

## Molecular mechanisms of hypoxia-mediated mitochondrial dysfunction and cell death: A review

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### Abstract

Hypoxic environments induce mitochondrial dysfunction, adversely affecting organs and cells. Hypoxia leads to reduced activity of key mitochondrial metabolic enzymes, suppressed protein synthesis, impaired respiratory chain function, abnormal fission and fusion processes, and disrupted calcium homeostasis. These changes result in decreased intracellular ATP production and excessive accumulation of reactive oxygen species (ROS). Hypoxia also diminishes mitochondrial membrane potential, causing leakage of cytochrome C (CytC). This activates the caspase cascade, ultimately inducing apoptosis. This paper systematically elucidates the core pathways of mitochondrial damage and cell death under hypoxia: loss of membrane potential, abnormal opening of the mitochondrial permeability transition pore, release of CytC and apoptosis-inducing factors, and ATP depletion. It also examines impaired respiratory chain activity under hypoxia, alongside reduced oxygen utilization efficiency that exacerbates energy metabolism dysfunction. Under these conditions, cells are forced to activate low-oxygen pathways, further damaging mitochondrial function and establishing a negative feedback loop between hypoxia and mitochondrial dysfunction. Hypoxia also induces alterations in mitochondrial membrane permeability, triggering abnormal exchange of protons and ions across the inner and outer membranes. This facilitates the release of pro-apoptotic factors (such as CytC, Apaf-1, and Smac/DIABLO), activates downstream apoptotic pathways, and exacerbates cellular damage. Additionally, hypoxia enhances the production of ROS in mitochondria, which in turn promote cellular demise by reacting with mitochondrial proteins, lipids, and DNA, consequently compromising mitochondrial structure and function.

**Keywords:** Cell death, Hypoxia, Mitochondrial dysfunction, Molecular mechanisms

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## **Introduction**

Hypoxia is broadly described as a condition in which oxygen availability is inadequate to sustain normal cellular activity. More specifically, it is usually defined as a relative reduction in oxygen concentration within cells, tissues, or organs compared with physiological levels, often falling below 2% (Zhou et al., 2024). Both physiological and pathological circumstances can trigger hypoxia, and it has been implicated in the development of diverse disorders, including malignancies, metabolic diseases such as diabetes, and chronic inflammatory states. Individuals residing at high altitudes are also particularly susceptible to oxygen insufficiency. To cope with reduced oxygen tension, cells employ adaptive mechanisms that influence gene transcription, protein synthesis and degradation, and enzymatic function. Central to this process are prolyl hydroxylases (PHDs), which act as oxygen sensors. When oxygen levels drop, PHD activity diminishes, allowing hypoxia-inducible factors (HIFs) to accumulate and translocate into the nucleus, where they regulate genes critical for mitochondrial function. Mitochondria, the primary site of cellular oxygen consumption, rely on oxygen for oxidative phosphorylation (OXPHOS) and other bioenergetic processes. Under hypoxic stress, mitochondrial dynamics—including fusion, fission, and energy metabolism—are disrupted, leading to organellar dysfunction and subsequent impairment of organismal physiology (Guo et al., 2024). Prolonged or severe hypoxia not only reshapes transcriptional programs but also contributes to structural and functional injury in major organs such as the brain, heart, lungs, and kidneys, thereby promoting disease initiation and progression.

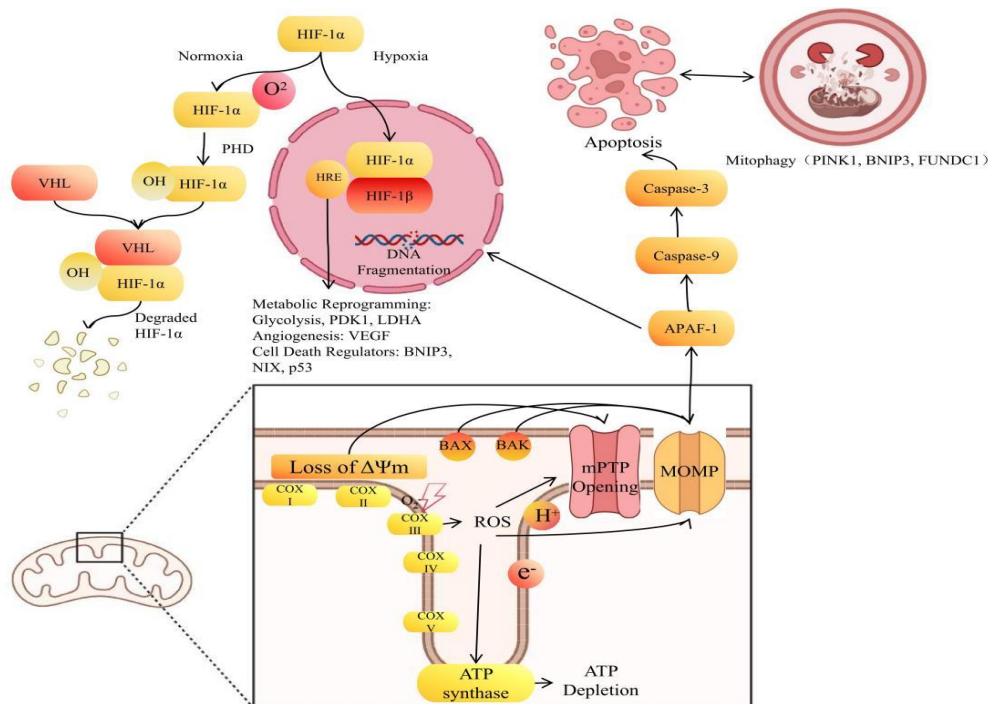
Hypoxia has been recognized as a pivotal contributor to the onset and progression of numerous pathological conditions, including malignancies, myocardial ischemia, metabolic disturbances, renal impairment, and reproductive complications such as pre-eclampsia. In solid tumors, the imbalance between accelerated oxygen consumption driven by uncontrolled cellular proliferation and the limited diffusion capacity of avascular regions leads to reduced intracellular oxygen tension, thereby intensifying hypoxic stress (Di Carlo and Sorrentino, 2024). Under such conditions, HIFs serve as essential regulators, enabling cells to survive by activating diverse downstream target genes (Liu et al., 2023). Cardiovascular pathologies are also closely associated

with oxygen deprivation. For example, hypoxia is a hallmark of heart failure, where diminished systolic activity of the left ventricle results in systemic oxygen deficiency and can further progress to pulmonary hypertension. Pulmonary hypertension, in turn, often coexists with chronic respiratory disorders such as Chronic Obstructive Pulmonary Disease (COPD) and obstructive sleep apnea, which collectively exacerbate vascular inflammation and atherosclerotic processes (Sobey et al., 2022). Chronic hypoxia as a causative pathway for adipose tissue dysfunction (Van Eyck et al., 2024). Metabolic tissues are also highly sensitive to oxygen insufficiency. In adipose depots, chronic hypoxia impairs glucose metabolism by altering glucose transporter (GLUT) expression through HIF-1 $\alpha$ , thereby promoting glycolysis and lactate accumulation (Basheeruddin and Qausain, 2024). Lipid turnover is similarly disrupted: hypoxia downregulates fatty acid transporters Fatty Acid Transport Protein 1 (FATP1), Cluster of Differentiation 36 (CD36) and transcriptional regulators such as Peroxisome Proliferator-Activated Receptor  $\gamma$  (PPAR $\gamma$ ) and CCAAT/Enhancer-Binding Protein  $\alpha$  (C/EBP $\alpha$ ), reducing lipid uptake and storage. Sustained oxygen deprivation inhibits adipocyte differentiation by decreasing PPAR $\gamma$  and fatty acid synthase (FAS), while simultaneously enhancing lipolysis in visceral and subcutaneous fat (Xing and Li, 2023). Moreover, hypoxia has been implicated in the whitening of brown adipose tissue, characterized by impaired  $\beta$ -adrenergic signaling, lipid droplet enlargement, and mitochondrial dysfunction (Huynh et al., 2025). Renal tissue is another major target of hypoxic injury. The occurrence of acute kidney injury (AKI) is usually associated with insufficient blood flow to the kidneys, nephrotoxic effects and urinary tract obstruction. When the injured kidney is not fully repaired, the disease will gradually evolve into chronic kidney disease (CKD). During the progression of AKI to CKD, phenomena such as tubular atrophy, decreased renal vascular density, and inadequate renal oxygen supply occur. These changes lead to tubular fibrosis, ultimately resulting in renal function decline (Huang et al., 2023). The oxygen transport capacity of glomerular capillaries is linked to renal microcirculation. However, hypoxia impairs renal microcirculatory function, diminishing oxygen transport capacity in glomerular capillaries and exacerbating hypoxia severity. Hypoxia induces sustained elevation of HIF-1 $\alpha$ , activating the

Transforming Growth Factor- $\beta$  (TGF- $\beta$ )-centered fibrosis signaling pathway. Excessive TGF- $\beta$  activation promotes myfibroblast proliferation and deposition of extracellular matrix components (e.g., collagen and fibronectin), thereby driving tubulointerstitial fibrosis (Ren et al., 2023). Studies indicate that abnormal proliferation of type I and IV collagen is significantly associated with prolonged hypoxia. Chronic hypoxia inhibits matrix metalloproteinase-1 (MMP-1) activity, and this inhibition accelerates renal tissue fibrosis (Xiao et al., 2023). Consequently, hypoxia catalyzes the progression of tubular fibrosis and contributes to the transition from AKI to CKD. In the reproductive system, inadequate placental blood flow and defective oxygen supply are the main mechanisms underlying the development of preeclampsia. It has been further shown that hypoxia can mediate mitochondrial quality control through FUN14 domain-containing 1 (FUNDC1)-dependent mitotic regulatory pathways (He et al., 2025). Nowadays, hypoxia-associated mitochondrial apoptosis is gaining

attention and its occurrence is often triggered by a combination of oxidative stress, inflammatory cascades and acidosis. The apoptotic process serves as a central component of hypoxic injury, tightly linking localized hypoxia to systemic tissue injury (Bhansali et al., 2021).

Hypoxia induces cell death through a complex signaling network, with its core mechanisms summarized as follows (Figure 1): Hypoxia stabilizes HIF, initiating adaptive responses and pro-survival metabolic reprogramming; However, prolonged hypoxia directly impairs mitochondrial function, triggering a vicious cycle of oxidative stress and inflammatory responses. Ultimately, these stresses converge on mitochondria, decisively initiating cell death programs such as apoptosis and autophagy through events including membrane potential collapse, membrane permeabilization, and energy crisis. The following sections will systematically elucidate the molecular mechanisms underlying each step within this logical framework.



**Figure-1.** Schematic representation of molecular interactions between hypoxia, mitochondrial dysfunction and cell death. Under hypoxic conditions, stabilized HIF is transported to the nucleus, activating transcriptional programs for relevant gene expression. Hypoxia directly impairs mitochondrial function, thereby activating both caspase-dependent and -independent apoptotic pathways. Hypoxia concurrently induces protective mitochondrial autophagy to clear damaged mitochondria. The intricate interplay between these pathways ultimately determines cellular fate.

While the individual pathways of hypoxia signaling, mitochondrial dysfunction, and cell death have been extensively reviewed, a critical synthesis focusing on their dynamic interconnections and decision-making nodes is lacking. Previous reviews have often treated HIF signaling, oxidative stress, and apoptosis as relatively linear events. However, the emerging paradigm is one of a complex network with extensive feedback and feedforward loops. For instance, the dual role of HIF in both promoting survival and priming cells for death, and the context-dependent switch between mitochondrial apoptosis and protective mitophagy, remain poorly integrated. This review uniquely emphasizes the crosstalk between these axes. We systematically explore how HIF-driven metabolic shifts (e.g., via Pyruvate Dehydrogenase Kinase 1 (PDK1)) not only adapt to hypoxia but also actively contribute to mitochondrial Reactive Oxygen Species (ROS) production and membrane destabilization. Furthermore, we critically assess the molecular mechanisms that determine whether a stressed mitochondrion is repaired via mitophagy or eliminated by apoptosis, highlighting the competition between pathways like Bcl-2 and N-myc interacting protein 3 (BNIP3) and the B-cell lymphoma-2 (Bcl-2) family. By framing mitochondrial dysfunction as the central hub that interprets and amplifies hypoxic stress, this review aims to provide a more integrated and mechanistic understanding, thereby identifying key knowledge gaps and potential therapeutic targets that lie at the interface of these pathways.

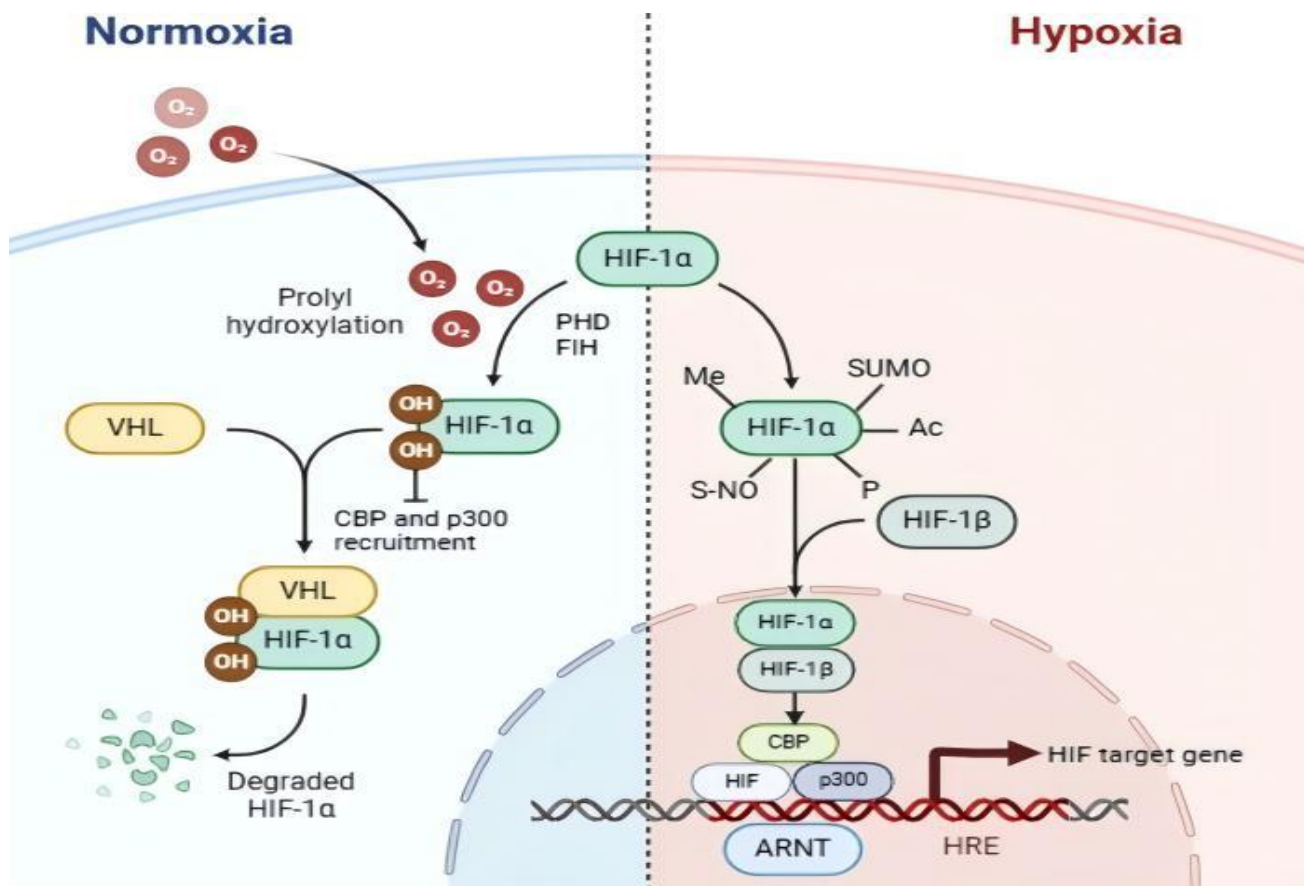
### **The biological basis of hypoxia and the HIF signaling pathway**

As the core molecular switch for cellular hypoxia sensing, the HIF plays a pivotal role in coordinating the expression of downstream genes. In hypoxic environments, the HIF signaling axis is a central regulatory mechanism for cellular adaptive responses. HIF consists of two subunits, HIF-1 $\alpha$  and HIF-1 $\beta$ , whose downstream-regulated genes are widely involved in glycolytic pathways, lactate metabolism, and angiogenesis. By activating this transcriptional network, the HIF pathway not only supports metabolic reprogramming under hypoxic stress, but also drives vascular remodeling and continued tumor progression (Obeagu, 2025). In normoxia, HIF- $\alpha$  is subject to hydroxylation modification by PHD1-3, which is subsequently recognized by the von Hippel-Lindau (VHL) E3 ubiquitin ligase complex and mediates its

proteasomal degradation (Liu et al., 2024). In addition, HIF inhibitory factor (FIH) similarly blocks the binding of HIF- $\alpha$  to the transcriptional cofactor CREB-binding protein (CBP)/p300 via hydroxylation, thereby further impairing its transcriptional activity (Wu et al., 2021). When cells are subjected to hypoxic conditions, the activity of PHDs and FIH is markedly reduced and HIF- $\alpha$  is able to escape degradation and accumulate in the nucleus. Subsequently, the subunit binds to the hypoxia response element (HRE) and initiates the transcription of hypoxia-responsive genes, which mediates a series of downstream biological effects (Wang et al., 2025)(Figure 2). These genes reduce oxygen demand by promoting glucose utilization, attenuating mitochondrial biogenesis, and stimulating mitophagy, thereby preserving Adenosine Triphosphate (ATP) levels under stress. In prolonged or severe hypoxia, HIF also participates in pro-death signaling. One mechanism involves stabilization of the tumor suppressor protein p53 (p53) by HIF-1 $\alpha$ , either directly or by interfering with the p53 ubiquitin ligase Murine Double Minute 2 (MDM2). Stabilized p53 induces cell-cycle arrest and apoptosis by modulating downstream effectors such as Bcl-2-associated X protein (Bax) and p21 (Jiang et al., 2025). A second pathway centers on HIF-mediated induction of the Bcl-2 Homology 3 (BH3)-only proteins BNIP3 and NIP3-like protein X (NIX). BNIP3 expression is markedly upregulated in hypoxic tumor peripheries, endothelial cells, and macrophages (Wu et al., 2024). Overexpressed BNIP3 interacts with and neutralizes the anti-apoptotic proteins Bcl-2 and Bcl-xL, leading to cell death in fibroblasts and Michigan Cancer Foundation-7 (MCF7) breast cancer cells (Nocquet et al., 2024). The presence of a Hypoxia-Response Element (HRE) in the BNIP3 promoter underscores its dependence on HIF-1, as HIF-deficient cells display reduced BNIP3 expression and diminished apoptosis (Hu et al., 2025). Beyond apoptosis, BNIP3 can also trigger necrotic-like mitochondrial damage distinct from classical apoptotic mediators, providing an alternative mechanism for rapid elimination of damaged cells (Zhou et al., 2021). HIF isoforms also differentially influence cellular metabolism. HIF-2 $\alpha$  promotes ROS generation by elevating intracellular iron levels, and in combination with agents such as dimethyl fumarate (DMF) or ferroptosis inducers, this effect can drive cell death. On the other hand, HIF-1 $\alpha$  inhibits mitochondrial respiration by inducing the expression of pyruvate dehydrogenase kinase 1 (PDK1), which in

turn inhibits pyruvate dehydrogenase activity and reduces the entry of acetyl coenzyme A into the tricarboxylic acid (TCA) cycle and its involvement in citrate synthesis. At the same time, HIF also upregulates lactate dehydrogenase A (LDHA), which promotes lactate production and skews pyruvate metabolism more towards the anaerobic glycolytic pathway (Zhang et al., 2024). Collectively, these metabolic reprogramming changes, as well as the transcriptional regulation of apoptosis-related factors by HIF, reveal the dual role of the HIF pathway in both promoting cellular adaptation and potentially driving cell death under hypoxic stress. The dual role of HIF—

orchestrating both pro-survival metabolic adaptation and the expression of pro-death mediators like BNIP3—highlights a critical paradox in hypoxic biology. The contextual factors that determine this life-or-death signaling output, such as cell type, duration of hypoxia, and the interplay with oncogenic signals, remain a central and unresolved question. HIF-mediated metabolic reprogramming, while sustaining cellular energy supply, inevitably disrupts normal mitochondrial function, thereby setting the stage for excessive reactive oxygen species production.



**Figure-2.** Hypoxia activates the HIF signaling pathway by affecting the activity of two key enzymes (PHD and FIH). Under normoxic conditions, PHD and FIH modify the HIF $\alpha$  protein, leading to its degradation and loss of transcriptional activity, respectively. Under hypoxic conditions, PHD and FIH become inactivated due to oxygen deprivation, allowing HIF $\alpha$  proteins to accumulate stably. This enables effective recruitment of coactivators, forming an active transcription complex that initiates expression of downstream target genes.

### **Hypoxia-Induced oxidative stress and free radical damage**

In fact, the explosive production of reactive oxygen species is one of the most direct attacks in hypoxia-induced damage. Hypoxia is often regarded as an important driver of induced oxidative stress, which can significantly contribute to the overproduction of ROS. These highly reactive molecules cause oxidative damage to key cellular macromolecules - including membrane lipids, proteins, and nucleic acids - which in turn destabilizes membranes, weakens organelle function, and ultimately triggers the apoptotic program. Excessive accumulation of ROS further disrupts the dynamic homeostasis of mitochondria, which are not only the main source of ROS generation but also their most vulnerable targets. A typical molecular event is the aberrant opening of the mitochondrial permeability transition pore (mPTP), a process that dramatically increases membrane permeability, leading to CytC leakage and ultimately initiating the caspase-dependent apoptotic signaling pathway (Zhou et al., 2022; Lee et al., 2023). Beyond direct mitochondrial impairment, ROS serve as second messengers that amplify pro-death signaling. Elevated ROS levels induce lipid peroxidation of phospholipids, mitochondrial membrane depolarization, and apoptotic cascade activation. They also interact with nucleic acids, producing strand breaks and base modifications, which in turn stimulate DNA repair kinases and stabilize p53, further reinforcing apoptotic signaling. Additionally, ROS-mediated activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) enhances transcription of inflammatory mediators such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), linking oxidative stress to inflammatory cascades that exacerbate tissue injury (Buckalew et al., 2020). Oxidative stress contributes to cell-cycle arrest as well, with ROS excess halting cells in the G0/G1 phase and promoting apoptosis through the release of mitochondrial proteins such as Second mitochondria-derived activator of caspases (Smac)/Direct IAP Binding protein with Low pI (DIABLO) and endonuclease G (EndoG)(Song et al., 2024). When electrons leak continuously in the respiratory chain, it leads to an increase in ROS and reactive nitrogen species (RNS). These include molecules like superoxide anion, hydrogen peroxide, hydroxyl radicals, peroxynitrite, and nitric oxide. Such molecules can cause more damage from oxidative stress and also activate inflammatory pathways, including the formation of inflammasomes (Zhou et

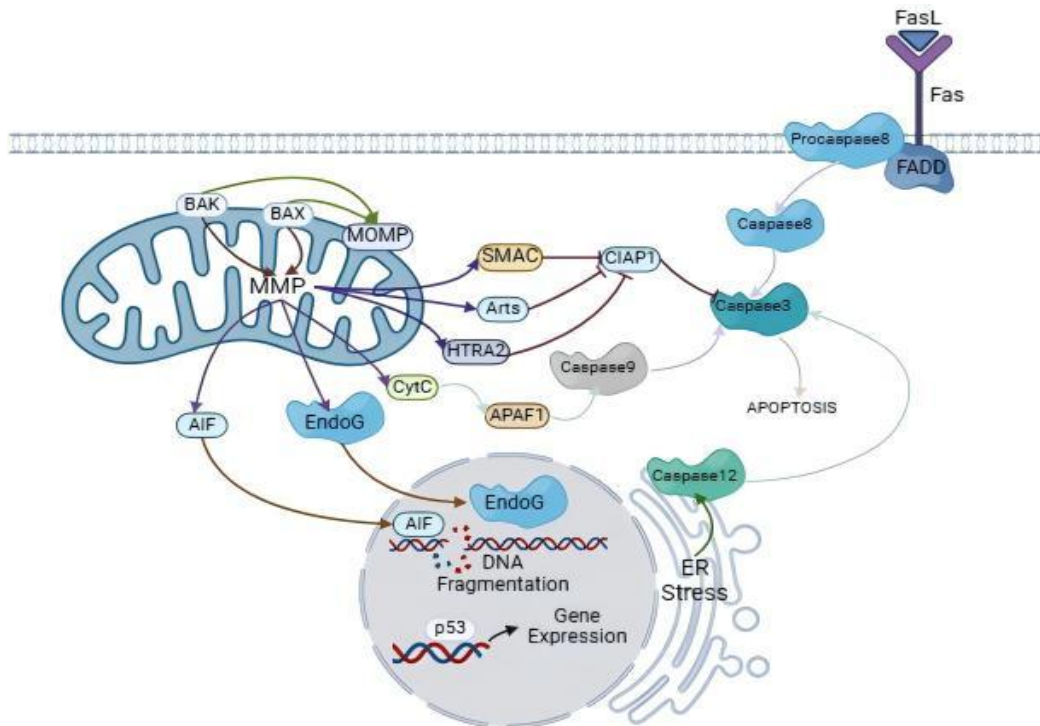
al., 2024). In this process, the series of events involving NACHT, LRR and PYD domains-containing protein 3 (NLRP3), Apoptosis-associated speck-like protein containing a CARD (ASC), and Cysteine-aspartate protease-1 (caspase-1) is essential because it results in the release of inflammatory cytokines, which keep the inflammation going. Overall, the connection between oxidative stress and mitochondrial problems is a key part of the cell damage and inflammation seen during low oxygen conditions (hypoxia) (Figure 3). Excessive ROS not only act as direct damaging molecules but also serve as crucial second messengers, activating broader inflammatory signaling networks.

### **Hypoxia-Associated inflammatory responses and cytokine networks**

This cascade of inflammatory signals triggered by hypoxia and oxidative stress further amplifies cellular damage. Under hypoxic conditions, inflammatory signaling pathways can be activated and cytokine secretion induced, thereby promoting cell death. TNF- $\alpha$  and various interleukins (ILs) constitute key components of cytokines, with TNF- $\alpha$  and ILs playing central roles in regulating apoptosis, pyroptosis, and inflammation (You et al., 2021). TNF- $\alpha$  directly amplifies inflammatory responses by activating the mitogen-activated protein kinase (MAPK) pathway and inducing the NF- $\kappa$ B signaling pathway, leading to enhanced transcription of multiple pro-inflammatory genes (Zheng et al., 2020). TNF- $\alpha$  also induces cell death and prompts neighboring immune cells to release secondary inflammatory mediators, thereby indirectly exacerbating local inflammation (Cabrera-Fuentes et al., 2025). Multiple types of cell death—such as secondary necrosis, necrotic apoptosis, and pyroptosis—are accompanied by the release of damage-associated molecular patterns (DAMPs). DAMPs interact with pattern recognition receptors (PRRs) to sustain and amplify inflammatory processes (DeWolf et al., 2022). The integrity of epithelial tissue barriers is compromised by TNF-induced apoptosis, and subsequent epithelial tissue damage enhances PRR responses to pathogen-associated molecular patterns (PAMPs), leading to the expansion of mucosal inflammation. The ubiquitin scaffolds generated by these E3 ligases recruit kinases that activate MAPK and canonical NF- $\kappa$ B pathways. Dissociation of Complex I promotes formation of Complex II in the cytoplasm, which incorporates caspase-8 and acquires cytotoxic capacity (Wang et

al., 2024). caspase-8 subsequently activates downstream effector caspases to induce apoptosis or cleaves gasdermin D (GSDMD), driving pyroptotic pore formation (Zhang et al., 2024). In parallel, Receptor-Interacting Protein Kinase 1 (RIPK1) within Complex II may interact with RIPK3, culminating in mixed lineage kinase domain-like protein (MLKL) phosphorylation, oligomerization, and plasma membrane translocation—events that characterize necroptosis (Ye et al., 2023). Pyroptosis also relies on caspase-1 activation, which mediates GSDMD cleavage and pore formation, resulting in cell swelling

and lysis. This process is typically accompanied by the secretion of IL-1 $\beta$  and IL-18, together with DAMP release, thereby reinforcing inflammatory responses and tissue injury (Li and Jiang, 2023). Collectively, hypoxia-induced inflammatory cytokines orchestrate diverse forms of programmed cell death, linking metabolic stress to both apoptotic and pro-inflammatory outcomes (Figure 3). The deterioration of the microenvironment caused by inflammatory factors ultimately concentrates stress on the cellular energy and survival hub—the mitochondria.



**Figure-3.** Activation of Bax/Bak leads to permeabilization of the mitochondrial outer membrane, releasing CytC which subsequently activates Caspase-9 and Caspase-3, thereby initiating apoptosis. Concurrently released proteins such as SMAC suppress apoptosis-inhibiting proteins, further promoting cell death. FAS ligand and others activate Caspase-3 either directly or indirectly by activating Caspase-8. Elevated Ca<sup>2+</sup> levels activate Caspase-12, thereby initiating apoptosis. AIF and EndoG are released from mitochondria into the nucleus, directly causing DNA damage.

### The direct effects of hypoxia on mitochondrial function

As cellular powerhouses and centers of apoptosis regulation, mitochondria are undoubtedly the core target organ for hypoxia-induced injury. Hypoxia directly damages mitochondria, impairing electron transport chain function and promoting proton leakage, leading to a decline in mitochondrial

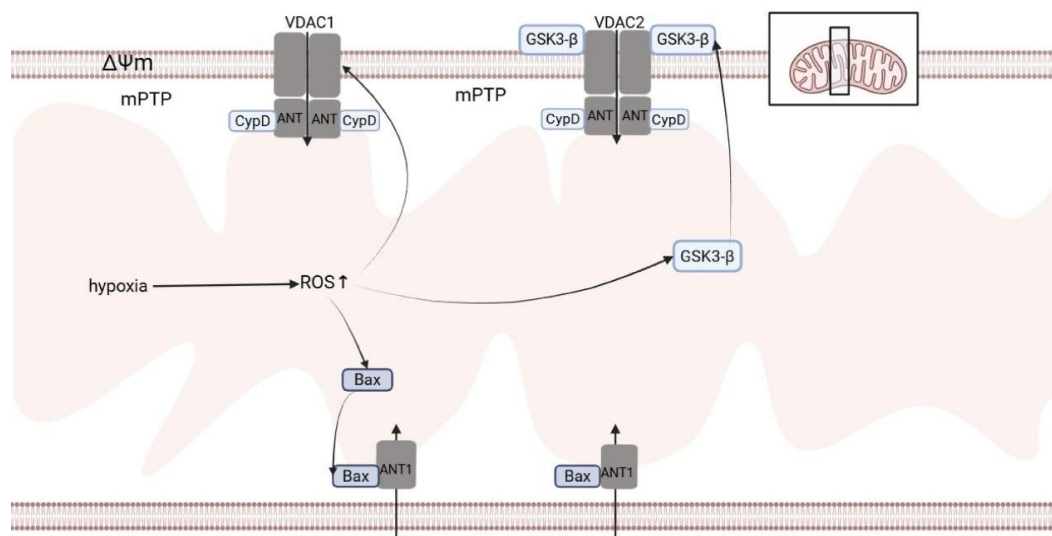
membrane potential ( $\Delta\Psi_m$ ). Adaptive regulation of OXPHOS involves remodeling electron transport chain (ETC) and tricarboxylic acid cycle (TCA) activity to counter reduced oxygen tension (Zotta et al., 2024). However, impaired electron transport causes leakage of electrons from the ETC, which combine with oxygen to generate ROS. Excessive ROS exacerbates mitochondrial dysfunction,

damaging proteins, lipids, and nucleic acids. This impedes ATP synthesis, leading to intracellular ATP depletion and triggering an energy crisis (Maldonado et al., 2023).

Hypoxia-induced mitochondrial calcium overload and oxidative stress serve as potent triggers for opening the mPTP. Hypoxia-induced mitochondrial damage impedes electron transport and promotes proton leakage across the inner membrane, thereby reducing  $\Delta\Psi_m$  and ultimately diminishing ATP synthase activity (Kuzmiak-Glancy et al., 2022). Key regulators of  $\Delta\Psi_m$  include respiratory substrates, proton-coupled transport systems, and uncoupling proteins, which collectively influence the magnitude of this potential. Under physiological conditions,  $\Delta\Psi_m$  is constrained within functional limits: proton leakage prevents excessive hyperpolarization, while excessively low  $\Delta\Psi_m$  disrupts intermediate metabolism and mitochondrial reactive oxygen species signaling. Another critical determinant of hypoxia-induced mitochondrial dysfunction is the opening of the mPTP (Xu et al., 2024). Upon homeostasis disruption, the highly conductive mPTP channel spanning the mitochondrial bilayer opens, facilitating ion flux and releasing pro-apoptotic factors (Oflaz et al., 2025). Elevated mitochondrial  $Ca^{2+}$  concentrations and oxidative stress are potent inducers of mPTP opening,

disrupting OXPHOS and promoting CytC release, thereby linking  $Ca^{2+}$  overload to apoptosis (Zhou et al., 2025).

The opening of the mPTP promotes the activation of pro-apoptotic proteins, disrupting the permeability of the mitochondrial outer membrane and facilitating the release of factors such as CytC. Pro-apoptotic Bcl-2 family proteins (such as Bax and Bak) can interact with voltage-dependent anion channels (VDACs) to destabilize the mitochondrial outer membrane, promoting CytC efflux and loss of  $\Delta\Psi_m$  (Zhang et al., 2024). Once released, CytC binds to Apoptotic Protease-Activating Factor-1 (APAF-1) to initiate caspase activation, ultimately leading to apoptosis. Beyond the classical caspase-dependent apoptotic cascade, mitochondria also regulate caspase-independent death mechanisms. Under severe hypoxia, released apoptosis-inducing factor (AIF) translocates to the nucleus, inducing chromatin condensation and extensive DNA fragmentation, thereby triggering programmed cell death independent of caspase activity. Once mitochondrial dysfunction exceeds a critical threshold, it irreversibly initiates a series of highly ordered cell death processes (Song et al., 2023)(Figure 4).



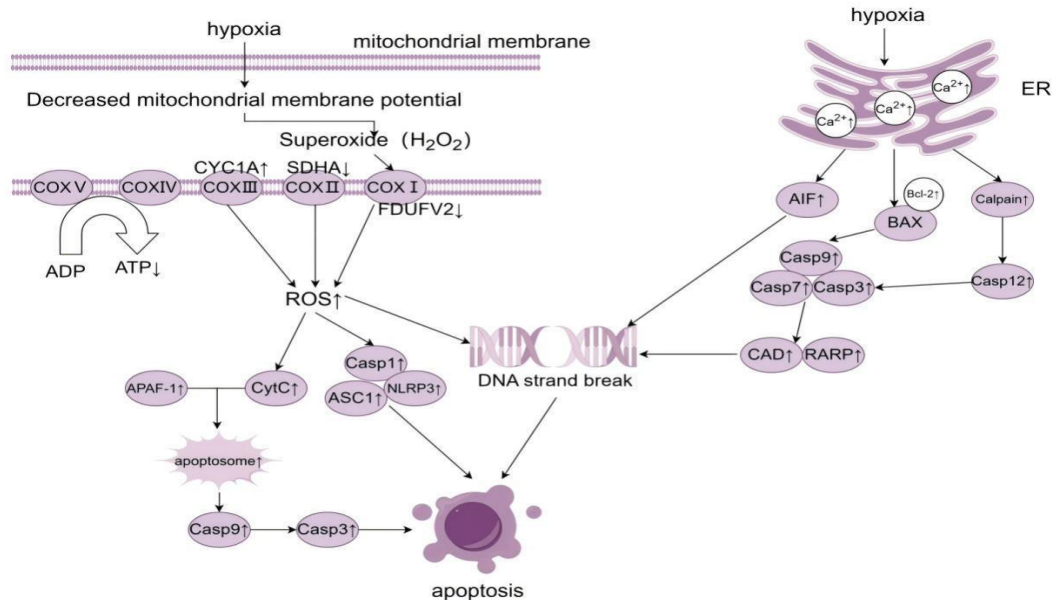
**Figure-4.** ROS is a potent inducer of mPTP opening, which directly triggers ion disruption and membrane potential collapse. Hypoxia upregulates VDAC-1 expression, increasing mitochondrial outer membrane permeability. ROS promotes the abnormal localization of GSK-3 onto the outer membrane protein VDAC-2, further facilitating mPTP opening. Hypoxia also increases the expression of ANT1/ANT2, which can form non-specific channels with the pro-apoptotic protein Bax on the mitochondrial membrane, collectively exacerbating the decline in membrane potential.

### **The primary pathway of hypoxia-induced cell death**

At the intersection of these pathways, cells ultimately decide their fate—whether to undergo apoptosis or autophagy—based on the extent of damage and contextual factors.

Hypoxia induces a variety of intracellular imbalances, including abnormally elevated  $\text{Ca}^{2+}$  levels, mitochondrial dysfunction, and excessive ROS accumulation, which together drive the initiation of the apoptotic program. The activation of proapoptotic factors within the Bcl-2 family, such as Bax and Bak, serves as the initiation mechanism for the apoptotic program. These proapoptotic factors subsequently induce mitochondrial outer membrane permeability (MOMP), followed by CytC release and the subsequent caspase cascade (Dadsena et al., 2021). Under hypoxic conditions, this leads to dysregulation of  $\text{Ca}^{2+}$  channel activity, resulting in intracellular  $\text{Ca}^{2+}$  overload and ultimately enhanced apoptotic signaling (Zhang et al., 2024). Bax and Bak, acting as pore-forming proteins, drive MOMP, causing CytC efflux into the cytoplasm (Li et al., 2025). Released CytC subsequently binds to apoptosis-related protein activator-1 (APAF-1) and dATP to form a complex, activating caspase-9 and cascading downstream effector molecule caspase-3 (Borgeaud et al., 2025). The formation of MOMP also leads to the release of mitochondrial DNA (mtDNA) into the cytoplasm. mtDNA binds to the transcription factor Transcription Factor A, Mitochondrial (TFAM), thereby activating the cyclic GMP-AMP Synthase Stimulator of Interferon Genes (cGAS-STING) signaling pathway and inducing the production of proinflammatory cytokines. Under normal physiological conditions, caspase activity acts as an inhibitor of the cGAS-STING pathway, maintaining

the anti-inflammatory nature of apoptosis (Zhou et al., 2021).  $\text{Ca}^{2+}$  serves as the primary messenger of the endoplasmic reticulum (ER). ER stress induces elevated intracellular  $\text{Ca}^{2+}$  levels, which activate  $\text{Ca}^{2+}$ -dependent enzymes such as calpain, leading to the cleavage and activation of cystopainin 12. Caspase-12 acts on both the initiator (caspase-9) and effector (caspase-7 and caspase-3) caspases to induce apoptosis (Denessiouk et al., 2020). Bax/Bak-mediated mitochondrial  $\text{Ca}^{2+}$  accumulation triggers CytC release and caspase activation, with cross-talk between the ER and mitochondria further amplifying the apoptotic signal (Guo et al., 2025). Formation of apoptotic vesicles containing CytC and APAF-1 stimulates caspase-9 activation, which in turn cleaves caspase-3 and caspase-7, driving execution of apoptosis (Wei et al., 2022). Extrinsic apoptotic pathways are also implicated in hypoxia-related cell death. Engagement of Fas ligand with its receptor recruits Fas-associated protein with death domain (FADD) and pro-caspase-8 through death domain interactions, resulting in assembly of the death-inducing signaling complex (DISC). Auto-cleavage of pro-caspase-8 activates caspase-3 directly or indirectly by cleaving Bid, which translocates to mitochondria and enhances the intrinsic apoptotic pathway (Araya et al., 2021). Activated BH3-interacting domain death agonist (Bid) stimulates BH3-only proteins, reducing Bcl-2 inhibition and promoting Bax oligomerization, which facilitates CytC release and apoptosome formation. Ultimately, these events converge on caspase-3 activation, committing cells to apoptosis. In addition to caspase-dependent mechanisms, mitochondria can initiate apoptosis through the release of AIF and EndoG, which translocate to the nucleus and promote DNA fragmentation in a caspase-independent manner (Liu et al., 2022) (Figure 5).



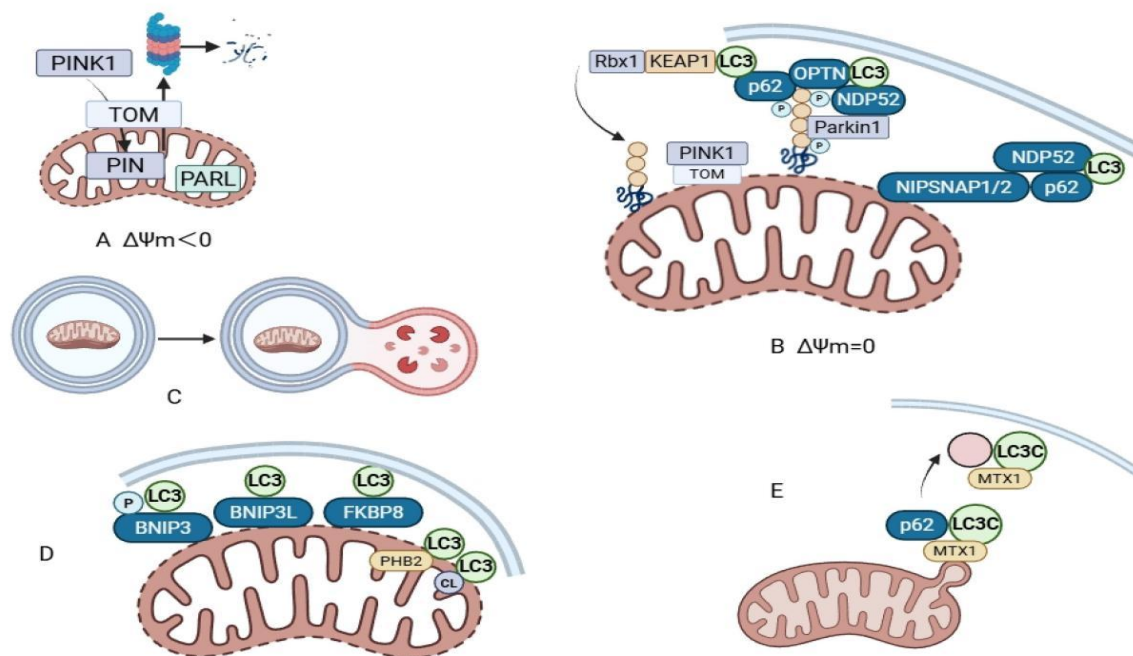
**Figure-5.** Hypoxia inhibits respiratory chain function, leading to reduced ATP synthesis, ROS bursts, and loss of mitochondrial membrane potential, thereby triggering cytochrome C release and activating the caspase apoptotic cascade. Excessive ROS not only directly damages mitochondria but also activates the NLRP3 inflammasome, promoting inflammatory apoptosis via Caspase-1. Hypoxia induces endoplasmic reticulum stress and calcium overload, activating Caspase-12 which synergizes with the mitochondrial pathway to jointly cause DNA damage and cell death.

Autophagy represents a fundamental adaptive mechanism under hypoxia, enabling cells to degrade and recycle damaged proteins and organelles, thereby maintaining energy supply and metabolic balance (Yi et al., 2022). Activation of autophagy under low oxygen tension not only supports cell survival but also suppresses apoptotic signaling pathways, thus preserving cellular homeostasis (Zhang et al., 2020). In mammalian cells, mitophagy primarily depends on the regulation of multiple signaling pathways, including the classical PTEN-induced putative kinase 1 (PINK1/Parkin) axis, BNIP3/BNIP3L, and FUNDC1-mediated pathways (Yan et al., 2025). Of these, the PINK1/Parkin pathway is particularly critical in recognizing and removing damaged mitochondria. Upon loss of mitochondrial membrane potential, PINK1 accumulates at the outer mitochondrial membrane and recruits the E3 ubiquitin ligase Parkin, thereby inducing ubiquitination of outer membrane proteins (Marchesan et al., 2024). This modification provides a recognition signal for autophagy receptors (e.g., Nuclear Dot Protein 52 kDa (NDP52) and Optineurin (OPTN)) to bind to Microtubule-

associated protein 1 Light Chain 3 (LC3) proteins on the surface of autophagosomes, thereby initiating mitosis. Meanwhile, components such as NipSnap homolog 1/2 (NIPSNAP1/2), p62, Autophagy-Linked FYVE protein (ALFY) and AuTophagy-related 8 (ATG8) are also involved in receptor recruitment and autophagosome assembly (Princely Abudu et al., 2019). In addition to the typical PINK1/Parkin-dependent pathway, cells have multiple alternative pathways, including BNIP3/NIX and FUNDC1-mediated mitophagy, as well as mechanisms associated with BCL2-L13, FK506-binding protein 8 (FKBP8), Prohibitin 2 (PHB2), Activating molecule in BECN1-regulated autophagy protein 1 (AMBRA1), and specific lipid signaling (e.g., cardiolipin, ceramide) (Lampert et al., 2019). In hypoxic environments, BNIP3/NIX and FUNDC1 directly bind LC3 and promote the generation of autophagic vesicles, thus serving as key pathways for the maintenance of mitochondrial homeostasis under hypoxic stress (Bian et al., 2024). In addition, the mitochondrial inner membrane protein PHB2 can act as an LC3 receptor and is located downstream of PINK1, and is thus regarded as an important marker of

mitophagy (Sun et al., 2022). Notably, mitochondria are not only targets of autophagy, but also key factors that regulate the balance between apoptosis and autophagy. By activating autophagy-related molecules such as ATGs, p53, and caspase, mitochondria are able to inhibit the release of CytC, limit the overaccumulation of ROS, and prevent aberrant fission, thus enabling selective clearance through mitosis (Benedi et al., 2025). Taken together, these signaling pathways highlight the protective role of mitophagy in maintaining mitochondrial quality

control and adaptive cell survival under hypoxic stress (Figure 6). While mitophagy is canonically a protective mechanism, emerging evidence suggests that excessive or dysregulated mitophagy can itself contribute to cell death, blurring the line between adaptive and pathological responses. The precise mechanisms by which mitophagic receptors like BNIP3 and FUNDC1 communicate with, and potentially inhibit, the core apoptotic machinery is an area of active investigation.



**Figure-6.** A: Under basal conditions, PINK1 is translocated to the mitochondrial matrix, where it undergoes cleavage by PARL into smaller fragments that are subsequently released into the cytoplasm for degradation by the proteasome. B: Following loss of mitochondrial membrane potential, PINK1 stabilizes on the outer membrane and becomes activated. Through phosphorylation of ubiquitin, it directly recruits and activates the E3 ligase Parkin, thereby inducing extensive ubiquitination of outer membrane proteins. In the absence of Parkin, p62 recruits the KEAP1-Rbx1 complex to ubiquitinate outer mitochondrial membrane proteins, generating a similar "phagocytic signal". This ubiquitin modification is recognized by autophagy receptors such as NDP52, OPTN, and p62. Concurrently, NIPSNAP1/2 on depolarized mitochondria further enhances recruitment of these receptors and the scaffold protein ALFY. All recruited receptors and scaffold proteins ultimately anchor damaged mitochondria to developing autophagosomes by binding to LC3/ATG8 family proteins on autophagosome membranes, completing targeted engulfment. C: Mitochondria are engulfed by double membrane vesicles known as autophagosomes, which fuse with lysosomes to facilitate mitochondrial turnover. D: PINK1 / Parkinson non-dependent mitochondrial autophagy: Outer mitochondrial membrane-bound autophagy receptors, such as BNIP3, BNIP3L, and FKBP8, interact with LC3 on the autophagosome membrane. Proteins such as CL and PHB2 in the inner mitochondrial membrane can also bind to LC3 to aid in the recruitment of damaged mitochondria to autophagosomes. E: Selective mitochondrial autophagy: The outer mitochondrial membrane protein MTX1 interacts with LC3C and p62 to transport MTX1 positive mitochondrial vesicles to autophagosomes.

Our synthesis reveals several critical knowledge gaps. First, the “molecular switch” that dictates the cell's commitment to apoptosis versus mitophagy under hypoxia is still enigmatic. While both processes are activated, the factors that tip the balance—such as the differential modification of proteins like FUNDC1 or the spatial-temporal dynamics of Bax/Bak activation relative to PINK1/Parkin recruitment—require urgent investigation. Second, the quantitative aspect of these pathways is often overlooked: how much ROS is protective versus lethal? What is the threshold of  $\Delta\Psi_m$  loss that irreversibly triggers MOMP? Addressing these questions will require live-cell imaging and mathematical modeling. Third, most studies focus on acute hypoxia; the adaptations and long-term consequences of chronic, intermittent hypoxia—a common feature in conditions like sleep apnea and solid tumors—on mitochondrial fitness and cell death susceptibility are far less understood and represent a fertile area for future research.

## Conclusions

This review systematically delineates the molecular cascades linking hypoxia to cell death, centering on mitochondrial dysfunction. The HIF serves as the master regulator, initiating responses that range from metabolic adaptation to the induction of pro-death genes. The ensuing mitochondrial compromise—characterized by energetic failure, loss of membrane potential, and permeability transition—creates a permissive environment for the escalation of oxidative stress and inflammation. These damaging signals converge to trigger mitochondrial outer membrane permeabilization, the release of apoptogenic factors such as cytochrome c and apoptosis-inducing factor, and the activation of caspase-dependent and -independent executioner pathways. Meanwhile, autophagy and mitophagy operate as critical, context-dependent modulators that can either promote survival or contribute to demise. The interplay among these pathways—HIF signaling, oxidative stress, inflammatory activation, and the mitochondrial execution machinery—forms a complex network that determines cellular fate under hypoxic stress. Future research should prioritize elucidating the precise molecular switches that govern the balance between adaptive and pro-death outcomes, particularly the crosstalk between mitophagy and apoptosis. Unraveling these intricacies will not only deepen our understanding of hypoxia-related pathologies but also

illuminate novel therapeutic avenues for conditions ranging from ischemic diseases to cancer.

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## Contribution of Authors

Ye Y & Li H: Conceptualized the study, designed research methodology, conducted experiments, collected data and wrote the original draft.

Liu F & Gao Y: Literature review, reference retrieval and manuscript write up and editing

Chamba Y & Shang P: Data analysis and interpretation, manuscript write up and editing

All authors read and approved the final draft of the manuscript.

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