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Mitophagy Dysfunction: A Crucial Molecular Mechanism Underlying Insulin Resistance and Type 2 Diabetes

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Abstract. Mitophagy refers to the selective degradation of impaired mitochondria by cells, a process vital for preserving intracellular metabolic equilibrium. This article elaborates on three types of mitophagy, the molecular mechanisms of both PINK1/Parkin-dependent and PINK1/Parkin-independent pathways, and the complex relationship between mitophagy and insulin resistance (IR) and type 2 diabetes mellitus (T2DM). Impaired mitophagy disrupts mitochondrial quality control, fostering oxidative stress and chronic low-grade inflammation in metabolically active tissues—including adipose, skeletal muscle, and liver—which in turn compromises insulin signaling and accelerates T2D progression. Therapeutic strategies targeting mitophagy, such as metformin and natural compounds like saponins, show potential in restoring mitochondrial quality control and improving insulin sensitivity. The review highlights the possibility of targeting mitophagy-related pathways in precision medicine for T2DM and advocates for the adoption of upstream molecular diagnostics to enable early intervention and personalized treatment. Moreover, an integrated understanding of mitophagy regulation and its metabolic impacts is essential for creating innovative therapies.

Keywords: Mitophagy, Insulin Signaling, Diabetes, Mitochondria.

1. Introduction

In 2022, there were 828 million adults worldwide with diabetes, an increase of 630 million compared to 1990 [1]. Among them, 445 million diabetes patients aged 30 years and older did not receive treatment, accounting for 59% of all cases -- 3.5 times higher than in 1990. More than 85% were type 2 diabetes mellitus (T2DM) [1]. T2DM can also increase the risk of other diseases. For example, patients with T2DM have a higher risk of cardiovascular disease [2]. With the increasing prevalence and serious health consequences, a more detailed analysis of the pathogenesis of T2DM is needed. T2DM is mainly caused by β-cell damage and insulin resistance (IR) [2]. These two key factors are influenced by multiple contributors, such as excessive fat and sugar intake, and irregular work and rest are their surface reasons. T2DM is a complex multi-system metabolic disorder involving skeletal muscle, liver, adipocytes and other tissue cells. Therefore, its molecular pathways are extremely complex and interconnected.

Mitochondria are central sites for cellular energy metabolism in cells and play a critical role in regulating intracellular reactive oxygen species (ROS), which are closely related to inflammatory

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pathways and cell viability [3]. Therefore, mitochondrial function has an important impact on IR and T2DM. Mitophagy, a specialized form of autophagy, selectively identifies and degrades damaged mitochondria, thereby maintaining cellular homeostasis [4]. As a key regulator in metabolic homeostasis, mitophagy may represent a promising therapeutic target for IR and T2DM.

This review summarizes the molecular regulation mechanism of mitophagy, the insulin signaling pathway and the causes of IR and T2DM. It further explores the relationship between impaired mitophagy, IR, and T2DM, emphasizing the potential of targeting the mitophagy-related signaling pathway in the design of drugs for T2DM. Unlike previous research that predominantly focuses on individual molecular pathways, this review integrates multifaceted mitophagic processes with insulin signaling to illuminate their interconnected role in metabolic disorders. By highlighting the therapeutic potential of modulating these pathways, this paper provides a valuable resource for researchers and clinicians seeking to develop targeted strategies for combating type 2 diabetes, thus underscoring the importance of mitophagy as a promising intervention point in precision medicine.

2. Molecular mechanism and regulation of mitophagy

2.1. Three types of mitophagy

Type I mitophagy is primarily induced by nutrient deprivation. Microtubule-associated protein 1 light chain 3 (LC3) diffuses in the cytoplasm under nutrient-rich conditions, with a fraction localized in small preautophagic structures (PAS) near mitochondria. Nutrient deficiency activates the phosphatidylinositol 3-kinase (PI3K) complex, which promotes the lipidation of LC3-I and its conversion to LC3-II [5]. PAS then expand into cup-shaped isolation membranes or phagosomes that encapsulate and sequester individual mitochondria into autophagosomes, where LC3-II predominantly accumulates on the autophagosome membrane [6]. Mitochondrial fission frequently occurs simultaneously with sequestration, while mitochondria maintain their membrane potential during this stage. Following isolation, the outer mitochondrial compartment undergoes acidification and depolarization, subsequently fusing with lysosomes and undergoing complete degradation.

Type II mitophagy differs from type I in that it is primarily triggered by mitochondrial damage. Under normal conditions, PINK1 is efficiently translocated into the inner mitochondrial membrane (IMM) of intact mitochondria, undergoes proteolytic processing, and is subsequently degraded, resulting in minimal cytosolic accumulation. In damaged mitochondria, the import and processing capacity of the IMM is impaired, preventing PINK1 degradation [7]. This blockage leads to PINK1 stabilization at the outer mitochondrial membrane (OMM), where it acquires its active kinase state. Activated PINK1 phosphorylates ubiquitin molecules bound to OMM proteins, thereby promoting the recruitment of Parkin from the cytoplasm to the OMM. PINK1 also directly phosphorylates Parkin, enabling its full activation. Activated Parkin ubiquitinates mitochondrial proteins, after which autophagy receptor proteins such as p62/SQSTM1 and optineurin (OPTN) specifically recognize and bind these ubiquitin chains via their UBA domains. Simultaneously, these receptors interact with LC3 proteins on the autophagosome membrane through their LIR domains, linking ubiquitin-labeled mitochondria to the forming autophagosome. Distinct from type I, this pathway operates independently of PI3K activity, lacks typical cup-shaped phagophore formation, and proceeds without significant mitochondrial fragmentation [8].

Type III mitophagy, also referred to as micromitophagy, is stimulated by oxidative stress, which promotes the generation of mitochondria-derived vesicles (MDVs). Unlike type II, this process proceeds without mitochondrial depolarization and delivers MDVs to lysosomes in an LC3-independent manner. MDV formation also does not rely on dynamin-related protein 1 (DRP1), a key

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GTPase mediating mitochondrial fission, which distinguishes it from type I mitophagy, where fission is evident. MDVs are subsequently engulfed into multivesicular bodies via a PINK1/Parkin-driven route; upon lysosomal fusion, the sequestered mitochondrial material is degraded by resident hydrolases [8].

2.2. Formation of mitophagosome

Type I and type II mitophagy both require the participation of LC3, and their main molecular pathways can be classified into three categories. The most extensively studied mechanism of mammalian mitophagy is PINK1/Parkin-mediated mitophagy. When mitochondrial membrane potential is reduced, full-length PINK1 accumulates on the OMM, where it phosphorylates the Ser65 site of ubiquitinated proteins such as voltage-dependent anion channel (VDAC) and mitochondrial Rho (Miro) [9]. Parkin is subsequently recruited from the cytoplasm to the OMM, where it is directly phosphorylated by PINK1 at Ser65. Once activated, Parkin catalyzes the formation of polyubiquitin chains on OMM proteins. For instance, the formation of K48-linked ubiquitin chains on mitofusin 1 or mitofusin 2 blocks mitochondrial fusion, while K48-linked chains on Miro halt mitochondrial movement [8]. By contrast, the formation of K63-linked ubiquitin chains on VDAC recruits autophagy receptors such as OPTN, NDP52, and p62. The functions of p62 and OPTN are independent of each other: knockout of p62 does not impair OPTN function, and knockout of OPTN does not affect p62 function [10].

The other two pathways operate independently of Parkin. Under hypoxic conditions, BCL2-interacting protein 3 (BNIP3) and NIX (Nip-like protein X) reduce mitochondrial membrane potential and promote depolarization. Their N-terminal cytoplasmic domains directly or indirectly interact with LC3, thereby tethering autophagosomes to mitochondria for targeted degradation. Similarly, FUN14 domain-containing protein 1 (FUNDC1), an OMM protein highly responsive to hypoxia, binds to LC3 to promote mitophagy under these conditions [8].

The third pathway involves cardiolipin-mediated mitophagy. Cardiolipin, normally localized in the IMM, translocates to the OMM upon exposure to external depolarizing toxins. This process is mediated by phospholipid scramblase 3 (PLSCR3), which facilitates the externalization of cardiolipin, allowing it to bind LC3. Cardiolipin-mediated mitophagy requires LC3 lipidation and is further regulated by TGF-β1 signaling, which enhances PLSCR3 expression [11]. The molecular cascades outlined above are schematically illustrated in Figure 1.

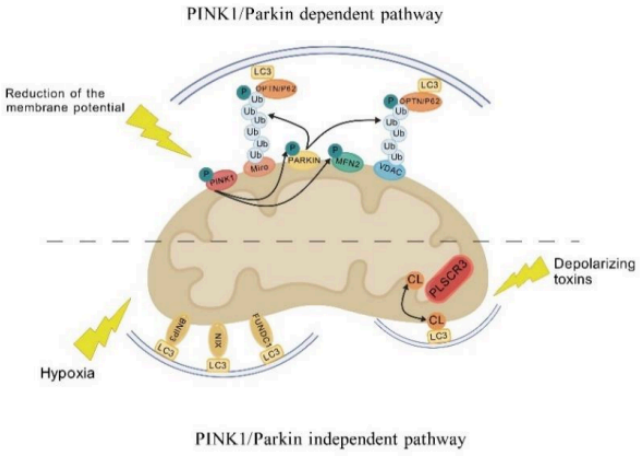

Figure 1. Formation of mitophagosome

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The PINK1/Parkin-dependent pathway begins when a drop in mitochondrial membrane potential leads to accumulation of PINK1 on the OMM. PINK1 then phosphorylates OMM proteins and activates Parkin, which in turn catalyzes the formation of polyubiquitin chains. These chains are recognized by receptor proteins such as OPTN or p62, which subsequently recruit LC3 to initiate mitophagy. In contrast, PINK1/Parkin-independent pathways operate under different stimuli. Under hypoxic conditions, OMM proteins such as BNIP3, NIX and FUNDC1 can bind LC3 directly and initiate mitophagy. Additionally, upon toxin stimulation, cardiolipin translocates from the IMM to the OMM and binds LC3, thereby recruiting autophagosomes to promote mitochondrial degradation.

3. Insulin signaling pathway

3.1. Initiation of insulin signaling

Prior to insulin binding, the insulin receptor exists on the cell membrane as a preformed homodimer. This receptor contains four potential binding sites, but binding of only one insulin molecule is sufficient to induce a conformational rearrangement that relieves inhibition of the intracellular tyrosine kinase domain of the β-subunit, thereby triggering its autophosphorylation and fully activating the receptor's kinase activity.

Insulin receptor substrates (IRS) serve as the primary substrates of the receptor's tyrosine kinase. Multiple tyrosine residues on IRS proteins become phosphorylated, creating docking sites that form a signaling platform for downstream effectors. Among these, phosphoinositide 3-kinase (PI3K) binds to phosphorylated IRS and becomes activated. Activated PI3K, in turn, promotes the activation of protein kinase B (AKT). Fully activated AKT functions as a central signaling hub, transmitting signals to multiple key downstream pathways.

AKT inhibits glucose production by regulating forkhead box O (FOXO) transcription factors, including FOXO1, FOXO3a, and FOXO4. It also regulates TBC1 domain family member 4 (TBC1D4), which facilitates glucose transporter type 4 (GLUT4) vesicle trafficking and thereby enhances glucose uptake. In addition, AKT modulates glycogen synthase kinase 3 (GSK3), ATP citrate lyase (ACLY), and 6-phosphofructo-2-kinase (PFKFB), thereby influencing glycogen synthesis, lipid synthesis, and glycolysis, respectively.

Furthermore, activated AKT stimulates the mammalian target of rapamycin (mTOR), which directly phosphorylates and activates S6 kinase (S6K) and sterol regulatory element-binding protein 1 (SREBP1). Activated S6K enhances protein translation, while SREBP1 promotes lipid synthesis in the liver and adipocytes [12].

3.2. Termination of insulin signaling

Termination of insulin signaling results from the integration of multiple regulatory mechanisms. Upon insulin binding, the insulin receptor is internalized, which directly blocks further ligand access to the binding site. In addition, several kinases activated by other pathways phosphorylate serine/threonine residues on the insulin receptor, thereby inhibiting its tyrosine kinase activity and ultimately suppressing insulin action [12].

During insulin stimulation, activated PI3K catalyzes the conversion of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which subsequently activates AKT through downstream pathways. Termination of this signaling is mediated by tyrosine phosphatases, which dephosphorylate the insulin receptor and attenuate downstream signaling. Phosphatase and tensin homolog (PTEN) converts PIP3 back to PIP2, thereby antagonizing insulin

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signaling [13]. Similarly, SH2 domain–containing inositol 5-phosphatase 1 (SHIP1) and SH2 domain–containing inositol 5-phosphatase 2 (SHIP2) exert comparable inhibitory functions.

In addition, growth factor receptor–bound protein 10 (Grb10) and growth factor receptor–bound protein 14 (Grb14) act as negative regulators. These adaptor proteins bind to the intracellular domain of the insulin receptor, interfering with its ability to interact with IRS proteins and thereby dampening signal propagation [13].

4. Insulin resistance and type 2 diabetes

IR refers to a diminished metabolic response of target cells to insulin, resulting in impaired glucose utilization. It is one of the major pathogenic mechanisms underlying T2DM.

In skeletal muscle cells, insulin binds to its receptor on the cell surface, triggering the translocation of GLUT4 from intracellular vesicles to the plasma membrane. This process facilitates glucose uptake from the bloodstream into the cell. Reduced or mutated expressions of the insulin receptor or GLUT4, or defects in upstream or downstream signaling pathways, impair glucose utilization by myocytes and contribute to hyperglycemia.

In hepatocytes, insulin normally suppresses gluconeogenesis by regulating FOXO1, thereby reducing hepatic glucose production, while also influencing lipid metabolism through downstream pathways. In the setting of hepatic insulin resistance, insulin signaling is insufficient to effectively inhibit gluconeogenesis and promote glycogen synthesis. At the same time, lipogenesis is enhanced, and inflammatory signaling pathways are activated, resulting in the production of proinflammatory cytokines. These cytokines exacerbate hepatic inflammation and further aggravate systemic IR.

In adipose tissue, obesity-associated activation of adenine nucleotide translocase 2 induces hypoxia in adipocytes, which promotes infiltration of proinflammatory immune cells such as M1 macrophages. This infiltration leads to the release of large amounts of proinflammatory molecules that circulate in the blood, reach muscle and liver tissues, and induce local as well as paracrine-driven systemic inflammation. The resulting inflammatory milieu impairs cellular metabolism and promotes IR. Moreover, IR in adipocytes reduces the ability to suppress lipolysis, leading to increased release of free fatty acids, which further contribute to systemic IR and progression to T2DM.

β-cell dysfunction is central to the development of T2DM, and multiple mechanisms contribute to its onset. Chronic hyperglycemia downregulates key transcription factors, including pancreatic/duodenal homeobox-1 and musculoaponeurotic fibrosarcoma oncogene family A (MafA), thereby impairing glucose-stimulated insulin secretion. In addition, inappropriate overexpression of normally disallowed genes, such as repressor element 1 silencing transcription factor, suppresses insulin secretion and activates dual-specificity tyrosine-regulated kinase 1A, which inhibits β-cell proliferation. Glucotoxicity caused by persistent hyperglycemia also promotes excessive ROS production, resulting in β-cell dysfunction and apoptosis. Furthermore, mitochondrial dysfunction enhances ROS generation, further disrupting insulin secretion [14].

5. Dysfunctional mitophagy and type 2 diabetes

5.1. Adipose tissue

Group 2 innate lymphoid cells (ILC2) reside in white adipose tissue, where they regulate both immune function and tissue metabolism. Obesity reduces the expression of liver kinase B1 (LKB1) in adipocytes. LKB1 is a key metabolic sensor and kinase that regulates multiple cellular processes,

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including energy metabolism, and under normal conditions, it inhibits programmed death 1 (PD-1) expression by suppressing the ROS-NFAT pathway. Reduced LKB1 expression increases ROS production, which in turn upregulates nuclear factor of activated T cells 2 (NFAT2). Consequently, this abnormal reduction of LKB1 dysregulates the ROS-NFAT pathway, leading to elevated PD-1 expression. PD-1 inhibits the expression of B-cell lymphoma-extra large (Bcl-xL), and excessive PD-1 causes a decrease in Bcl-xL levels. Since Bcl-xL normally prevents Parkin recruitment to dysfunctional mitochondria, its depletion results in excessive mitophagy. Loss of mitochondrial mass reduces ATP production, causing dysfunction or death of ILC2 cells. Given that ILC2 is central to type 2 immunity, its impairment leads to a marked decrease in eosinophils and M2-type macrophages, an increase in proinflammatory M1-type macrophages, and ultimately adipose tissue inflammation. Inflammation in adipose tissue contributes to IR and T2DM [15].

Furthermore, loss of thioredoxin 2 (Trx2) in adipocytes also contributes to IR and T2DM. Trx2 plays a critical role in removing intracellular ROS. When Trx2 is deficient or dysfunctional, ROS accumulates, activating NF-κB signaling: IκB kinase becomes phosphorylated, leading to IκBα phosphorylation and degradation. This increases phosphorylation of the p65 subunit, further activating NF-κB signaling. Activation of NF-κB is accompanied by increased expression of p62/SQSTM1, a key protein in mitophagy. Elevated p62 promotes the formation of numerous autophagosomes around mitochondria, reflecting excessive mitochondrial autophagy. Abnormal mitophagy impairs adipocyte function, causing local inflammation and release of non-esterified fatty acids (NEFA) into the liver. NEFA promotes hepatic gluconeogenesis by increasing acetyl-CoA levels, ultimately raising blood glucose [16]. These pathological cascades linking dysfunctional mitophagy to adipose tissue inflammation and metabolic dysregulation are schematically summarized in Figure 2.

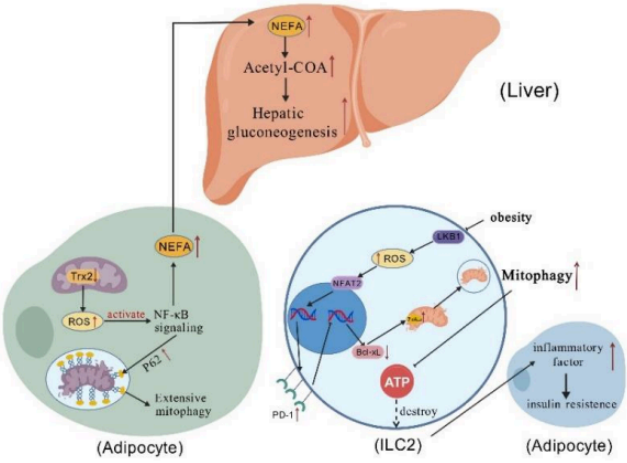

Figure 2. Association of dysfunctional mitophagy in adipose tissue with IR and T2DM

In white adipose tissue, obesity reduces LKB1 expression in ILC2 cells, which enhances PD-1 expression via the ROS–NFAT pathway. This, in turn, suppresses Bcl-xL, triggering excessive mitophagy. Excessive mitophagy decreases ATP production and disrupts ILC2 function, thereby weakening type 2 immunity, promoting adipose tissue inflammation, and ultimately contributing to IR and T2DM. In addition, the loss of Trx2 in adipocytes leads to ROS accumulation, activation of NF-κB signaling, and upregulation of p62. This cascade drives excessive mitophagy and adipocyte dysfunction, promotes the release of non-esterified fatty acids (NEFA) into the liver, and enhances gluconeogenesis, leading to hyperglycemia.

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5.2. Skeletal muscle

The expression of deubiquitinating enzymes, including USP13, USP15, and USP30, is upregulated in the skeletal muscle of T2DM patients. Overexpression of USP15 and USP30 inhibits Parkin activity, impairing the production of ubiquitin chains—particularly K63 chains—that are normally catalyzed by Parkin. This reduces the expression of p62 and LC3, ultimately compromising mitochondrial quality control. Additionally, overexpression of USP15 and USP30 directly affects the insulin signaling pathway by inhibiting AKT activation.

Mitochondrial division is regulated by DRP1, which is over-activated in skeletal muscle cells of T2DM patients, leading to excessive mitochondrial fission and fragmentation [17]. Short-term high-fat diet can also induce mitochondrial dysfunction and acute IR in skeletal muscle cells. The specific manifestations of mitochondrial dysfunction include structural damage, increased expression of the fission protein DRP1, and decreased citrate synthase activity, ATP content, and mitochondrial DNA content. Acute IR is primarily reflected by elevated blood glucose and insulin levels. Both mitochondrial function and acute IR can be improved by administration of mitochondrial division inhibitor 1 [18]. These mechanisms linking dysfunctional mitophagy and mitochondrial dynamics to insulin signaling defects in skeletal muscle are schematically depicted in Figure 3.

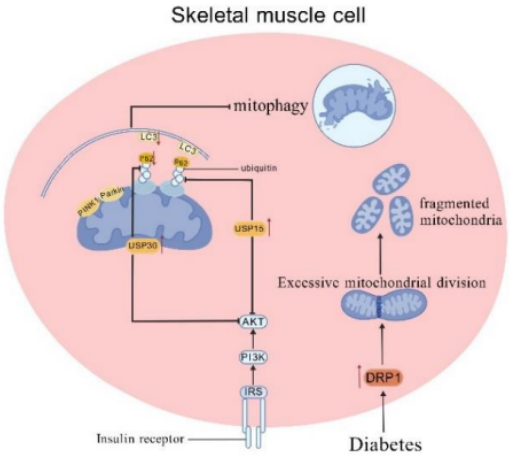

Figure 3. Association of dysfunctional mitophagy in skeletal muscle with IR and T2DM

In the skeletal muscle of T2DM patients, the expression of the deubiquitinating enzymes USP15 and USP30 is upregulated, which inhibits Parkin-mediated ubiquitination and mitochondrial quality control, thereby directly impairing AKT activation and insulin signaling. Meanwhile, DRP1 overactivation promotes excessive mitochondrial fission and fragmentation, further compromising mitochondrial function.

5.3. Liver tissue

In insulin-resistant liver cells, the activity of 5’-adenosine monophosphate-activated protein kinase (AMPK), which mediates mitophagy, is significantly inhibited. Under diabetic conditions, phosphorylated AMPK (p-AMPK) is markedly decreased, accompanied by reduced levels of LC3B-II and increased levels of p62, indicating impaired mitophagy and a reduction in intracellular mitophagic activity. Abnormal mitochondrial autophagy leads to elevated malondialdehyde (MDA) and ROS, while antioxidant substances such as glutathione and superoxide dismutase are decreased, resulting in oxidative stress that damages liver cells and exacerbates IR. Administration of the

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AMPK agonist 5-Aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR) increases p-AMPK levels, alleviating the inhibition of AMPK activity. Concurrently, increases in LC3B-II and PINK1, along with a decrease in p62, indicate that AICAR restores mitophagy, as also confirmed by electron microscopy. ROS levels are reduced, and pathological damage to liver tissue is mitigated [19].

Under normal conditions, Olfactomedin 4 (OLFM4), located on the mitochondrial membrane, regulates p62 and maintains its functional homeostasis. Loss of OLFM4 leads to abnormally elevated p62 levels, disrupting homeostasis and inhibiting mitophagy. This impairment of mitochondrial autophagy is further evidenced by decreased PINK1 and Parkin expression. Abnormal mitophagy impairs oxidative phosphorylation, causing dysregulation of cellular energy metabolism. The accumulation of damaged mitochondria increases ROS production, which promotes inflammatory factor release and activates kinases such as c-Jun N-terminal kinase (JNK). Activated JNK drives serine/threonine phosphorylation of IRS instead of normal tyrosine phosphorylation, thereby blocking downstream insulin signaling and ultimately contributing to IR [20]. These AMPK- and OLFM4-dependent events linking defective mitophagy to hepatic oxidative stress and insulin resistance are schematically summarized in Figure 4.

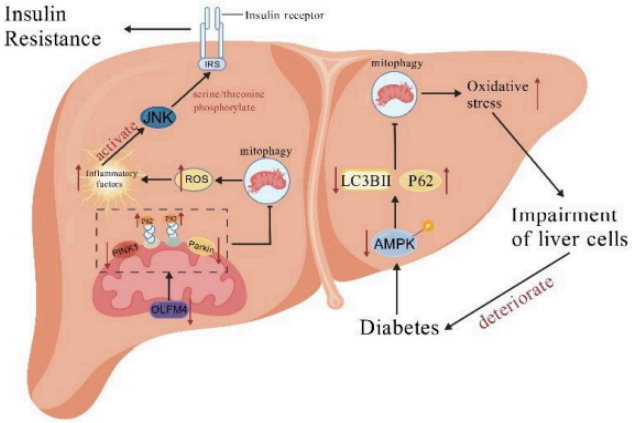

Figure 4. Association of dysfunctional mitophagy in liver tissue with IR and T2DM

In the hepatocytes of T2DM patients, AMPK activity is inhibited, resulting in impaired mitophagy, as evidenced by decreased LC3B-II and increased p62. This defect promotes oxidative stress, hepatocyte damage, and progression of T2DM. Additionally, the loss of the mitochondrial protein OLFM4 further disrupts mitophagy, indicated by abnormal p62 accumulation and reduced PINK1 and Parkin expression. These alterations lead to ROS accumulation and inflammatory responses, which interfere with insulin signaling via JNK activation and ultimately promote IR.

6. Conclusion

T2DM is closely linked to impaired mitophagy, often characterized by reduced expression of PINK1 and Parkin and inhibited AMPK activity. These abnormalities weaken mitochondrial quality control, exacerbate oxidative stress, and contribute to IR. Therapeutic strategies that restore mitophagy have shown promising potential for improving metabolic homeostasis in T2DM patients.

Pharmacological interventions remain central. The first-line agent metformin enhances mitophagy, lowers ROS and suppresses TNF-α, collectively improving cellular insulin sensitivity and reducing IR [21]. Similarly, saponins derived from Korean red ginseng up-regulate PINK1 and Parkin expression and promote AMPK phosphorylation in hepatocytes, thereby enhancing

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mitophagy and accelerating mitochondrial turnover. Consequently, ROS and P-JNK levels fall, IRS and AKT phosphorylation increase, and insulin signaling is restored [22].

Lifestyle and dietary interventions are equally important. Obesity-induced adipose tissue dysfunction contributes to systemic IR in muscle and liver; limiting excessive fat intake alleviates adipose inflammation, improves peripheral insulin signaling and slows T2DM progression.

Prospects for precision medicine are expanding. T2DM is a complex, multisystem metabolic disorder driven by diverse upstream molecular pathways that converge on hyperglycemia. Future clinical workflows could incorporate upstream biomarkers—AMPK activity, PINK1/Parkin expression, JNK activity—to guide individualized mitophagy-targeted therapies, moving management from glucose-centric reaction to mechanism-based prevention.

Collectively, restoring mitophagy through pharmacological agents, dietary control and precision strategies offers a promising and unifying approach to improve insulin sensitivity and metabolic outcomes in T2DM. As research on mitophagy regulation advances, novel mitochondrial quality-control therapeutics should provide more effective, personalized management of type 2 diabetes.

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