated Protein 1 (KEAP1) inhibitor complex and then moves to the nucleus to induce the expression of antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (Ngo and Duennwald, 2022). Together with the glutathione and thioredoxin redox systems, this mechanism maintains redox stability and prevents oxidative damage that could potentially trigger apoptosis or necrosis (Georgiou-Siafis and Tsiftsoglou, 2023).

Another crucial type of stress response is the UPR, which is activated

Table 2. Summary of recent advances in cellular biology.

Field of progress	Technology / Key concepts	Scientific contributions	Implications in research / Clinical practice	References
Single-cell omics	scRNA-seq, ATAC-seq, and single-cell proteomics	Revealing cellular heterogeneity, mapping gene regulation, and identifying rare cell subpopulations.	Mapping of organ cell atlases, identification of new differentiation pathways, and characterization of tumor microenvironments.	(Li *et al*., 2021)
Live-cell imaging	STORM, PALM, and SIM; dynamic fluorescent biosensor	Real-time visualization of cellular processes, mapping of Ca^{2+} signals, ROS, and kinase activity.	Understanding stress responses, studying organelle dynamics, and protein interactions at subcellular resolution.	(Alieva *et al*., 2023)
Genome engineering	CRISPR-Cas, CRISPRa/i, prime editing, and base editing	High-precision gene manipulation without DNA damage, lineage tracking, and in vivo genome visualization.	Precision gene therapy, epigenetic studies, and cell-based disease modeling.	(Boti *et al*., 2023)
Organelle dynamics	Mitochondrial fission–fusion regulation (DRP1, MFN1, and OPA1); lysosomal function	Understanding changes in organelle morphology and inter-organelle communication.	Explanation of metabolic, neurodegenerative, and cancer pathologies; organelle-specific therapeutic targets.	(Hockenberry *et al*., 2024)
Liquid–Liquid Phase Separation (LLPS)	Formation of nucleoli, stress granules, and P-bodies	Explaining membrane-less cell compartments and the spatiotemporal regulation of biomolecules.	Understanding protein aggregation diseases (ALS and FTD), transcription regulation, and stress response.	(Peng *et al*., 2021)

when there is an accumulation of misfolded proteins in the ER stress (Ren *et al*., 2021). The UPR is mediated by three main sensors, Protein kinase RNA-like ER kinase (PERK), Inositol-Requiring Enzyme 1 (IRE1), and Activating Transcription Factor 6 (ATF6), which work to reduce the protein load through a decrease in global translation, an increase in protein folding capacity, and the activation of the protein degradation pathway in the ER-associated degradation (ERAD) (Ajoolabady *et al*., 2022). If the stress cannot be resolved, the UPR can switch signaling towards the apoptosis pathway through the activation of C/EBP Homologous Protein (CHOP) and caspases, marking a shift from adaptive mechanisms to elimination-based protective mechanisms (Ma *et al*., 2024). Figure 2 illustrates how key signaling pathways converge on proteostasis to maintain cellular homeostasis.

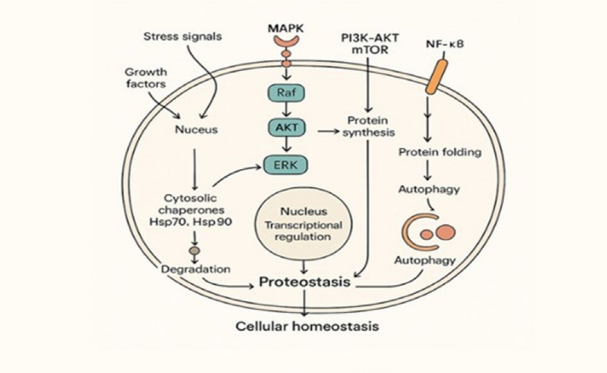

Figure 2. Integration of major signaling pathways with proteostasis.

Recent advances in cellular biology

Advances in cell biology technology over the past two decades have revolutionized our understanding of molecular dynamics, functions, and regulation within cells (Beatrice, 2024). Modern approaches such as single-cell omics, live-cell imaging, and Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-based genome engineering have shifted the research paradigm from aggregate cell population analysis to high-precision characterization of individual cells (Yiu *et al*., 2025). These developments have opened up tremendous opportunities for identifying cellular heterogeneity, mapping gene regulatory networks, and understanding organelle dynamics in both physiological and pathological contexts (Jung, 2025). Table 2 summarizes the latest advances in cell biology that have transformed modern research approaches.

Single-cell omics technologies, including single-cell RNA sequencing (scRNA-seq), Assay for Transposase-Accessible Chromatin using sequencing (ATAC-seq), and single-cell resolution proteomics, enable researchers to uncover differences in gene expression, chromatin accessibility, and protein profiles between cells within a single tissue that appears homogeneous (Li *et al*., 2021). This approach has identified rare cell subpopulations, novel differentiation pathways, and regulatory patterns that were previously invisible in bulk analyses (Märtens *et al*., 2023). Single-cell omics has also become an important foundation for mapping cellular atlases of various organs, understanding embryonic development, and characterizing the molecular microenvironment of tumors (Wen *et al*., 2022).

Another significant development comes from high-resolution live-cell imaging, including super-resolution microscopy (Stochastic Optical Reconstruction Microscopy (STORM), Photoactivated Localization Microscopy (PALM), Structured Illumination Microscopy (SIM), and dynamic fluorescence-based imaging techniques (Alieva *et al*., 2022). This technology enables real-time visualization of cellular processes with subcellular resolution, such as vesicle movement, protein interactions, cytoskeletal dynamics, and organelle reorganization (Petroni *et al*., 2023). The combination of live-cell imaging with fluorescent biosensors allows for the spatiotemporal mapping of molecular signals such as Ca^{2+}, ROS, and kinase activity, providing deep insight into how cells respond to stress or external signals directly (Mehta and Zhang, 2021).

In the field of genome engineering, the CRISPR-associated proteins (CRISPR-Cas) system has become the primary tool for manipulating gene expression with high precision (Liu *et al*., 2022c). In addition to DNA cutting, innovations such as CRISPR activation (CRISPRa), CRISPR interference (CRISPRi), prime editing, and base editing enable genetic modulation without causing excessive DNA damage (Boti *et al*., 2023). The use of CRISPR for lineage tracing and visualization of genome localization in vivo further enriches our understanding of epigenetic regulation, cell differentiation, and chromatin dynamics (Chaudhary *et al*., 2021).

At the subcellular level, recent studies reveal that organelles are dynamic structures that undergo constant morphological changes and interactions (Chaudhary *et al*., 2021). Mitochondria, for example, exhibit a cyclical pattern of fission and fusion regulated by the proteins Dynamin-Related Protein 1 (DRP1), Mitofusin 1 (MFN1), and Optic Atrophy 1 (OPA1). Imbalances in this dynamic are associated with metabolic, neurodegenerative, and cancerous diseases (Hockenberry *et al*., 2024). Similarly, lysosomes are no longer viewed merely as degradation organelles, but as metabolic signaling hubs that play a role in mTORC1 activation, autophagy, and interorganelle communication through membrane contact sites (Bar-Peled and Kory, 2022).

One new concept that is gaining attention in cell biology is liquid-liquid phase separation (LLPS) (Tong *et al*., 2022). This phenomenon explains the formation of membraneless organelles such as nucleoli, stress granules, and P-bodies (Hirose *et al*., 2023). These structures are formed through the phase separation of biomolecules, which allows for the concentration of proteins and RNA in temporary compartments without membranes (Roden and Gladfelter, 2021). LLPS plays an important role

Table 3. Physiological changes in cells under various disease conditions.

Disease category	Normal cell physiology mechanism	Changes / Disruption in disease	Pathological consequences	References
Metabolic diseases (Obesity, Insulin Resistance, and Type 2 Diabetes)	Integration of metabolic signals via PI3K–AKT; stable energy homeostasis; normal endoplasmic reticulum function.	PI3K–AKT pathway dysfunction inhibits glucose transport; ER stress activates UPR; chronic activation of NF-κB and JNK.	Insulin resistance, metabolic inflammation, and energy homeostasis disorders.	(Zhao *et al*., 2023)
Cancer	Cell cycle regulation by p53, Rb, MAPK; apoptosis proceeds normally; cell metabolism is efficient.	Mutations in p53, Rb, MAPK; uncontrolled proliferation; Warburg effect; TME interactions increase survival and metastasis.	Tumor growth, metastasis, and immune evasion.	(Setiawan *et al*., 2023)
Neurodegenerative diseases (Alzheimer's, Parkinson's, and Huntington's)	Mitochondria maintain energy production; proteostasis is stable; autophagy functions optimally; calcium homeostasis is maintained.	Mitochondrial and oxidative dysfunction; ROS accumulation; autophagy disruption; misfolding protein aggregation.	Progressive neuron degeneration, and synaptic dysfunction.	(Alqahtani *et al*. 2023)
Infectious diseases (Viruses and bacteria)	The innate immunity pathway is balanced; cytokine production is controlled; phagocytosis and adaptive apoptosis proceed normally.	Pathogens exploit cellular pathways (MAPK, interferon); protein synthesis inhibition; excessive inflammatory activation.	Tissue damage, severe inflammation, and impaired pathogen elimination.	(Lalbiaktluangi *et al*., 2023)

in transcription regulation, stress response, and cytoplasmic organization. Disruption of this mechanism is associated with pathologies such as Amyotrophic Lateral Sclerosis (ALS), frontotemporal dementia, and other protein aggregation disorders (Naskar *et al*., 2023).

Cellular physiology in health and disease

Cell physiology is the basis of all biological processes that sustain life (Sies *et al*., 2022). Each cell performs a series of coordinated mechanisms from energy production, signal transduction, gene regulation, to interactions with the microenvironment, to maintain homeostasis (Carthew, 2021). When these mechanisms are disrupted, small changes at the molecular level can develop into pathologies that affect tissues, organs, and even the entire organism (Gusev and Zhuravleva, 2022). Therefore, a deep understanding of cell physiology in normal and pathological conditions is key to explaining the etiology of various modern diseases and designing more effective therapeutic interventions (Patial *et al*., 2024). Table 3 provides a systematic summary of how cell physiology functions in normal conditions and how disruptions in these cellular mechanisms trigger the emergence of various metabolic, cancerous, neurodegenerative, and infectious diseases.

Metabolic diseases such as obesity, insulin resistance, and type 2 diabetes arise due to impaired metabolic signaling integration at the cellular level (Saltiel, 2021). Dysfunction of the PI3K–AKT pathway inhibits glucose transport, while endoplasmic reticulum stress triggers the activation of the UPR, which contributes to insulin resistance (Ramasubbu and Rajeswari, 2023). In addition, chronic metabolic inflammation, regulated by NF-κB and JNK activation, produces proinflammatory cytokines that impair the ability of cells to maintain energy homeostasis (Zhao *et al*., 2023). This combination of metabolic and inflammatory dysregulation suggests that metabolic diseases are not merely systemic disorders, but are primarily rooted in changes in cellular physiology that fail to adapt to nutritional stress (Kivimäki *et al*., 2023).

Cancer is the most obvious example of cellular physiology disruption (Wong, 2011). Mutations in cell cycle regulators such as p53, Rb, or the MAPK pathway result in uncontrolled proliferation and loss of apoptosis control (Wang, 2021). In addition to genetic changes, cancer cells also adopt metabolic reprogramming, such as increased aerobic glycolysis (Warburg effect), to support high energy and biosynthesis demands (Schiliro and Firestein, 2021). Furthermore, interactions with the tumor microenvironment (TME), including fibroblasts, immune cells, and the extracellular matrix, reinforce the ability of tumor cells to survive and metastasize (Setiawan *et al*., 2023). Thus, cancer can be viewed as a condition in which the regulation of normal cellular physiology is replaced by biological systems that support pathological growth (Brown *et al*., 2023).

Neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, arise from the failure of neurons to maintain proteostasis and organelle function (Wong, 2011). Neurons are highly dependent on mitochondrial integrity for energy production and calcium homeostasis (Perrone *et al*., 2023). When oxidative dysfunction, ROS accumulation, autophagy disruption, or misfolding protein aggregation occur, neurons lose their ability to maintain synaptic function and undergo progressive degeneration (Alqahtani *et al*., 2023). The limited regenerative capacity of nerve tissue makes physiological disturbances in neurons a critical factor that is difficult to reverse, so modern studies focus on autophagy modulators, mitochondrial stabilizers, and proteostasis-based therapies (Matuz-Mares *et al*., 2022).

In infectious diseases, pathogens often exploit host cell physiological mechanisms to ensure their survival and replication (Kellermann *et al*., 2021). Viruses can inhibit host protein synthesis, modify interferon pathways, or hijack the cell replication machinery for their own benefit (Lalbiaktluangi *et al*., 2023). Pathogenic bacteria use effectors to alter MAPK pathways, inhibit phagocytosis, or trigger excessive inflammation (Nandi and Aroeti, 2023). The cellular response to infection through activation of innate immunity pathways, cytokine production, and programmed apoptosis reflects physiological adaptations that determine the success of pathogen elimination (Nedeva, 2021). An imbalance in this response can result in excessive inflammation or widespread tissue damage (Tu and Li, 2023).

Advances in knowledge of cell physiology have given rise to a new paradigm in therapy development (Buja, 2021). Medical interventions are now increasingly oriented toward specific molecular mechanisms, such as the use of kinase inhibitors for cancer, metabolic pathway agonists for diabetes, autophagy modulation for neurodegenerative diseases, and cell-engineered immune therapies (Karnas *et al*., 2023). In addition, technologies such as single-cell transcriptomics, CRISPR gene editing, and in vitro organoids enable precise mapping of cellular heterogeneity, allowing therapies to be tailored to individual molecular characteristics (Madan *et al*., 2025). This approach makes cell physiology not only a theoretical basis but a key pillar in the transformation of medicine towards precision therapy (Akhoon, 2021). As illustrated in Figure 3, perturbations in insulin signaling, oncogenic signaling pathways, and neuronal quality-control mechanisms give rise to distinct metabolic, cancer, and neurodegenerative phenotypes.

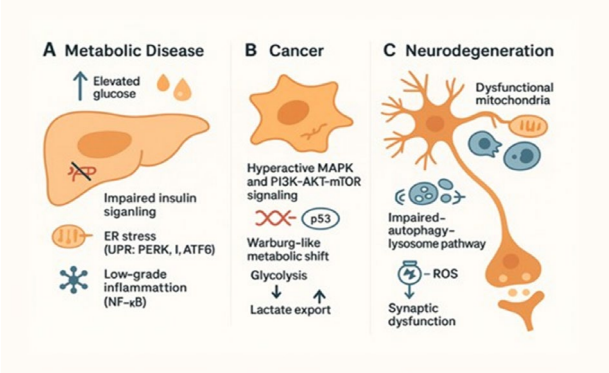

Figure 3. Disrupted cellular regulatory networks in metabolic disease, cancer, and neurodegeneration.

Challenges and future perspectives

Despite advances in cell physiology and molecular biology that have led to a more comprehensive understanding of the mechanisms of life at the microscopic level, a number of scientific and technical challenges still limit the maximum application of this knowledge (Beck *et al*., 2024). These challenges are not only related to methodological limitations, but also include the inherent biological complexity of cellular systems (Dehghani, 2024).

Several fundamental aspects of cell physiology remain open questions in modern biology (Sies *et al*., 2022). The mechanisms of coordination between simultaneously operating signaling pathways, the dynamics of real-time changes in cell phenotype, and organelle interactions under stress conditions are still difficult to explain completely (Valls and Esposito, 2022). In addition, cellular heterogeneity in tissues, including differences in responses between cell subpopulations, makes it difficult to generalize experimental results (Corvera, 2021). The discrepancy between in vitro models and in vivo biological conditions is also a major obstacle to understanding complex processes such as signal transduction, cellular immune response, and metabolic reorganization (Urzì *et al*., 2023).

The era of systems biology has produced enormous volumes of data, covering genomics, transcriptomics, proteomics, metabolomics, and epigenomics (Veenstra, 2021). However, the effective integration of multi-omics data remains a major challenge (Kang *et al*., 2021). Each analytical platform has different biases, resolutions, and sensitivities, so combining data often results in inconsistent interpretations (Miller *et al*., 2022). In addition, advanced computational models are needed to analyze the relationships between data layers holistically (Krzywanski *et al*.,

2024). Other challenges include limitations in reproducibility, validation standards, and the need for consistent reference databases (Simkus *et al*. 2025). Without proper integration, the potential of multi-omics to reveal comprehensive cellular and molecular regulation cannot be optimally utilized (Baysoy *et al*., 2023).

Innovative technological developments have opened up significant opportunities to address these limitations (Bresciani *et al*., 2022). Platforms such as single-cell RNA sequencing (RNA-seq), spatial transcriptomics, CRISPR-based functional genomics, and high-resolution live-cell imaging enable cell analysis at a level of precision never before achieved (Pandey *et al*., 2025). In addition, the use of organoids, complex co-culture systems, and microfluidic organ-on-chip technology allows for the modeling of physiological environments that more closely resemble actual biological conditions (Baptista *et al*., 2022). Advances in artificial intelligence and machine learning also have the potential to accelerate the integration of multi-omics data and identify regulatory patterns that cannot be captured by conventional analysis (Yetgin, 2025). Overall, these technologies are projected to revolutionize cell physiology research in the coming decade and pave the way for next-generation precision therapies (Dasgupta, 2024).

Conclusion

Understanding modern cell physiology confirms that all life processes, from metabolism and intercellular communication to stress responses, depend on highly coordinated molecular regulation. When these mechanisms are disrupted, various pathological conditions arise, such as metabolic diseases, cancer, neurodegeneration, and infections. A synthesis of recent findings shows that an integrative approach based on systems biology, multi-omics, and genetic manipulation technologies offers great opportunities for a more comprehensive understanding of cellular regulation. Thus, cell physiology is not only the basis for biological understanding but also an important foundation for the development of precision therapies and biomedical innovations in the future.

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Conflict of interest

The authors have declared no conflict of interest.

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