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REVIEW

Research Progress on Pathology, Molecular Mechanisms, and Intervention Strategies of Cognitive Dysfunction Associated with Type 2 Diabetes

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Abstract: Type 2 diabetes–associated cognitive dysfunction (DACD) is a major neurological complication of type 2 diabetes mellitus (T2DM). Against the backdrop of global population aging and the rising prevalence of T2DM, DACD poses a substantial challenge to public health. The pathogenesis of DACD involves the interplay of multiple signaling pathways and pathological processes, which remain incompletely understood. This review aims to systematically delineate the interconnections and regulatory networks among core mechanisms in DACD, including glucose transporter dysfunction, the oxidative stress–mitochondrial dysfunction–neuroinflammation axis, ferroptosis, the microbiota–gut–brain axis, autophagy, and epigenetic modifications. By integrating recent research advances in these mechanisms, this review provides a comprehensive understanding of the pathology of DACD and proposes multi-target intervention strategies from an integrated perspective, thereby offering insights for the development of future therapeutic approaches. This integrated framework is expected to provide new theoretical perspectives for clinicians and translational medicine researchers, to promote the development of diagnostic tools integrating multi-omics biomarkers, and to offer references for optimizing combination treatment strategies targeting key nodes across multiple mechanisms. The primary limitation of this review is that the conclusions are based predominantly on preclinical evidence; future clinical translation will require further validation through large-scale studies.

Plain Language Summary: A growing number of patients with type 2 diabetes experience declines in cognitive abilities and memory—a condition known as diabetes-associated cognitive dysfunction (DACD). This disorder imposes a substantial burden on families and society. Researchers have found that DACD is not caused by a single factor but rather by multiple interconnected brain abnormalities that influence each other like a network. This review aims to elucidate these complex mechanisms—including oxidative stress, mitochondrial dysfunction, neuroinflammation, ferroptosis, gut microbiota–brain communication, autophagy, and epigenetic regulation—and explain how they interact to ultimately impair cognitive function. Importantly, we summarize various potential treatment strategies based on these new findings, including pharmacological agents, natural metabolites, and non-pharmacological therapies. By providing this integrated perspective, we hope to guide the development of more effective preventive and therapeutic strategies in the future, ultimately improving the quality of life for individuals with diabetes.

Keywords: type 2 diabetes, cognitive dysfunction, oxidative stress, ferroptosis, microbiota–gut–brain axis, neuroinflammation

Introduction

Type 2 diabetes mellitus (T2DM) is a globally prevalent chronic metabolic disease. In 2019, the number of diagnosed cases worldwide reached 463 million, and this number is projected to increase to 700 million by 2045, with a prevalence rate of

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nearly 20% among individuals aged 65–69 years.[1,2] Owing to its insidious onset, slow progression, and frequent delayed diagnosis, DACD is emerging as one of the leading causes of disability in patients with T2DM.[3] DACD exhibits distinct progressive pathological features and can be divided into three stages: diabetes-associated cognitive decline (occurring in the prediabetic stage, characterized by mild cognitive changes that do not affect daily life); mild cognitive impairment (MCI, characterized by objective cognitive impairment with preserved basic self-care abilities, representing a high-risk state for dementia); and dementia (severe impairment in multiple cognitive domains resulting in loss of independent living ability).[2,4,5] Diabetes is a major risk factor for cognitive decline, especially during the progression from MCI to dementia, placing a substantial care burden on families and society.[6]

Historically, the pathogenesis of DACD was often attributed to a single pathological mechanism, such as insulin resistance or hyperglycemia. However, recent evidence suggests that DACD arises from the synergistic interaction of multiple mechanisms that are dynamically intertwined.[2,5] For instance, the cerebral energy metabolism crisis triggered by dysfunction of glucose transporters serves as an upstream event that initiates subsequent pathological cascades;[7–9] the oxidative stress-mitochondrial dysfunction-neuroinflammation axis forms a vicious cycle that initiates neuronal damage;[10–12] ferroptosis and impaired autophagy further exacerbate damage at the levels of regulated cell death and cellular homeostasis maintenance, respectively;[13–15] the microbiota-gut-brain axis links peripheral metabolic disorders with central neuronal damage through microbial metabolites;[16–19] and epigenetic modifications provide a molecular basis for the transformation of metabolic disturbances into persistent neuronal damage by regulating gene expression.[20–22] Although significant progress has been made in research targeting individual mechanisms, the pathological process of DACD is not driven by a single factor, and there remains a lack of early diagnostic tools integrating key targets across multiple mechanisms, as well as combined therapeutic strategies targeting multiple pathways.[13,23] By synthesizing evidence from recent basic and clinical studies, this review aims to elucidate the pathological contributions and interactions of the aforementioned mechanisms, with the goal of transcending the limitations of single-mechanism research, providing a comprehensive perspective on disease pathology, and facilitating the translation of basic research findings into clinical applications. This review thoroughly discusses these common core pathogenic pathways and briefly illustrates the detailed mechanisms in Figure 1.

Materials and Methods

This Review is a narrative review aimed at systematically summarizing research progress on the multi-mechanism regulatory networks underlying type 2 diabetes–associated cognitive dysfunction. A comprehensive literature search was conducted in the PubMed, Web of Science, and Scopus databases, covering the period from database inception to January 2026. The search strategy employed the following core keywords and their Boolean combinations: “type 2 diabetes–associated cognitive dysfunction”, “diabetic encephalopathy”, “oxidative stress”, “mitochondrial dysfunction”, “neuroinflammation”, “ferroptosis”, “microbiota–gut–brain axis”, “autophagy”, “mitophagy”, “epigenetic regulation”, “glucose transporters”, “lactylation”, and other relevant pathway terms.

Glucose Transporter Dysfunction: An Upstream Trigger of Energy Metabolism Crisis

Brain energy metabolism is critically dependent on a continuous supply of glucose. In type 2 diabetes mellitus (T2DM) and its associated cognitive impairment (DACD), dysfunction of glucose transporters (GLUTs) across different cell types constitutes the upstream trigger of the cerebral energy metabolism crisis.[7,8,24] GLUT1 is primarily expressed in astrocytes and endothelial cells and is responsible for glucose transport across the blood–brain barrier; GLUT3 is the main glucose transporter in neurons; and GLUT4, an insulin-sensitive transporter, is crucial for its expression and membrane translocation in response to brain insulin signaling.[7,8,25] Under T2DM conditions, dysfunction of these GLUTs directly leads to an imbalance in brain energy metabolism, serving as a key initiating factor for cognitive impairment.

Impaired GLUT1-mediated transport across the blood-brain barrier is the initial step in cerebral energy deficiency. Downregulation of GLUT1 expression in the hippocampus of T2DM rats leads to impaired brain glucose uptake and hyperphosphorylation of tau protein.[7] Optimizing the ratio of n-6/n-3 polyunsaturated fatty acids in the diet can upregulate GLUT1, restore cerebral glucose homeostasis, and improve cognitive function.[24] Dysfunction of neuronal GLUT3 is equally critical: in late-stage T2DM rats, GLUT3 exhibits compensatory abnormal overexpression in the brain, but glucose metabolism does not improve because of impaired insulin signaling. Intervention with silicon-rich meat (Si-

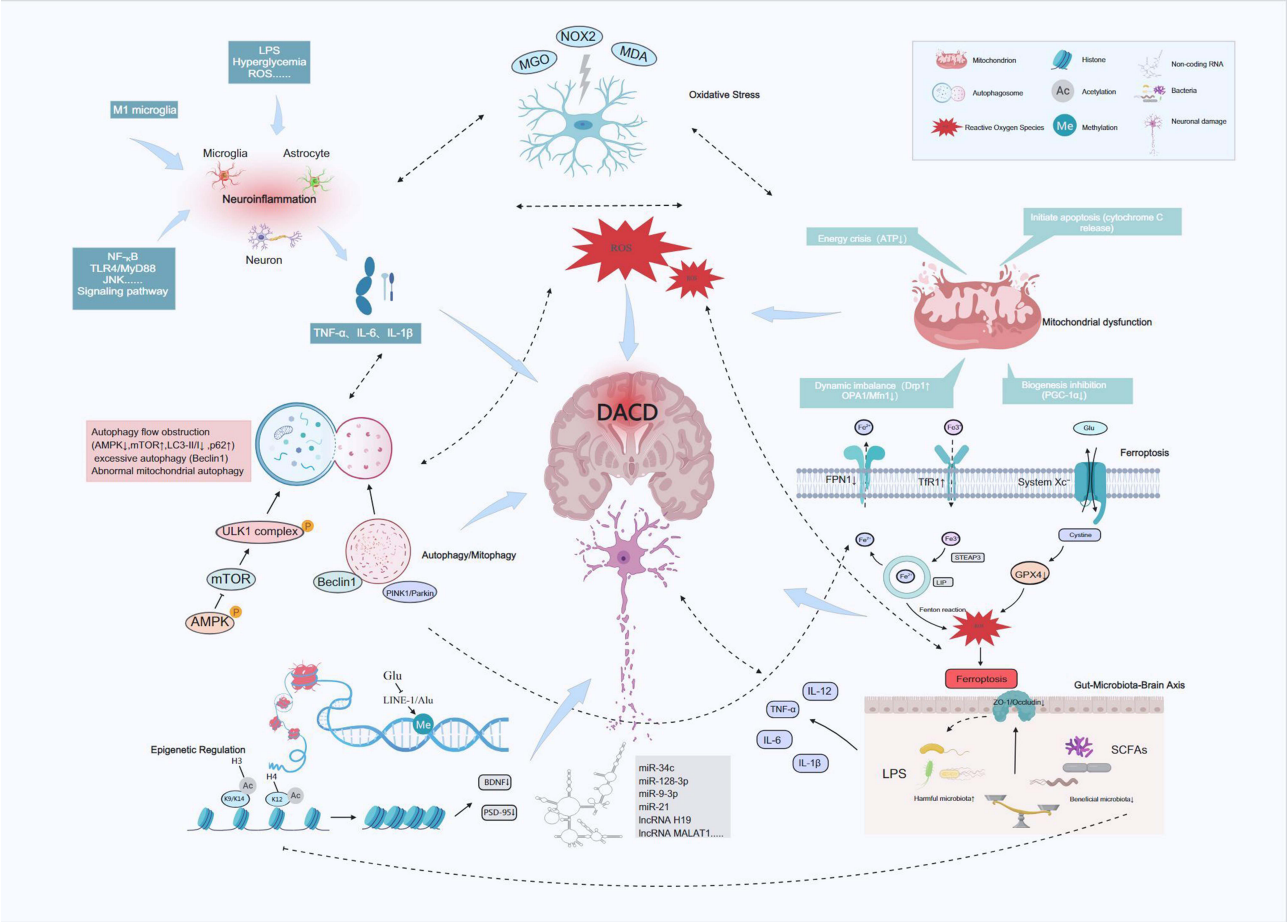

Figure 1 Schematic diagram of the core pathophysiological mechanisms underlying diabetes-associated cognitive dysfunction (DACD) This figure systematically illustrates the interplay among core mechanisms, including oxidative stress, mitochondrial dysfunction, neuroinflammation, ferroptosis, autophagy/mitophagy, the microbiota–gut–brain axis, and epigenetic regulation, which collectively drive neuronal damage and cognitive decline, forming the pathophysiological basis of DACD. Arrows indicate promotion or activation, whereas T-shaped symbols represent inhibition or blockade. Solid lines denote regulatory relationships within individual mechanisms, and dashed lines indicate cross-talk between different mechanisms.

Abbreviations: DACD, type 2 diabetes–associated cognitive dysfunction; ROS, reactive oxygen species; LPS, lipopolysaccharide; GPX4, glutathione peroxidase 4; TfR1, transferrin receptor 1; FPN1, ferroportin 1; SCFAs, short-chain fatty acids; AMPK, adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; TLR4, Toll-like receptor 4; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; BDNF, brain-derived neurotrophic factor; miRNA, microRNA; lncRNA, long non-coding RNA.

RM) can restore insulin signaling and normalize GLUT3 expression.[25] Additionally, 1-Deoxynojirimycin (DNJ) can upregulate GLUT3 and GLUT4 expression by activating the insulin signaling pathway, enhancing neuronal glucose uptake.[26]

The role of GLUT4 is more complex, as it connects peripheral and central insulin signaling and is involved in the regulation of neuroinflammation. Hyperinsulinemia can specifically inhibit the membrane translocation of GLUT4 in microglia, leading to energy metabolism disorders and driving microglia polarization toward the pro-inflammatory M1 phenotype, thereby triggering neuroinflammation and cognitive deficits.[9] The insulin signaling pathway is central to regulating GLUT4 function: loss of Tau protein function or Tau aggregation (TauO) can induce inhibitory phosphorylation of IRS1 and block the PI3K/Akt signaling pathway by activating the p38 MAPK pathway, impairing GLUT4 membrane translocation and glucose uptake. This tightly links peripheral insulin resistance with Alzheimer's disease (AD) pathology at the molecular level.[27] Various therapeutic strategies improve GLUT4 function by restoring insulin signaling, such as Mori Cortex radicis extract (MCR), treadmill training, Gypenoside LXXV (GP-75), and intranasal administration of 15d-PGJ2. These approaches upregulate GLUT4 expression or promote its membrane translocation by activating the IRS-1/PI3K/Akt or PPARγ/PGC-1α pathways, thereby restoring cerebral glucose uptake.[28–30] Additionally, methionine restriction (MR) upregulates GLUT4 expression by activating the liver-brain axis FGF21/FGFR1/AMPK signaling pathway.[31] In contrast, estrogenic endocrine

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disruptors (EEDs),such as bisphenol A interfere with GLUT4 function by disrupting estrogen receptor activity and inhibiting the membrane localization of the IRAP/GLUT4 complex.[32]

In summary, dysfunction of GLUT1, GLUT3, and GLUT4 across different cell types collectively forms the molecular basis of the energy metabolism crisis in DACD. Targeting various GLUT subtypes to restore cerebral glucose metabolic homeostasis represents a highly promising strategic direction for treating DACD.

Oxidative Stress-Mitochondrial Dysfunction-Neuroinflammation Axis: The Core Pathological Hub of DACD

DACD is pathologically characterized by oxidative stress, mitochondrial dysfunction, and neuroinflammation. The complex interplay among these three factors forms a core pathological hub that drives the rapid progression of DACD. Chronic hyperglycemia triggers this cascade through multiple pathways, establishing a deleterious cycle of oxidative stress–mitochondrial damage–neuroinflammation that ultimately leads to neuronal damage and apoptosis.[10–12]

Oxidative Stress: A Key Initiating Factor in DACD

The defining characteristic of oxidative stress is an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense capacity. Under conditions of persistent hyperglycemia in diabetes, the toxic metabolite methylglyoxal (MGO) accumulates excessively. On one hand, it directly promotes the generation of large amounts of ROS; on the other hand, it impairs the antioxidant defense system by reducing the activity of key enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH). Additionally, MGO can elevate the levels of the lipid peroxidation marker malondialdehyde (MDA) and impair mitochondrial membrane potential, thereby exacerbating oxidative stress.[33,34] For example, compounds such as ginsenoside Rb1 (abbreviated as Rb1), which activates the PI3K-Akt pathway, and liraglutide, which directly inhibits MGO-induced ROS production, have been shown to ameliorate MGO-mediated neuronal damage, highlighting the critical role of MGO in the pathogenesis of DACD.[35,36] In addition to the MGO pathway, chronic hyperglycemia can exacerbate oxidative stress by activating the NADPH oxidase (NOX) signaling pathway. Genipin (GEN) has been demonstrated to inhibit the NOX2 signaling pathway, reduce intracellular ROS generation, and prevent the translocation of p47phox/p67phox to the cell membrane, thereby alleviating lipid accumulation in microglia, reducing inflammatory responses, and improving cognitive dysfunction in diabetic patients.[37]

The antioxidant signaling pathway composed of nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream target gene heme oxygenase-1 (HO-1) plays a crucial role in combating diabetic encephalopathy and protecting cognitive function. Nrf2 is a key transcription factor that regulates oxidative stress and inflammatory responses, capable of maintaining intracellular redox homeostasis and enhancing resistance to oxidative damage, making it a primary target for various oxidative stress intervention strategies. Swietenolide, a natural limonoid compound extracted from the fruit of Swietenia macrophylla, can directly bind to Nrf2, enhance its activity, and synergistically upregulate antioxidant enzymes such as SOD and GSH, while inhibiting thioredoxin-interacting protein/NOD-like receptor protein 3 (TXNIP/NLRP3) inflammasome pathway. Its protective effects are attributed to the activation of Nrf2.[38] Strawberry leaf extract achieves bidirectional regulation of oxidative stress and neuroinflammation by activating the Nrf2-HO-1 signaling pathway. This extract effectively inhibits the production of ROS and MDA in hippocampal tissue, reduces the levels of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), and increases the levels of anti-inflammatory cytokines IL-4 and IL-10, thereby breaking the harmful feedback loop between oxidative stress and neuroinflammation.[39] The exogenous hydrogen sulfide (H_2S) donor sodium hydrosulfide (NaHS) can dose-dependently activate the Nrf2/HO-1 axis and inhibit the activation of the NLRP3 inflammasome, thereby bidirectionally alleviating oxidative stress and neuroinflammation.[40] Vanillic acid (VA) exerts neuroprotective effects by enhancing the activities of SOD and glutathione peroxidase (GPx), reducing MDA levels, and inhibiting the nuclear factor-κB (NF-κB)/TNF-α pathway. These findings collectively indicate that modulating the Nrf2 pathway is an effective strategy for simultaneously achieving antioxidant and anti-inflammatory effects, helping to break the harmful cycle of oxidative stress-induced neuroinflammation.[41]

Mitochondrial Dysfunction: A "Bridge" Connecting Oxidative Stress and Neuronal Damage

As the cellular energy hub, mitochondrial dysfunction plays a central role in DACD, serving not only as a common pathological basis linking metabolic dysregulation and neurodegeneration, but also as one of the core mechanisms driving cognitive decline.[42,43] The brain is the organ with the highest energy consumption in the human body, and it is critically dependent on ATP generated by mitochondria. Chronic hyperglycemia and insulin resistance lead to impaired glucose uptake and utilization in neurons, resulting in insufficient mitochondrial energy production to meet the high energy demands of synaptic plasticity, neurotransmitter synthesis, and signal transduction, thereby directly impairing learning and memory functions.[44,45]

Hyperglycemia and a high-fat environment induce bidirectional dysregulation of mitochondrial dynamics: On the one hand, the phosphorylation level at Ser616 of dynamin-related protein 1 (DRP1) in hippocampal neurons is significantly elevated, leading to excessive mitochondrial fission and fragmentation, accompanied by widening of the synaptic cleft, thinning of the postsynaptic dense zone, and a reduction in the number of dendritic spines;[46] On the other hand, the stability of mitofusin 1 (Mfn1) in microglia is reduced due to ubiquitin-mediated degradation catalyzed by the E3 ligase Hrd1, which impedes the mitochondrial fusion process and further exacerbates energy metabolism disorders and oxidative stress.[37] In response to these metabolic dysregulations, metformin can directly inhibit DRP1 phosphorylation via a non-AMPK-dependent pathway, thereby blocking excessive fission and restoring mitochondrial morphology;[46] Genipin, on the other hand, reduces the ubiquitin-mediated degradation of Mfn1 by inhibiting Hrd1 expression, thereby stabilizing the Mfn1 protein and promoting mitochondrial fusion.[37]

Another key manifestation of mitochondrial dysfunction is the vicious cycle that develops between oxidative stress and apoptosis. Under sustained high-glucose and high-fat stimulation, electron leakage from the mitochondrial respiratory chain increases, leading to massive production of ROS; at the same time, the antioxidant defense system collapses completely due to impaired Nrf2 nuclear translocation and overexpression of Keap1.[42] Excessive ROS production directly induces neuronal apoptosis by activating the JNK/CHOP pathway, upregulating the Bax/Bcl-2 ratio, and activating the caspase-3 cascade;[47–49] on the other hand, by activating the NOX2 signaling pathway in microglia, promoting the translocation of p47phox and p67phox to the cell membrane, thereby further amplifying the inflammatory response and compromising the integrity of the blood–brain barrier.[37,42] It is noteworthy that sustained activation of JNK signaling also inhibits Akt activity, leading to excessive phosphorylation of tau protein and abnormal accumulation of amyloid β (Aβ), thereby exacerbating synaptic damage and neuronal loss at multiple levels.[49] In response to the aforementioned complex mechanisms, multiple intervention strategies have demonstrated clear protective effects: the combination therapy of g alpha-lipoic acid (ALA) and metformin synergistically activates the Nrf2-AMPK pathway, restoring antioxidant enzyme activity and mitochondrial biogenesis;[42] the traditional Chinese medicine compound Nao-Fu-Cong reduces apoptosis and restores mitochondrial membrane potential by inhibiting the JNK/CHOP/Bcl2 pathway;[47] S-9-PAHSA enhances mitochondrial function and antioxidant defense by upregulating carbonic anhydrase III (CAIII) to activate the AMPK/Sirt1/PGC1α axis;[48] Exendin-4 improves insulin resistance, restores mitochondrial function, and promotes neurite growth and dendritic spine maturation by activating the AKT/ ERK signaling pathway;[50] while walnut (Gimcheon 1ho cultivar) inhibits JNK phosphorylation, restores Akt activity, reduces tau protein phosphorylation and Aβ accumulation, upregulates HO-1 expression, suppresses the release of inflammatory factors TNF-α and IL-1β, and simultaneously improves mitochondrial function and synaptic plasticity.[49] Mitochondrial dysfunction, as a central link connecting oxidative stress, neuroinflammation, apoptosis, and structural damage, has become a key target for DACD interventions.

Neuroinflammation: The "Amplifier" of the Vicious Cycle of Oxidative Stress-Mitochondrial Dysfunction

Pro-inflammatory cytokines produced by neuroinflammation can directly or indirectly exacerbate oxidative stress and mitochondrial damage. Under conditions of chronic hyperglycemia, oxidative stress and mitochondrial damage activate microglia, causing them to polarize into the pro-inflammatory M1 phenotype, as evidenced by the upregulation of markers such as CD16 and C-X-C motif chemokine ligand 10 (CXCL10), while the anti-inflammatory M2 phenotype is suppressed. These activated microglia secrete large amounts of pro-inflammatory factors, including TNF-α, IL-6, and IL-

1β, leading to neuronal apoptosis and synaptic damage. Concurrently, the abnormal activation of astrocytes further exacerbates the harmful neuroinflammatory microenvironment.[37,48,51,52] Oxidative stress and mitochondrial damage trigger neuroinflammation through the following key mechanisms: ROS directly activate the NF-κB signaling pathway, promoting the transcription of pro-inflammatory factors; mitochondrial-derived damage-associated molecular patterns (DAMPs) bind to pattern recognition receptors on microglia, initiating an innate immune response; The energy crisis in neurons lowers their tolerance threshold to inflammatory damage.[37,47,48] Neuroinflammation, in turn, further exacerbates oxidative stress and mitochondrial damage by activating the NOX system and signaling pathways that mediate the release of inflammatory factors, creating a robust vicious cycle. Recent studies have revealed that this vicious cycle is also profoundly influenced by epigenetic and endogenous regulatory molecules. As a novel epigenetic modification, histone lactylation, under the hyperglycemic conditions of T2DM, leads to the accumulation of histone H3 lysine 18 lactylation (H3K18la) in the promoter region of Toll-like receptor 4 (TLR4), directly driving M1 microglial polarization and neuroinflammation;[53] Conversely, the endogenous molecule Lipin2 exerts anti-inflammatory effects by inhibiting the JNK/ERK-NLRP3 axis, and its downregulated expression in DACD is a key factor in the dysregulation of neuroinflammation.[54]

Interventions targeting neuroinflammation can effectively break this vicious cycle. Strawberry leaf extract improves oxidative stress and neuroinflammatory states by activating the Nrf2-HO-1 pathway, inhibiting oxidative stress, down-regulating pro-inflammatory factors such as IL-6 and TNF-α, and upregulating anti-inflammatory factors such as IL-4 and IL-10.[39] S-9-PAHSA enhances intestinal barrier function, reducing the entry of lipopolysaccharide (LPS) into the blood-stream, thereby inhibiting the excessive activation of the PI3K/AKT/mTOR pathway in the hippocampus and alleviating astrocyte activation and neuroinflammation.[48] Melatonin specifically regulates microglial autophagy via the TLR4/Akt/mTOR pathway, clears inflammatory complexes, reduces microglial hyperactivation, and alleviates the inflammatory microenvironment.[55] Inhibiting lactate production or overexpressing histone deacetylase 3 (HDAC3) can reduce H3K18 lactylation levels, thereby attenuating M1 microglial polarization and cognitive impairmen;[53] conversely, restoring Lipin2 expression or inhibiting the JNK/ERK pathway may block the excessive activation of the NLRP3 inflammasome.[54]

Ferroptosis: A Novel Regulatory Mechanism of Neuronal Damage in DACD

The defining characteristic of ferroptosis is iron-dependent, lipid peroxidation–induced disruption of the cell membrane. Ferroptosis has now been identified as a novel key mechanism underlying neuronal damage in DACD and is closely associated with neurodegeneration. Dysregulated iron metabolism, oxidative stress, lipid peroxidation, and neuroinflammation all regulate ferroptosis, thereby providing new targets for multimodal interventions.[13–15]

Core Molecular Characteristics of Ferroptosis in the Hippocampus in DACD

The hippocampus is a key brain region regulating cognitive function, and ferroptosis of hippocampal neurons is one of the pathological features of DACD. Studies have shown that in T2DM animal models (eg., db/db mice), hippocampal tissue exhibits typical characteristics of the ferroptosis pathway: upregulation of transferrin receptor 1 (TfR1) promotes iron uptake, while its downstream iron exporter ferroportin 1 (FPN1) is significantly downregulated. This leads to an imbalance in the labile iron pool (LIP) within cells, triggering iron metabolism disorders. Simultaneously, the activity of glutathione peroxidase 4 (GPX4), a key enzyme responsible for reducing lipid hydroperoxides, is impaired, resulting in the accumulation of toxic lipid peroxides (eg., malondialdehyde [MDA]). These defects ultimately trigger mitochondrial atrophy in hippocampal neurons and disrupt synaptic integrity, manifested as decreased levels of postsynaptic density protein 95 (PSD95) and synapsin (SYN), findings that are associated with significant cognitive decline.[56,57] Liraglutide, a GLP-1 receptor agonist, has been shown to alleviate iron overload and lipid peroxidation by downregulating TfR1 and upregulating the expression of FPN1 and GPX4. Furthermore, liraglutide can reduce neuronal and synaptic damage and reverse cognitive deficits, providing direct evidence that hippocampal iron-induced neuronal death is a key pathological event in DACD.[56] Inhibiting iron metabolism signaling pathways can reverse this process, thereby alleviating ferroptosis. For example, activated AMPK improves DACD by inhibiting hippocampal ferroptosis, highlighting the critical role of the AMPK signaling pathway in regulating ferroptosis.[58] Caveolin-1 modulates neuronal ferroptosis and mitochondrial homeostasis, inhibits iron-dependent lipid peroxidation, and alleviates DACD.[15] Furthermore, the role of erythropoietin

(EPO) in improving DACD is also closely associated with the inhibition of ferroptosis. EPO reduces lipid peroxidation levels and iron content both in vivo and in vitro, and regulates the expression of ferroptosis-related proteins, thereby exerting its beneficial effects on DACD by inhibiting iron overload and ferroptosis.[59]

Cell-Specific Regulation of Ferroptosis: The Synergistic Amplification Effect of Microglia

Microglial ferroptosis coexists with neuronal ferroptosis, exacerbating nerve damage through paracrine effects and playing a unique synergistic amplification role in DACD. The T2DM animal model induced by streptozotocin (STZ) combined with a high-fat diet causes persistent hyperglycemia by disrupting pancreatic β-cell function, serving as a classic model for studying DACD.[60] In a hyperglycemic environment, central nervous system cells undergo metabolic stress and damage, leading to the accumulation of advanced glycation end products (AGEs) and elevated levels of oxidative stress, which in turn promotes the release of DAMPs, including high mobility group box 1 (HMGB1), heat shock proteins, and mitochondrial DNA.[33,60] High glucose triggers the upregulation of triggering receptor expressed on myeloid cells 1 (TREM1), a microglia-specific inflammatory amplifier, which activates the protein kinase R-like endoplasmic reticulum kinase (PERK) pathway of endoplasmic reticulum stress. The aforementioned DAMPs act as endogenous danger signals that can bind to TREM1 specifically expressed on the surface of microglia.[60,61] Activation of TREM1 further triggers the downstream PERK signaling pathway, inducing endoplasmic reticulum stress, upregulating the expression of the iron-binding protein TfR1, and simultaneously inhibiting GPX4 activity. This leads to iron overload, lipid peroxidation, and inactivation of the antioxidant system within microglia, ultimately inducing ferroptosis in microglia.[57,61] This process enhances the expression of iron-binding proteins and inhibits GPX4 activity, leading to iron-mediated cell death in microglia and the release of pro-inflammatory factors such as IL-1β and TNF-α.[33,60,61] These released cytokines further activate neighboring microglia and astrocytes, stimulating the production of additional inflammatory mediators and ROS, thereby forming a positive feedback loop. This cycle not only exacerbates ferroptosis within microglia but also propagates neuronal ferroptosis via paracrine mechanisms, constituting a cascade of microglia ferroptosis–neuroinflammation–neuronal ferroptosis.[60] Therefore, the TREM1/DAMPs/PERK signaling axis serves as a central molecular hub linking STZ-induced hyperglycemia to microglial ferroptosis. LP17, a specific inhibitor of TREM1, can reduce iron accumulation and lipid peroxidation in the brains of high-fat diet/streptozocin(HFD/STZ) induced T2DM mice by blocking the PERK pathway, thereby improving cognitive function. This result confirms the critical regulatory role of microglial ferroptosis in DACD.[57] Astrocytic ferroptosis is also involved in the pathogenesis of DACD. The peroxisome proliferator-activated receptor α (PPARα) agonist gemfibrozil specifically targets astrocytes, restoring iron homeostasis by upregulating FPN1 and downregulating TfR1. Simultaneously, it enhances the antioxidant defense system by increasing the activity of SOD and GPx, thereby inhibiting astrocytic ferroptosis and preserving their neuroprotective functions.[62] This suggests that ferroptosis in different glial cells is regulated by distinct mechanisms.

Targeted Intervention Strategies for Ferroptosis in DACD

Due to their inherent multi-target regulatory properties, natural products have shown great potential in modulating ferroptosis. For example, dihydroquercetin inhibits the JNK pathway, reduces the release of pro-inflammatory factors such as IL-6 and TNF-α, upregulates GPX4 expression, and lowers Fe^{2+} levels and lipid peroxidation in the hippocampus of rats with type 2 diabetes mellitus (T2DM), ultimately improving cognitive impairment.[63] Salidroside can directly bind to PPARγ, activating the PPARγ/Nrf2 signaling axis, thereby alleviating ferroptosis in hippocampal neurons.[64] Both artemisinin and dendrobine can activate the Nrf2/GPX4 axis, enhance antioxidant capacity, inhibit ferroptosis in hippocampal neurons of T2DM mice, and improve cognitive function.[65,66] Quercetin can bind to Keap1 through its molecular structure, presumably blocking the inhibitory effect of Keap1 on Nrf2, activating the Nrf2/HO-1 signaling pathway, and upregulating the expression of ferroptosis-related proteins such as GPX4, SLC7A11, and FTH1, thereby achieving multifaceted inhibition of ferroptosis.[19]

Non-pharmacological therapies and drug repurposing also show therapeutic potential. For instance, electroacupuncture treatment can promote autophagy, aiding in the clearance of excessive intracellular iron and damaged mitochondria. This autophagy-dependent reduction of ferroptosis alleviates hippocampal neuronal damage and cognitive dysfunction in HFD/

STZ-induced T2DM mice.[67] Deferoxamine, an iron chelator, directly binds free iron, reduces iron-dependent lipid peroxidation, and protects the neurovascular unit while indirectly enhancing cognitive function in a T2DM model combined with stroke.[68] The interaction between the systemic metabolic microenvironment and ferroptosis reveals new therapeutic avenues for DACD. For example, resveratrol can inhibit the expression of miR-9-3p in exosomes derived from diabetic adipose tissue, thereby relieving the miRNA-mediated suppression of SLC7A11, restoring glutathione synthesis, and ultimately inhibiting hippocampal neuronal ferroptosis to improve cognitive function. This finding unveils a previously unrecognized pathway—the adipose tissue–hippocampus axis—which regulates ferroptosis via exosomal miRNA.[69]

Microbiota-Gut-Brain Axis: The "Peripheral-Central" Pathological Pathway of DACD

The bidirectional communication system connecting the gut microbiota, the gut, and the brain involves neural pathways, endocrine signaling, and immune interactions. Dysfunction of this system can promote the development of DACD through metabolic abnormalities, gut barrier dysfunction, and neuroinflammation. These findings provide potential peripheral intervention targets for disease management.[16–19]

Gut Microbiota Dysbiosis in T2DM: The Initiating Link of DACD

The hyperglycemic environment characteristic of T2DM disrupts the structural and functional homeostasis of the gut microbiota, which is a key peripheral component in the pathogenesis of DACD. Studies have revealed significant gut dysbiosis at the genus level in ZDF rats (a well-established T2DM model), characterized by a reduction in beneficial genera (such as Butyricimonas) and an increase in potentially harmful genera (such as Lachnospiraceae_NK4A136_group, Romboutsia, Clostridium_sensu_stricto_1, Dorea, and Turicibacter). This dysbiosis exerts profound effects via the gut-brain axis, leading to decreased levels of short-chain fatty acids (SCFAs) in the gut (particularly isobutyric acid and valeric acid) and impaired intestinal barrier function (downregulation of tight junction proteins ZO-1, occludin, claudin-5, and MUC2), which in turn triggers elevated levels of pro-inflammatory factors (IL-1β, TNF-α) and reduced levels of anti-inflammatory factors (IL-4, IL-10) in the hippocampus, along with decreased expression of the synaptic protein PSD95, ultimately leading to cognitive impairment.[70,71]

Another study, also conducted in the ZDF rat model, found that alterations in the gut microbiota in this model (a decrease in the potentially harmful genus *Coprococcus* and an increase in the potentially beneficial genus *Streptococcus*) can regulate the expression of proteins involved in Aβ metabolism (amyloid precursor protein (APP), beta-site APP-cleaving enzyme 1 (BACE1), receptor for advanced glycation end products (RAGE), low-density lipoprotein receptor-related protein 1 (LRP1), insulin-degrading enzyme (IDE), neprilysin (NEP)), enhance the structural integrity of the blood-brain barrier (BBB), reduce central and peripheral Aβ deposition, and delay diabetes-related cognitive decline.[72] Clinical studies have confirmed that DACD patients with poorer cognitive function often exhibit reduced gut microbiota diversity. Specifically, beneficial bacteria such as *Bifidobacterium* and *Anaerobutyricum* are reduced, while inflammation-associated bacteria such as *Intestinibacter* and *Blautia* are increased. Furthermore, the microbial composition becomes more unstable and disorganized. This microbial dysbiosis is strongly negatively correlated with cognitive decline, providing direct evidence for the involvement of the microbiota-gut-brain axis in the pathogenesis of DACD.[73]

In this context, a hallmark of gut microbiota dysbiosis is a significant reduction in bacteria that produce short-chain fatty acids (SCFAs), accompanied by an increase in pro-inflammatory bacterial species.[74,75] For instance, in a T2DM model induced by a high-fat, high-sucrose diet combined with STZ, a marked decrease in the abundance of SCFA-producing bacteria was observed, particularly within *Lachnospiraceae_NK4A136_group* and *norank_f_Muribaculaceae*.[70]

Gut Microbial Metabolites: Key Signaling Molecules in the Microbiota-Gut-Brain Axis

SCFAs (including acetate, butyrate, and propionate) are key microbial metabolites that mediate gut-brain communication through multiple mechanisms: (1) serving as neuronal energy substrates after crossing the blood-brain barrier; (2) acting as ligands for G protein-coupled receptors (such as GPR41, GPR43) on enteroendocrine cells, initiating neuroendocrine signaling cascades; (3) regulating intestinal immune homeostasis and inhibiting the release of pro-inflammatory cytokines.[19] T2DM is associated with a reduction in SCFA-producing bacteria, leading to decreased concentrations of total fecal SCFAs, isobutyrate, and valerate.[70]

Regulating probiotics and SCFA-producing bacteria can improve DACD. Introducing live or pasteurized Akkermansia muciniphila (an acetate-producing bacterium) enhances insulin sensitivity and cognitive function in db/db mice, restores acetate availability, and alters bile acid metabolism.[76] Sarcandra glabra extracted residue polysaccharide and White hyacinth bean polysaccharide improve cognitive function in diabetic mice by promoting SCFA-producing bacteria such as Bifidobacterium and enhancing intestinal SCFA levels.[77,78] Phlorizin increases the levels of SCFA-producing bacteria and β-hydroxybutyrate (BHB)-related bacteria, while elevating metabolites such as SCFA and BHB. These metabolites can cross the blood-brain barrier or stimulate intestinal receptors, regulating the extracellular signal-regulated kinase (ERK)/cAMP response element-binding protein (CREB)/brain-derived neurotrophic factor (BDNF) and NF-κB pathways, enhancing synaptic plasticity, and alleviating neuroinflammation.[79]

Intestinal Barrier Disruption and Systemic Inflammation: The Link Connecting the Gut to Brain Injury

In T2DM, gut microbiota dysbiosis (such as an increase in Proteobacteria) can downregulate the expression of intestinal epithelial tight junction proteins (eg., zonula occludens-1 (ZO-1) and occludin), thereby increasing intestinal permeability. This impairment of barrier function promotes the translocation of microbial products, particularly lipopolysaccharide (LPS), into the systemic circulation. Circulating LPS triggers peripheral immune cells to release pro-inflammatory mediators (including IL-1β and TNF-α), which can compromise the integrity of the blood-brain barrier. Subsequently, these inflammatory factors activate microglia and astrocytes in the brain, ultimately exacerbating neuroinflammation, causing synaptic damage, and leading to cognitive decline.[70,80,81]

Total Alkaloids of Rhizoma Corydalis (TAC) enhance the integrity of the intestinal immune barrier by increasing the levels of IL-22/IL-23/regenerating islet-derived protein 3γ (Reg3γ) and ZO-1/occludin, while regulating the composition of the gut microbiota (eg., significantly reducing the abundance of Lachnoclostridium and further increasing the abundance of Bacteroides). This leads to a reduction in the levels of pro-inflammatory factors such as IL-1β, IL-18, and TNF-α in the serum and hippocampus, inhibits NLRP3/Caspase-1/GSDMD (Gasdermin D)-mediated pyroptosis and downstream xCT/GPX4-related neuronal ferroptosis, thereby alleviating cognitive decline in diabetic rodents.[82] Pterostilbene enhances the integrity of the intestinal and blood-brain barriers by altering the gut microbiota (increasing the abundance of SCFA-producing bacteria) and upregulating the expression of tight junction proteins. This further inhibits the activation of the TLR4/myeloid differentiation factor 88 (MyD88)/NF-κB pathway, reducing the levels of IL-6 and IL-1β in colon and brain tissues.[83] S-9-PAHSA enhances intestinal barrier function by increasing ZO-1 levels and goblet cell counts, while altering the composition of the gut microbiota (increased Bacteroidetes, decreased Firmicutes). It also inhibits the abnormal activation of the hippocampal PI3K/AKT/mTOR pathway, reducing astrocyte activation and neuroinflammation.[84]

Intervention Strategies Based on the Microbiota-Gut-Brain Axis

Probiotic and prebiotic supplementation are fundamental intervention strategies. For example, administration of Lactobacillus plantarum can alleviate DACD by restoring a healthier gut microbiota composition, improving oxidative stress status, and upregulating the BDNF/TrkB/CREB signaling pathway. Omega-3 polyunsaturated fatty acids can modulate the gut microbiota, increasing levels of SCFA-producing bacteria and probiotics such as Bifidobacterium. They improve intestinal barrier integrity by increasing the expression of tight junction proteins, while simultaneously regulating pro-inflammatory and anti-inflammatory factor levels to suppress neuroinflammation and enhance synaptic function by restoring PSD95 expression in the hippocampus.[70]

Fecal microbiota transplantation (FMT) and drug–microbiota synergistic regulation have shown considerable potential for efficacy. Transplanting fecal microbiota from healthy donors into DACD model rats can alleviate spatial memory deficits by improving glucose and lipid metabolism, reducing brain insulin and leptin resistance, and decreasing Aβ deposition in the brain. The combination of naringin and metformin increases the abundance of butyrate-producing bacteria such as Romboutsia and elevates SCFA levels.[85] Butyrate, a key SCFA, can cross the blood-brain barrier and activate the hippocampal IRS/PI3K/AKT insulin signaling pathway, enhancing CREB phosphorylation and BDNF

expression, while simultaneously inhibiting Aβ production by suppressing BACE1/APP processing. Notably, the naringin-metformin combination achieves significant improvements in blood glucose control and cognitive function using only one-third of the standard dose of metformin, demonstrating a powerful synergistic strategy of "glucose control–microbiota regulation–neuroprotection".[86,87] Semaglutide may enhance cognitive function by upregulating genes such as Grin2d and Ghr in the brain through pathways such as the activation of neuroactive ligand-receptor interactions via the microbiota-gut-brain axis.[87]

Due to their favorable safety profile, lifestyle interventions and natural products are garnering increasing interest. Both intermittent fasting and aerobic exercise have been shown to improve cognitive function in T2DM mice, an effect associated with an increased abundance of SCFA-producing bacteria. The underlying mechanism may involve microbial metabolites subsequently inhibiting oxidative stress and protecting mitochondrial function.[2,88] Hispidulin can reduce the presence of harmful inflammatory bacteria such as Desulfovironia and lower systemic inflammation levels (IL-6, TNF-α), thereby alleviating peripheral and central neuroinflammation (eg., inhibiting hippocampal microglial activation). In this process, it can trigger the PI3K/AKT pathway in the brain and inhibit the p38MAPK pathway, promoting the survival of hippocampal neurons.[89] Total flavonoids from *Astragalus membranaceus* (TFA)have been confirmed to repair brain damage in diabetic mice by modulating the gut-brain axis, with their protective effects linked to gut microbiota-mediated suppression of inflammation.[90] The ZiBu PiYin Recipe (ZBPYR) demonstrates potential in alleviating diabetes-associated cognitive decline in ZDF rats by improving gut microbiota diversity, regulating the expression of Aβ metabolism-related proteins, enhancing the structural integrity of the blood-brain barrier (BBB), and reducing central and peripheral Aβ accumulation.[72] However, most existing studies are limited to animal models. Future research should focus on large-scale clinical studies to further elucidate the precise regulatory mechanisms of the microbiota-gut-brain axis in human DACD, identify key bacterial species and metabolites, and develop personalized intervention strategies.[70,72,90] Based on the aforementioned gut-brain axis-related dysbiosis, impaired intestinal barrier, inflammatory cascade, and altered metabolites, the core pathological mechanisms and intervention strategies of this axis in DACD are summarized in Table 1.

Autophagy: The "Double-Edged Sword" in Maintaining Cellular Homeostasis

Autophagy is a catabolic process by which cells degrade and recycle damaged organelles and abnormal proteins via the lysosomal pathway and is essential for maintaining cellular homeostasis.[91,92] Mitophagy is a selective form of autophagy that plays a crucial role in the clearance of damaged mitochondria and serves as a key mechanism for maintaining mitochondrial quality control.[15,93,94] In DACD, autophagy dysfunction can manifest as either reduced function or hyperactivity. This

Table 1 Core Mechanisms and Intervention Strategies of the Gut Microbiota in Type 2 Diabetes–Associated Cognitive Dysfunction

Regulatory Component	Core Pathological Changes	Key Mechanisms and Representative Interventions	References
Gut Microbiota Dysbiosis	↓ Diversity, ↓ SCFA-producing bacteria, ↑ Pro-inflammatory bacteria	Probiotics/synbiotics, traditional Chinese medicine formulations, intermittent fasting, and aerobic exercise reshape gut microbiota composition	[2,71,72,76,81,82,84]
Intestinal Barrier Disruption	↓ Tight junction proteins, ↑ Intestinal permeability	n-3 PUFAs, pterostilbene, white hyacinth bean polysaccharide, total alkaloids of Rhizoma Corydalis, and urolithin A repair intestinal barrier integrity	[18,70,82,84]
Inflammatory Cascade	LPS translocation into circulation, TLR4/NF-κB activation, microglial activation	Pterostilbene inhibits the TLR4/NF-κB pathway; total alkaloids of Rhizoma Corydalis inhibit NLRP3 inflammasome activation; sinomenine activates the Nrf2/HO-1 pathway	[71,81,82]
Brain Insulin Resistance and Synaptic Damage	IRS/PI3K/AKT inhibition, GSK-3β activation, ↓ Synaptic proteins, Aβ deposition	ZiBu PiYin Recipe (ZBPYR) and the naringin–metformin combination activate the IRS/PI3K/AKT pathway; targeting ApoE4 inhibits GSK-3β	[71,72,80,86]
Metabolite Regulation	↓ SCFAs, dysregulation of tryptophan and bile acid metabolism	White hyacinth bean polysaccharide (SCFAs activate G protein-coupled receptors); total flavonoids from Astragalus membranaceus (butyrate activates the AMPK/PGC-1α pathway); intermittent fasting (IPA, 5-HT, TUDCA)	[2,78,90]

dysfunction disrupts signaling pathways and interacts with other pathological mechanisms, ultimately mediating neuronal damage and positioning autophagy as a double-edged sword in the regulation of cellular homeostasis.[55,95,96]

Dysregulation of Autophagy Regulatory Pathways: The Core Mechanism of Autophagy Abnormalities

Under high-glucose conditions, multiple autophagy regulatory pathways in hippocampal neurons become dysregulated, leading to either impaired or excessive autophagy, which constitutes a central pathological mechanism of DACD. The JNK/SIRT1/Foxo3a signaling pathway serves as a critical hub regulating autophagy and apoptosis. Under sustained high-glucose stimulation, this pathway is significantly suppressed, leading to decreased expression of autophagy-related proteins (such as ATG7, Lamp2, and LC3), impaired autophagy, and increased neuronal apoptosis. The medicinal compound Banxia Xiexin Decoction (BXXXD) can restore autophagy and alleviate oxidative stress and apoptosis by activating this pathway.[94] The AMPK/mTOR pathway is a classic energy-sensing pathway that regulates the initiation of autophagy. The AMPK/mTOR pathway is a classic energy-sensing pathway that regulates the initiation of autophagy. In DACD, this pathway is characterized by reduced AMPK phosphorylation and excessive mTOR activation, which inhibits the initiation of autophagy and autophagosome-lysosome fusion; fingolimod (FTY720) enhances autophagy by activating AMPK and inhibiting mTOR, increasing the Beclin-1-to-LC3II/LC3I ratio, and reducing p62 expression, thereby restoring autophagic flux and reducing neuronal apoptosis.[95] As a central pathway in insulin signaling, dysfunction of the Akt/mTOR pathway also contributes to autophagy dysregulation. Carnosine (β-alanyl-L-histidine) treatment dose-dependently activates the Akt/mTOR pathway, upregulates p-Akt and p-mTOR expression, reduces LC3B-II and p62 levels, restores autophagic flux, alleviates structural damage to neurons in the hippocampal CA1 region, and improves cognitive function.[97]

Under different pathological conditions, the Tangzhiqing decoction (TZQD) exhibits bidirectional regulation of autophagy. Yao et al observed impaired autophagy in a mouse model of T2DM induced by a high-fat diet combined with STZ.TZQD enhanced autophagy by activating the AMPK/mTOR pathway, increasing Beclin1 expression and the LC3II/LC3I ratio, reducing p62 levels, and restoring autophagic flux. In contrast, Shi et al found excessive autophagy activation in another study using a similar modeling approach, where TZQD suppressed excessive autophagy by modulating the Akt/mTOR pathway, reducing Beclin1, ATG7, and the LC3II/LC3I ratio, increasing p62, and restoring Lamp2 expression, thereby alleviating autophagosome accumulation and functional dysregulation. This suggests that autophagy is a dynamic process, and targeting the restoration of autophagic homeostasis is an important therapeutic direction for DACD.[98,99]

Interaction of Autophagy with Neuroinflammation and Ferroptosis: Synergistic Pathological Mechanisms of DACD

High glucose-induced autophagy inhibition can lead to excessive activation of the NLRP3 inflammasome, triggering the release of pro-inflammatory factors such as IL-1β, thereby stimulating neuroinflammation.[100,101] Huang-Lian-Jie-Du decoction (HLJDD) and melatonin improve the inflammatory microenvironment by enhancing autophagy activity, clearing inflammatory complexes, and inhibiting microglial activation. The mechanism of melatonin has been more systematically elucidated, as it precisely regulates microglial autophagy through the TLR4/Akt/mTOR pathway.[55,102] A-kinase anchor protein 8-like (AKAP8L) is specifically upregulated in microglia, interacts with mTORC1, activates the NLRP3 inflammasome, and induces pyroptosis, suggesting that cell-specific autophagy regulation exerts different effects on DACD and that AKAP8L is a potential therapeutic target.[103]

Insufficient autophagy activity exacerbates ferroptosis, whereas activation of autophagy (particularly mitochondrial autophagy) can suppress ferroptosis by clearing damaged mitochondria and reducing mitochondrial-derived reactive oxygen species and iron.[67,96] Electroacupuncture treatment enhances netrin-1 expression in the hippocampus of T2DM mice, inhibits the mTOR pathway, and promotes autophagy activation. This activated autophagy increased the expression of GPX4 and SLC7A11, reduced lipid peroxidation, and ultimately suppressed ferroptosis. These findings suggest that electroacupuncture establishes a synergistic protective mechanism by regulating the "netrin-1-autophagy-ferroptosis"

axis, offering a potential non-pharmacological intervention strategy.[67] Caveolin-1 regulates PTEN-induced kinase 1 (PINK1)/Parkin-dependent and UNC-51-like kinase 1 (ULK1)-dependent mitochondrial autophagy pathways by activating AMPK. This process clears dysfunctional mitochondria, reduces ROS and iron released from mitochondria, blocks ferroptosis, and ultimately restores mitochondrial homeostasis.[15]

Mitophagy Dysfunction: A Key Link in Neuronal Damage

High glucose induces neuronal damage by disrupting mitophagy, which is a key pathological mechanism. Impaired mitophagy leads to the accumulation of dysfunctional mitochondria, subsequently triggering oxidative stress and metabolic dysfunction, and this pathological cascade lays the foundation for the initiation of ferroptosis.[104,105] Mitophagy is regulated by multiple pathways. For example, the long non-coding RNA MEG3 promotes FUNDC1-associated mitophagy through the Rac1–ROS axis to reduce mitochondria-derived apoptosis and alleviate diabetic cognitive impairment.[56] Under oxidative stress induced by high glucose or AGEs, the Keap1-Nrf2-prohibitin 2 (PHB2) pathway is inhibited, leading to decreased PHB2 expression, which in turn suppresses mitophagy in hippocampal neurons.[106]

Hyperglycemia can activate phosphorylation of the WW domain-containing oxidoreductase (WWOX) at tyrosine residue 33, enabling it to form a complex with p53 and translocate to mitochondria. This WWOX-p53 complex disrupts mitochondrial membrane potential, inhibits respiratory chain function, and impairs mitochondrial homeostasis, leading to dysregulation of mitochondrial dynamics (eg., reduced Mfn1 and increased p-DRP1). The specific WWOX inhibitor Zfra1-31 can partially restore mitophagy activity and neuronal viability by blocking these detrimental processes.[104] Sodium butyrate (NaB) disrupts the RELA-HDAC8 complex by inhibiting RELA nuclear translocation and directly blocking histone deacetylase 8 (HDAC8) activity, thereby restoring Parkin (PRKN) expression. This restoration promotes the clearance of damaged mitochondria, reduces neuronal apoptosis, and enhances spatial learning and memor.[105] High glucose disrupts lipophagy in microglia, leading to mislocalization of lipid droplets within these cells. These accumulated lipid droplets bind to perilipin 2 (PLIN2) and colocalize with TREM1, preventing their degradation, which activates the NLRP3 inflammasome and indirectly inhibits mitophagy.[96] However, electroacupuncture can elevate levels of a newly identified mitophagy receptor, DISC1 (Disrupted-in-Schizophrenia 1), by stimulating specific acupoints, triggering mitophagy (marked by increased Beclin1 and LC3-II/I, and decreased P62). This process helps clear damaged mitochondria, reduces $A\beta_{1-42}$ accumulation in the hippocampus, alleviates neuronal damage in the hippocampal CA1 region, and improves cognitive function in diabetic rats.[68]

Restoring Autophagy: A Key Strategy for Improving Cognitive Function

Restoring autophagic flux, the complete process of autophagosome formation, maturation, fusion with lysosomes, and degradation of contents, is a key strategy for improving cognitive function in DACD. By restoring autophagic flux, abnormal proteins and damaged organelles can be effectively cleared, reducing neuronal damage. Liraglutide can rescue impaired autophagic flux by promoting autophagosome-lysosome fusion (upregulating Lamp2), reducing Aβ deposition, and repairing synaptic function.[107] The natural steroidal alkaloid tomatidine can promote the nuclear translocation of TFEB via the AMPK–TFEB pathway, accelerating the clearance of p62 and pT231 tau proteins and alleviating tau hyperphosphorylation.[108] Electroacupuncture exerts a dual protective effect by directly clearing damaged mitochondria through the activation of autophagy pathways and inhibiting ferroptosis to reduce neuronal loss.[67] Fingolimod enhances autophagic flux and reduces neuronal apoptosis by activating the AMPK/mTOR pathway; its effect is independent of blood glucose regulation, providing a new therapeutic approach for DACD patients with poor glycemic control. TZQD bidirectionally regulates autophagic activity through the AMPK/mTOR and MAPK/Foxo pathways, capable of both inhibiting excessive autophagy and activating insufficient autophagy, while simultaneously improving lysosomal function to restore autophagic flux.[95,98] The novel 5-PAHSA regulates autophagy and restores autophagic flux by inhibiting the phosphorylation of the mTOR–ULK1 pathway.[109] These findings validate the potential of targeting the restoration of autophagic flux as a therapeutic strategy for DACD.

Epigenetic Regulation: The "Molecular Bridge" Connecting Metabolic Disorders and Neuronal Damage

Epigenetic modifications refer to mechanisms that regulate gene expression through reversible modifications of chromatin structure independently of DNA sequence alterations, primarily including DNA methylation, histone modification, and non-coding RNA regulation. In the pathogenesis of DACD, epigenetic mechanisms serve as a crucial molecular bridge linking peripheral metabolic disorders with central nervous system damage. In recent years, growing evidence has demonstrated that epigenetic mechanisms play an important role in the development and progression of DACD.

DNA Methylation: A Key Mechanism for Gene Regulation in Neural Function

DNA methylation typically occurs at CpG islands in gene promoter regions, which can inhibit transcription factor binding and lead to gene silencing. Hypermethylation of the 5'-flanking region of the *SORL1* gene is associated with the development of MCI in patients with T2DM, accompanied by higher plasma $A\beta_{1-42}$ levels, and is linked to the progression of MCI in these patients.[110] Individuals with T2DM and presymptomatic dementia (PSD) exhibit unique methylation patterns of LINE-1 and Alu retrotransposons in peripheral blood, suggesting that retrotransposons may be involved in regulating gene expression and influencing cognitive decline.[20] Elevated glucose and lipid levels exacerbate the dysregulation of DNA methylation in neurology-related genes. The presence of the ApoE4 genotype aggravates high-fat diet-induced abnormal DNA hydroxymethylation, modifying genes involved in key pathways such as purine and glutamate metabolism, leading to impaired spatial learning and memory functions.[111] Recent studies have further elucidated the complex role of DNA methylation in DACD. In the prefrontal cortex of mice with type 2 diabetes, chronic hyperglycemia can induce upregulation of DNA methyltransferases (DNMT1, DNMT3a, DNMT3b), and methyl-CpG-binding protein 2 (MeCP2) in the prefrontal cortex of mice with type 2 diabetes, leading to high methylation and silencing of the promoters of neuroprotective genes such as heat shock factor 1 (HSF1), BDNF, and PSD95, thereby impairing protein homeostasis, neuronal survival, and synaptic transmission.[112] This methylation abnormality is not limited to the nervous system. Methylation of the insulin resistance-associated gene *CPT1A* exhibits opposite patterns in peripheral blood and brain tissue: hypermethylation of *CPT1A* in peripheral blood suppresses its expression, potentially improving insulin sensitivity by influencing lipid metabolism; conversely, hypermethylation at the same site in brain tissue is associated with worsening Alzheimer's disease pathology, suggesting that downregulation of *CPT1A* in the brain may impair neuronal energy metabolism.[113] In addition to classical CpG methylation, non-CpG methylation also contributes to disease pathogenesis. In the hippocampus of diabetic mice, upregulated DNMT3b mediates CpA methylation in the promoter region of the contactin 1 (CNTN1) gene, enhancing the binding of the transcriptional repressor REST (silencing transcription factor), leading to CNTN1 silencing and impeding oligodendrocyte maturation and myelination; supplementation with recombinant CNTN1 protein promotes myelin regeneration and improves cognitive function, revealing the critical role of the DNMT3b/REST/CNTN1 axis.[114]

The potential reversibility of abnormal DNA methylation makes it a viable target for intervention. Supplementation with folic acid and vitamin B12 can partially reverse abnormal methylation through the one-carbon metabolism pathway.[20] Recent studies have revealed that n-3 PUFAs (such as DHA) and B vitamins (folic acid, B12) work synergistically to maintain the dynamic balance of DNA methylation and demethylation in the brain, collectively improving cognitive function.[115] Additionally, another study confirmed that folic acid can increase the methylation level of protein phosphatase 2A (PP2A) by regulating methyl donor metabolism and DNMT1 expression, ultimately inhibiting the hyperphosphorylation of Tau protein and exerting neuroprotective effects.[116] At the non-CpG methylation level, supplementation with recombinant CNTN1 protein can restore CNTN1 expression by intervening in the DNMT3b/REST axis, promoting remyelination.[114]

Histone Modification Imbalance: The Core of Chromatin Structure and Gene Expression Regulation in DACD

Histone acetylation is dynamically regulated by HATs and HDACs, and an imbalance in this homeostasis directly affects neuronal function and memory formation.[21] Under T2DM conditions, upregulated expression of HDAC2/3 disrupts this

balance, leading to reduced acetylation levels at H3K9/14 and H4K12 sites and inhibiting the transcription of synaptic plasticity genes (including BDNF, SYP, and PSD-95), thereby leading to cognitive impairment.[117] Dysfunctional HDAC3 not only affects synaptic genes but also directly impairs hippocampal neurogenesis. Studies have shown that AGEs accumulated in a diabetic environment can lead to increased HDAC3 expression in NSCs, thereby inhibiting their differentiation into neurons.[118]

Furthermore, analysis of hippocampal samples from diabetic patients revealed reduced expression of GLUT4 (a key regulator of neuronal glucose uptake) in neurons, accompanied by abnormal HDAC3 activity. In vitro studies have shown that the pro-inflammatory cytokine TNF inhibits the transcription of solute carrier family 2 member 4 (SLC2A4, the gene encoding GLUT4) via the NF-κB pathway, while HDAC3-induced histone deacetylation exacerbates this inhibitory mechanism.[119] In addition to classical Class I/II HDACs, dysregulation of Class III HDACs (the Sirtuin family) plays a critical role in cognitive decline associated with diabetes. Significant downregulation of SIRT1 in the hippocampus leads to increased acetylation at the K174 site of tau protein, exacerbating cognitive impairment.[120]

In addition to the classic acetylation modifications, the recently discovered novel modification—lactylation—also plays a significant role in DACD. High glucose levels induce lactate accumulation, which promotes the enrichment of histone H3 lysine 18 lactylation (H3K18la) at the TLR4 promoter via p300/CBP. This activates microglial M1 polarization and the release of inflammatory factors, leading to neuronal damage.[53] This discovery directly links three pathological processes: glucose metabolism disorder (lactate), epigenetic modification (lactylation), and neuroinflammation (TLR4 pathway). The traditional Chinese medicine Nao-Fu-Cong reduces lactate production by downregulating the glycolytic enzymes HK2 and PDK2, lowers H4K8la levels, relieves transcriptional repression of the Hrh4 receptor, and alleviates oxidative stress and neuroinflammation.[121] Furthermore, in high-glucose environments, neurons upregulate pyruvate dehydrogenase kinase 1 (PDK1) through negative feedback to reduce reactive oxygen species production. This process relies on H3K9ac to activate PDK1 transcription; however, in diabetes, the downregulation of hypoxia-inducible factor 1 (HIF-1) causes this protection to fail, whereas overexpressing PDK1 can restore the protective effect.[122] Emodin, an active component of radix polygoni multiflori (RPM), reduces hippocampal neuronal apoptosis by inhibiting HDAC4 and blocking the JNK pathway.[123] Therapeutic interventions targeting histone modifications have shown considerable potential. The HDAC inhibitors TSA and RGFP-966 have demonstrated efficacy in restoring histone acetylation levels, enhancing the expression of synapse-related genes, and improving cognitive function;[117,119] targeting specific HDAC isoforms, such as HDAC3, holds promise for improving synaptic plasticity and neural regeneration;[118] specific deacetylation of tau protein by restoring SIRT1 expression in the hippocampus can induce neuroprotective effects;[120] short-chain fatty acids such as butyrate can hinder the assembly of the RELA-HDAC8 complex, reduce histone deacetylation, and enhance mitophagy, thereby demonstrating multifaceted protective effects across multiple pathways;[105] the traditional Chinese medicine Naofukang regulates H4K8la levels by inhibiting lactate production;[121] PDK1 overexpression can reconstruct H3K9ac-mediated protective mechanisms;[122] at the level of cell death, emodin exerts anti-apoptotic effects by inhibiting the HDAC4/JNK pathway.[123] Targeting specific HDAC subtypes, such as HDAC3, may improve synaptic plasticity and neural regeneration;[118] Restoring SIRT1 expression in the hippocampus to specifically deacetylate tau protein can induce neuroprotective effects;[120] short-chain fatty acids such as butyrate can hinder the assembly of the RELA–HDAC8 complex, reduce histone deacetylation, and enhance mitophagy, thereby demonstrating multifaceted protective effects across multiple pathways;[105] The traditional Chinese medicine Nao-Fu-Cong regulates H4K8ac levels by inhibiting lactate production;[121] PDK1 overexpression can restore the H3K9ac-mediated protective mechanism;[122] at the level of cell death, emodin exerts an anti-apoptotic effect by inhibiting the HDAC4/JNK pathway.[123]

Non-Coding RNA Regulation: A Fine-Tuned Modulator of DACD Gene Expression

Non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), play a crucial role in epigenetic regulation. They finely tune the expression of genes associated with DACD by targeting mRNA or acting as competitive endogenous RNAs (ceRNAs).[124–127] Among them, miRNAs primarily inhibit gene expression at the post-transcriptional level by binding to the 3' untranslated region of target genes.

In the pathophysiology of DACD, abnormal expression of various miRNAs has been shown to contribute to cognitive impairment. For example, AGEs upregulate miR-34c via the ROS–JNK–p53 pathway, thereby inhibiting the expression of SYT1, leading to synaptic abnormalities and cognitive impairment; intranasal administration of a miR-34c antagonist restores

SYT1 levels and improves cognitive function.[125] In patients with type 2 diabetes (T2DM)-associated mild cognitive impairment, hsa-miR-128-3p is significantly downregulated, thereby weakening its inhibitory effect on galectin-3 (LGALS3), leading to elevated Gal-3 levels and exacerbating neuroinflammation and cognitive decline.[128] Furthermore, a high-glucose environment enhances the expression of miR-34a (which inhibits CREB) and reduces the expression of miR-212 (anti-apoptotic) and miR-29c (pro-differentiation), whereas tirzepatide (TIR), a dual GIP/GLP-1 receptor agonist, selectively reverses these changes, activates the pAkt/CREB/BDNF pathway, and exerts neuroprotective effects.[129]

In recent years, numerous studies have further elucidated the specific roles of various miRNAs in the various pathological stages of DACD. Regarding neurotransmitter metabolism, the diabetic metabolite methylglyoxal downregulates miR-190a and miR-214, thereby relieving the suppression of COMT and SNCA, leading to enhanced dopamine degradation and α-synuclein accumulation, which damages dopaminergic neurons.[130] Regarding oxidative stress, gut dysbiosis upregulates hippocampal miR-493-3p via fecal supernatant, which specifically inhibits the antioxidant protein RAF1, thereby exacerbating oxidative stress and neuronal apoptosis.[131] Regarding synaptic plasticity, hyperglycemia downregulates nuclear receptor coactivator 3 (NCOA3), reduces Argonaute 2 (AGO2) expression, and induces the specific upregulation of miR-138-5p, which subsequently inhibits the synaptic proteins SYP and PSD-95.[132] At the level of protein homeostasis, the circular RNA circCwc27 is elevated in the brains of patients with Alzheimer's disease and T2DM, promoting tau protein expression and phosphorylation while simultaneously affecting peripheral glycogen metabolism, thereby serving as a common molecular link between neurodegeneration and metabolic disorders.[133] Regarding neurotrophic support, downregulation of miR-216a-5p in the hippocampus lifts the inhibition of death-associated protein kinase 1 (DAPK1). DAPK1 phosphorylates hepatic nuclear factor 1α (HNF1A), which subsequently suppresses Netrin-1 transcription, leading to impaired synaptic function and neuronal apoptosis.[134] Regarding endoplasmic reticulum stress, downregulation of miR-702-5p lifts the inhibition of 12/15-lipoxygenase, leading to lipid peroxidation and Aβ accumulation; conversely, overexpression of miR-702-5p alleviates pathological changes.[135] Regarding the mechanisms of intervention by drugs and natural products, resveratrol demonstrates the ability to regulate miRNAs through multiple targets: on the one hand, it can inhibit GSK-3β by upregulating miR-21, thereby improving insulin signaling and alleviating oxidative stress, while simultaneously downregulating miR-9-3p to restore SLC7A11 expression and reduce exosome-mediated hippocampal iron-induced cell death;[69] on the other hand, it can also inhibit thioxanthin-interacting protein (TXNIP) by upregulating miR-146a-5p, thereby alleviating endoplasmic reticulum stress.[136] Furthermore, metformin restores PP2A and Sirt1 by downregulating miR-141, promoting tau dephosphorylation and inhibiting NF-κB-mediated neuroinflammation;[137] downregulation of miR-130b leads to upregulation of PTEN, inhibiting the PI3K/Akt pathway and exacerbating oxidative stress and neuronal apoptosis, whereas overexpression of miR-130b alleviates the damage.[138]

Unlike miRNAs, lncRNAs primarily participate in regulation through the ceRNA mechanism. For example, the lncRNA H19 binds to miR-15b, lifting its inhibition of BACE1 and thereby promoting Aβ deposition; conversely, aerobic exercise induces the upregulation of the lncRNA MALAT1 in serum exosomes, where it competitively binds to miR-382-3p, lifting its inhibition of BDNF and improving cognitive function.[126,139] The recently discovered lncRNA NONRATG-022419 is downregulated in the hippocampus of diabetic mice, and its sponging effect on miR-18a is weakened; and the increased levels of free miR-18a subsequently inhibit the translation of proline-rich G protein-related protein 1 (PRG-1), leading to attenuated BDNF/trombospondin receptor kinase B (TrkB) signaling and cognitive impairment.[140]

In summary, non-coding RNAs are deeply involved in the onset and progression of DACD through complex regulatory networks; these findings provide new insights and potential targets for precise interventions in this disease.

The Interaction Between Epigenetics, Signaling Pathways, and Non-Pharmacological Interventions

The reversibility of epigenetic modifications makes them important targets for drug intervention. For example, the DNA methylation inhibitor 5-aza-2'-deoxycytidine (azadC) can reverse diabetes-induced genome-wide DNA hypermethylation, restore the expression of neuroprotective factors such as heat shock proteins, thereby improving hippocampal neuronal structural integrity and enhancing cognitive function.[141]

Various non-pharmacological interventions also improve DACD through epigenetic mechanisms. High-intensity interval training upregulates the anti-inflammatory miR-146a in the hippocampus, inhibits the IRAK1/TRAF6/NF-κB

pathway, and alleviates neuroinflammation;[142] low- and moderate-intensity exercise restores hippocampal monocarboxylate transporter 2 (MCT2) expression and activates the BDNF pathway via the exosomal lncRNA MALAT1;[139,143] aerobic exercises such as tai chi and brisk walking, combined with health education, downregulate plasma miR-134-5p levels.[144] Consistent with the above findings, overexpression of miR-146a in hippocampal microglia similarly reverses M1 polarization and rescues cognitive deficits.[145] Furthermore, switching from a high-fat diet to a low-fat diet reverses ApoE4-associated abnormal DNA methylation and metabolic dysregulation, restoring cognitive function.[111] Taken together, these findings suggest that epigenetic modifications serve as a key molecular basis for the neuroprotective effects of various signaling pathways and non-pharmacological interventions.

Core Signaling Pathways: Multi-Level Regulatory Hubs of DACD Pathogenesis

The complex pathological mechanisms of DACD involve the interaction and integration of multiple core signaling pathways, as shown in Figure 2.The complex pathogenesis of DACD involves the interplay and integration of multiple core signaling pathways. These pathways tightly link upstream metabolic stress (hyperglycemia, insulin resistance) with downstream cellular dysfunction (autophagy, apoptosis, inflammation, ferroptosis), collectively forming a pathological network.[13,67,125]

PI3K/Akt Signaling Pathway, Tau Pathology, and Apoptosis

The PI3K/Akt pathway is the core of insulin signal transduction. After insulin binds to its receptor, it activates PI3K, which in turn phosphorylates and activates Akt. Activated Akt regulates cell survival, metabolism, and synaptic plasticity by phosphorylating downstream substrates.[146,147] In T2DM, peripheral and central insulin resistance lead to a decrease in Akt Ser473 phosphorylation in hippocampal tissue. This, on one hand, releases the inhibition of downstream GSK-3β and, on the other hand, weakens its inhibitory effect on apoptotic signals.[147–149]

GSK-3β is a serine/threonine kinase that is inhibited and inactivated by Akt under normal insulin signaling. Following Akt inactivation, GSK-3β becomes abnormally activated, directly promoting the hyperphosphorylation of tau at sites such as Ser396 and Thr231. This disrupts microtubule stability, leads to axonal transport impairment, and ultimately results in the formation of neurofibrillary tangles.[148–150] Tau-tubulin kinase 1 (TTBK1) is another tau kinase that is upregulated under PI3K/Akt inhibition, working synergistically with GSK-3β to promote tau hyperphosphorylation.[147] The upstream origin of this pathological chain lies in impaired insulin receptor signaling, manifested by increased inhibitory phosphorylation of IRS-1.[82,149] Liraglutide and pramlintide can alleviate tau hyperphosphorylation by activating the PI3K/Akt pathway and inhibiting GSK-3β and TTBK1.[147] Platycodin D and swertiamarin reduce tau hyperphosphorylation by activating the PI3K/Akt/GSK3β pathway, which inactivates GSK3β through phosphorylation at the Ser9 site.[148,150]

Inactivation of Akt also directly affects neuronal survival. Akt exerts anti-apoptotic effects through mechanisms such as phosphorylating the Bcl-2-associated death promoter (BAD) and inhibiting caspase-9. A decrease in Akt activity leads to reduced expression of its downstream anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), increased expression of the pro-apoptotic protein Bcl-2-associated X protein (Bax), and activation of the caspase-3 cascade, ultimately inducing apoptosis in hippocampal CA1 neurons.[149,151] The active component of Astragalus, Jaranol, restores Akt phosphorylation by directly binding to the A329 site of AKT1, thereby blocking this apoptotic process.[151] Berberine promotes GSK3β Ser9 phosphorylation by restoring PI3K/Akt activity, inhibiting tau hyperphosphorylation and axonal pathology.[149]

TLR4/MyD88/NF-κB Signaling Pathway and Neuroinflammation

The TLR4/MyD88/NF-κB pathway is the central axis mediating neuroinflammation-induced cognitive impairment in type 2 diabetes. Hyperglycemia induces the entry of enteric LPS into the brain, where it activates TLR4 receptors on microglia, recruits MyD88 to initiate downstream cascades, promotes the degradation of IκBα and the nuclear translocation of NF-κB p65, upregulating the release of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6, driving microglial polarization toward the pro-inflammatory M1 phenotype, damaging hippocampal neurons, and inhibiting the CREB/BDNF pathway and synaptic plasticity, ultimately leading to impaired learning and memory.[152–154]

This pathway also forms a vicious cycle with epigenetic regulation and microRNAs, amplifying inflammatory damage. High glucose levels lead to lactic acid accumulation, which mediates H3K18 acetylation and upregulates TLR4 transcription, thereby exacerbating the excessive activation of the pathway;[53] Downregulation of SIRT1 in the hippocampus of T2DM

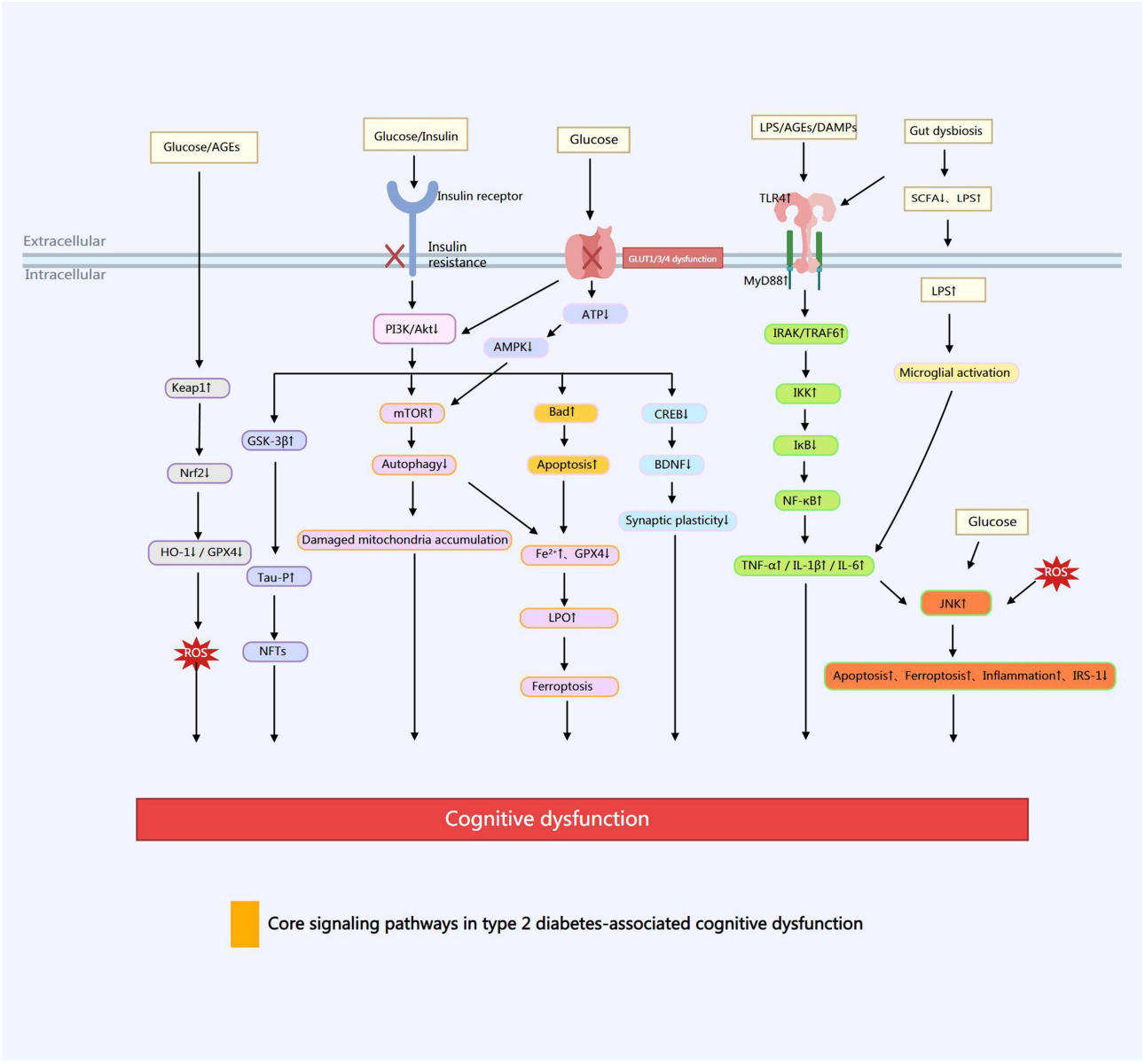

Figure 2 Core signaling pathways in DACD PI3K/Akt, AMPK/mTOR, ferroptosis, NF-κB-mediated inflammation, the gut–brain axis, Nrf2-mediated antioxidant defense, and JNK-mediated stress responses. Upstream triggers—including hyperglycemia, advanced glycation end products (AGEs), lipopolysaccharide (LPS), and gut microbiota dysbiosis—suppress PI3K/Akt and AMPK signaling through insulin resistance and impaired glucose transport, thereby initiating downstream pathological events: activation of GSK-3β (leading to tau tangles), activation of mTOR (resulting in autophagy inhibition and subsequent ferroptosis), activation of Bad (promoting apoptosis), and inhibition of CREB (contributing to synaptic damage). Reduced AMPK activity further exacerbates autophagic dysfunction and converges with ferroptosis pathways. The gut–brain axis, via gut dysbiosis, intestinal barrier disruption, and translocation of LPS into the circulation, activates the TLR4/NF-κB axis, leading to the release of pro-inflammatory cytokines and the initiation of neuroinflammation. These inflammatory factors activate JNK, which in turn promotes apoptosis, ferroptosis, inflammation, and inhibition of IRS-1, establishing a positive feedback loop. Concurrently, suppression of the Nrf2 antioxidant pathway exacerbates oxidative stress. Collectively, these interconnected mechanisms drive neuronal injury and cognitive dysfunction.

Abbreviations: AGEs, advanced glycation end products; GLUT3/4, glucose transporters 3/4; TLR4, Toll-like receptor 4; MyD88, myeloid differentiation factor 88; NF-κB, nuclear factor kappa-B; JNK, c-Jun N-terminal kinase; IRS-1, insulin receptor substrate 1; PI3K/Akt, phosphatidylinositol 3-kinase/protein kinase B; AMPK, adenosine monophosphate–activated protein kinase; mTOR, mammalian target of rapamycin; GSK-3β, glycogen synthase kinase 3β; Nrf2, nuclear factor erythroid 2–related factor 2; HO-1, heme oxygenase-1; GPX4, glutathione peroxidase 4; Tau-P, phosphorylated tau protein; NFTs, neurofibrillary tangles; BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; Bad, Bcl-2-associated death promoter; LPO, lipid peroxides; ROS, reactive oxygen species; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids.

patients lifts the acetylation-mediated inhibition of NF-κB, further amplifying the inflammatory response;[155] meanwhile, low expression of miR-146a can specifically activate IRAK1/TRAF6, synergistically enhancing NF-κB-mediated inflammatory signaling, thereby exacerbating neuronal apoptosis and cognitive impairment.[145]

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Multiple targeted intervention strategies can exert significant neuroprotective effects by blocking the TLR4/MyD88/NF-κB signaling pathway. Exercise intervention upregulates the expression of the myokine irisin, thereby inhibiting abnormal activation of this pathway, promoting the polarization of microglia toward the M2 anti-inflammatory phenotype, and reshaping hippocampal neurogenesis homeostasis.[154] Compound Danshen Dripping Pills and urolithin A can repair damaged intestinal barriers, reduce the translocation of gut-derived LPS into the bloodstream, and block the initiation and cascade amplification of inflammatory pathways from the upstream source.[153,156] Semaglutide, vitamin D_3, and D-chiral inositol directly inhibit the excessive activation of the NF-κB pathway while upregulating hippocampal BDNF expression, synergistically alleviating central nervous system inflammatory damage and improving the overall pathological progression of DACD.[157–159]

AMPK/mTOR Signaling Pathway and Autophagy–Ferroptosis Interaction Imbalance

The AMPK/mTOR signaling axis serves as a central hub for cellular energy metabolism and autophagy regulation. Under DACD conditions, chronic hyperglycemia suppresses AMPK activity in hippocampal neurons (reduced Thr172 phosphorylation levels), leading to excessive mTOR activation, which in turn inhibits autophagy initiation and autophagosome-lysosome fusion. This is manifested by a decreased LC3II/I ratio, reduced Beclin-1 expression, and p62 accumulation, resulting in the failure to timely clear damaged mitochondria and toxic proteins.[15,95,98,160] Both Tangzhiqing decoction and fingolimod can enhance autophagic flux by activating the AMPK/mTOR pathway, thereby exerting neuroprotective effects.[95,98]

AMPK inactivation also drives ferroptosis by regulating molecules involved in iron metabolism. AMPK upregulates the lipid peroxide scavenger GPX4 and downregulates the iron transporter LCN2. AMPK inactivation leads to downregulation of GPX4 and upregulation of LCN2; the former impairs lipid peroxide scavenging capacity, while the latter exacerbates intracellular iron accumulation. Together, these effects synergistically promote the Fenton reaction and lipid peroxidation, inducing ferroptosis in hippocampal neurons.[58] Impaired mitochondrial autophagy further exacerbates these pathological processes. The PINK1/Parkin pathway is a classic regulator of mitochondrial autophagy, while ULK1 is a key kinase involved in autophagy initiation; the activity of both is positively regulated by AMPK. Reduced AMPK phosphorylation leads to simultaneous impairment of these two pathways, resulting in the accumulation of damaged mitochondria and the release of reactive oxygen species, which in turn promotes ferroptosis. PINK1 can break this vicious cycle by simultaneously initiating mitochondrial autophagy and inhibiting ferroptosis through the activation of AMPK.[15] Furthermore, AMPK inactivation also inhibits the nuclear translocation of the transcription factor EB (TFEB), further impairing the function of the autophagy-lysosome system.[108]

Nrf2/HO-1 Signaling Pathway and the Oxidative Stress-Ferroptosis Axis

Nrf2 is a key transcription factor that regulates antioxidant responses and iron metabolism; under normal conditions, it binds to the cytoplasmic repressor protein Keap1 and remains in an inactive state. Upon oxidative stress stimulation, Nrf2 dissociates from Keap1 and translocates into the nucleus, where it initiates the transcription of antioxidant enzyme genes such as HO-1, GPX4, SLC7A11, and NAD(P)H quinone oxidoreductase 1 (NQO-1), thereby maintaining intracellular redox balance.[39,66,161] In DACD, a high-glucose environment and the accumulation of AGEs induce excessive generation of reactive oxygen species, while simultaneously inhibiting the nuclear translocation and transcriptional activity of Nrf2, leading to decompensation of the antioxidant defense system.[39,66,162] The specific mechanism involves the upregulation of Keap1 expression, which promotes the ubiquitination and degradation of Nrf2, preventing it from effectively entering the nucleus to initiate downstream gene transcription.[162]

GPX4 is a key enzyme responsible for clearing lipid peroxides, and its expression is regulated by Nrf2. Downregulation of GPX4 leads to the accumulation of lipid peroxides, which, together with iron ion overload, drives ferroptosis in hippocampal neurons.[58,65,66] SLC7A11 is a cystine/glutamate antiporter, and its downregulation reduces glutathione synthesis, further weakening the antioxidant capacity of GPX4.[65] PHB2 is a mitophagy receptor localized in the mitochondrial inner membrane. As a downstream target gene of Nrf2, decreased expression of PHB2 prevents damaged mitochondria from being effectively cleared by autophagosomes. The accumulated damaged mitochondria further release reactive oxygen species, creating a vicious cycle where oxidative stress and autophagy dysfunction mutually reinforce each other.[162] Artemisinin inhibits ferroptosis in hippocampal neurons by activating Nrf2 nuclear translocation and initiating the transcription of HO-1 and

GPX4. Quercetin exerts a protective effect by binding to Keap1 and blocking the ubiquitination degradation of Nrf2.[65] Under high-glucose conditions, decreased expression of epidermal growth factor (EGF) further weakens the activation signal of Nrf2. Sinomenine can restore Nrf2 function by upregulating EGF.[163]

The JNK Signaling Pathway and Apoptosis, Pyroptosis, and Epigenetic Regulation

JNK is a member of the mitogen-activated protein kinase (MAPK) family, activated under stress conditions, and involved in regulating cell apoptosis, autophagy, and inflammatory responses. High glucose and AGEs induce the generation of reactive oxygen species, which activates JNK phosphorylation and initiates multiple downstream pathological pathways.[63,125] On one hand, activated JNK inhibits the expression of the synaptic protein SYT1 via the p53/miR-34c axis, impairing synaptic vesicle release and leading to reduced dendritic spine density and impaired synaptic plasticity.[125] On the other hand, it promotes CHOP expression, inhibits the anti-apoptotic protein Bcl-2, activates the mitochondrial apoptotic pathway, and triggers the activation of caspase-9 and caspase-3, thereby inducing neuronal apoptosis.[47] JNK activation can also promote iron accumulation by upregulating inflammatory cytokines, inhibiting GPX4 activity and inducing ferroptosis. Dihydromyricetin can block these processes by inhibiting JNK phosphorylation.[63]

The activation of the JNK pathway involves multiple upstream mechanisms. HDAC4, a member of the histone deacetylase family, can activate JNK through deacetylation when its expression is upregulated, establishing a cascade relationship between abnormal epigenetic modifications and JNK-mediated apoptosis.[123] HECT domain-containing E3 ubiquitin ligase 3 (HECTD3), an E3 ubiquitin ligase, stabilizes mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1) via K63-linked polyubiquitination. MALT1, a scaffold protein involved in immune signal transduction, subsequently activates the JNK/c-Jun pathway, upregulates NLRP3 inflammasome components, and promotes pyroptosis.[164] Additionally, JNK activation interacts with the NF-κB pathway: JNK promotes NF-κB nuclear translocation, while NF-κB target gene products can feedback-activate JNK, collectively amplifying neuroinflammatory responses.[49,63] Walnut extract restores Akt activity, reduces tau pathology, and protects mitochondrial function by inhibiting JNK phosphorylation.[49] Similarly, Nao-Fu-Cong blocks the apoptotic cascade by inhibiting JNK phosphorylation, downregulating CHOP, and upregulating Bcl-2.[47]

Biomarkers and Brain Imaging Technology: Precise Assessment From Molecules to Structure

Based on the cognitive assessment framework recommended by the American Diabetes Association (ADA), the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), and the Short Cognitive Assessment (SCA) can effectively quantify the degree of cognitive impairment in patients with DACD. Their scores are closely correlated with various biomarkers, providing important evidence for the precise assessment of the disease and research into its mechanisms.[110,165,166] Regarding biomarkers, confirmed associations show that neurodegenerative markers ($A\beta_{1-42}$, phosphorylated Tau (p-Tau)), inflammatory factors (IL-6, TNF-α, Gal-3), AGEs, and microRNAs (hsa-miR-128-3p, miR-9-3p) are significantly correlated with cognitive scores. Among these, $A\beta_{1-42}$ shows the strongest correlation with MoCA scores ($r=0.78$), and the area under the curve (AUC) for multi-biomarker combined prediction of MCI progression to dementia can reach 0.86.[69,128,167,168] Furthermore, hypermethylation of the 5'-flanking region of the SORL1 gene is associated with decreased MoCA scores and increased $A\beta_{1-42}$, suggesting that this epigenetic modification participates in cognitive impairment by regulating Aβ deposition.[110]

At the level of underlying mechanisms, there is a clear causal relationship between ferroptosis mediated by abnormal iron metabolism and cognitive impairment. In animal models, the expression of iron homeostasis regulatory proteins is significantly altered, while liraglutide can reverse these changes and effectively improve SCA scores.[56,57] Regarding inflammation, IL-6, TNF-α, HMGB1, and high-sensitivity C-reactive protein (hs-CRP) are negatively correlated with cognitive scores, while IL-10 shows a positive correlation; specifically, decreased IL-10 and elevated TNF-α are independent risk factors for MCI.[124,167,169,170] AGEs-related indicators (glycated albumin to glycated hemoglobin ratio (GA/HbA1c)), carboxymethyllysine (CML), and RAGE are significantly negatively correlated with cognitive function, with the diagnostic efficacy of CML/RAGE combined with retinal nerve fiber layer (RNFL) thickness being particularly prominent.[167,171] Among oxidative stress

biomarkers, SOD, adiponectin, and irisin are positively correlated with cognitive scores, while 8-hydroxy-2'-deoxyguanosine (8-OHdG) and oxidized low-density lipoprotein (ox-LDL) are negatively correlated.[165,171,172] In addition, novel biomarkers such as leptin, apelin, neurotrophins, and the exosomal miR-125a-5p also demonstrate good diagnostic value, with AUC values exceeding 0.85 in combined diagnostic models.[166,168,173–175]

Regarding the relationship between brain imaging techniques and biomarkers, multimodal brain imaging has further validated the integrated changes in biomarkers, brain structure, function, and metabolism. Structural imaging has shown that structural parameters such as RNFL thickness and hippocampal volume are clearly associated with cognitive function and related biomarkers, establishing a molecular-structural-functional pathway of damage;[168,171] in terms of functional imaging, resting-state functional magnetic resonance imaging (fMRI) has revealed that neuroproteins can influence regional coherence; in terms of metabolic imaging, proton magnetic resonance spectroscopy (^{1}H-MRS) found that the hippocampal N-acetylaspartate/ creatine (NAA/Cr) ratio is positively correlated with cognitive scores and negatively correlated with inflammatory markers, while amide proton transfer (APT) imaging suggests that temporal lobe metabolic abnormalities contribute to cognitive impairment.[170,175,176] These imaging-biomarker correlations provide multidimensional evidence for understanding the brain network disconnection and metabolic disturbances in DACD.

In summary, the integration of cognitive scales, multi-class biomarkers, and multimodal brain imaging techniques can provide critical support for the precise staging, mechanistic classification, and targeted treatment of DACD, thereby facilitating a shift from symptomatic intervention to precision prevention and control of the disease.[72,104,177]

Discussion

The pathological progression of DACD is not a linear development driven by a single mechanism, but rather a dynamic interactive network formed by the interplay of multiple core mechanisms, including energy metabolism disorders, the oxidative stress-mitochondrial damage-neuroinflammation axis, ferroptosis, autophagy dysregulation, gut microbiota-gut-brain axis disruption, and epigenetic regulation.[13,67,125] The core value of this review lies in systematically elucidating the interactions among these mechanisms within the network, providing a comprehensive perspective on disease pathology and facilitating the translation of basic research findings into clinical applications.

The energy metabolism crisis is the initiating link that triggers the entire pathological network. Dysfunction of glucose transporters directly leads to neuronal energy deficiency, disrupts autophagy homeostasis by activating the AMPK/mTOR pathway, and simultaneously creates conditions for oxidative stress and mitochondrial damage.[7–9,32] Oxidative stress and mitochondrial damage constitute the core hub of the network. Hyperglycemia-induced oxidative stress is both a trigger for mitochondrial dysfunction and a key signal for activating microglia and initiating neuroinflammation.[37,42,43,48] DAMPs released by damaged mitochondria further amplify the inflammatory response, while inflammatory factors can, in turn, feedback to inhibit insulin signaling and autophagic flux, forming a vicious cycle of "oxidative stress-mitochondrial damage-neuroinflammation-autophagy dysfunction".[13,33,55,60,125] ROS regulation is located at the core upstream of the oxidative stress-mitochondrial dysfunction-neuroinflammation axis. Excessive accumulation of ROS can lead to neuronal damage through ferroptosis and apoptosis pathways.[47,48,56,57] Targeting ROS (such as activating the Nrf2/HO-1 pathway) not only reverses the aforementioned damage but also promotes the restoration of autophagic flux.[38,39,64,67] This evidence collectively indicates that the ROS regulatory mechanism is a core target for the prevention and intervention of DACD.

Ferroptosis and autophagy form a bidirectional regulatory "autophagy-ferroptosis axis." Autophagy (particularly mitophagy) can inhibit ferroptosis by clearing damaged mitochondria and excess iron ions;[67,96] conversely, autophagy dysfunction leads to iron accumulation and exacerbates lipid peroxidation, promoting ferroptosis.[96,105] The gut-brain axis closely links peripheral metabolic disorders with central pathology. SCFA deficiency and LPS translocation not only directly activate central inflammation but also exacerbate neural damage by affecting autophagy and ferroptosis.[70,81,178] Epigenetic mechanisms solidify acute stress into persistent injury. The newly discovered H3K18la lactylation directly connects glucose metabolism with neuroinflammation;[53] non-CpG methylation (DNMT3b/REST/CNTN1) reveals a novel mechanism of myelination impairment;[114] various non-coding RNAs (such as miR-493-3p, miR-130b, circCwc27) act as bridges across multiple pathways, including microbiota, metabolism, inflammation, and cell death.[131,133,138]

Based on this integrated perspective, future research can advance clinical translation in the following directions. At the diagnostic level, a single biomarker is insufficient to fully capture the heterogeneity of DACD. Integrating multiple

indicators—such as neurodegeneration markers (Aβ, p-Tau), inflammatory markers (IL-6, TNF-α), ferroptosis markers (TfR1, GPX4), gut microbiota metabolites (SCFAs), and epigenetic markers (specific miRNAs, DNA methylation sites)—into a combined detection approach holds promise for improving the sensitivity and specificity of early diagnosis.[23,57,69,72,73,128] Building on this, incorporating brain imaging techniques like structural MRI, metabolic PET, and functional fMRI can further enable the development of multimodal diagnostic models that span molecular to imaging levels, providing a basis for precise subtyping.[168,175,176] In terms of treatment strategies, based on the mechanism interaction network, the efficacy of single-target drugs may be limited, while combination intervention strategies have the potential for synergistic effects. The specific molecular mechanisms and targets of representative intervention strategies are shown in Table 2.

In terms of therapeutic strategies, based on mechanistic interaction networks, the efficacy of single-target drugs may be limited, whereas combination therapy holds potential for synergistic effects. For example, GLP-1 receptor agonists (such as liraglutide) combined with HDAC inhibitors can simultaneously improve insulin signaling, autophagy, and epigenetic imbalances;[56,107,117,119] Nrf2 activators combined with ferrocytosis inhibitors (such as Ferrostatin-1) can simultaneously block oxidative stress and lipid peroxidation;[64,68] and probiotics/prebiotics combined with autophagy inducers (such as rapamycin) may exert synergistic neuroprotective effects by regulating the gut-brain axis and cellular autophagy.[76,86,95,98] Furthermore, non-pharmacological interventions such as electroacupuncture and exercise, when combined with pharmacological treatments, can achieve synergistic effects through multi-pathway integration, thereby enhancing therapeutic efficacy and reducing adverse reactions.[67,88,179]

Table 2 Multi-Mechanism Interaction-Based Intervention Strategies for Type 2 Diabetes–Associated Cognitive Dysfunction

Intervention	Mechanism Interaction Type	Specific Molecular Mechanisms	References
Pharmacological Agents			
Liraglutide	Oxidative stress, ferroptosis, autophagy	Inhibits MGO-induced ROS production; downregulates TfR1, upregulates FPN1 and GPX4, and inhibits ferroptosis; upregulates LAMP2, promotes autophagosome–lysosome fusion, and restores autophagic flux	[36,56,107]
Melatonin	Autophagy, neuroinflammation	Regulates microglial autophagy via the TLR4/Akt/mTOR pathway, clears inflammatory complexes, and alleviates neuroinflammation	[55,102]
Sodium butyrate	Epigenetic regulation, autophagy	Disrupts the RELA–HDAC8 complex, restores PRKN expression, and promotes mitophagy	[105]
Genipin	Oxidative stress, mitochondrial dysfunction	Inhibits the NOX2 pathway and reduces ROS production; inhibits Hrd1-mediated ubiquitin degradation of Mfn1 and promotes mitochondrial fusion	[37]
Natural Compounds			
Strawberry leaf extract	Oxidative stress, neuroinflammation	Activates the Nrf2–HO-1 pathway, inhibits ROS and MDA production; downregulates IL-6 and TNF-α, and upregulates IL-4 and IL-10	[39]
S-9-PAHSA	Mitochondrial dysfunction, microbiota–gut–brain axis	Activates the AMPK/Sirt1/PGC-1α pathway and improves mitochondrial function; modulates gut microbiota, enhances intestinal barrier integrity, and inhibits the PI3K/AKT/mTOR pathway	[48,84]
Resveratrol	Epigenetic regulation, ferroptosis	Upregulates miR-21 to inhibit GSK-3β; inhibits exosomal miR-9-3p, restores SLC7A11 expression, and inhibits ferroptosis	[69]
Traditional Chinese Medicine Formulations/ Extracts			
Huang-Lian-Jie-Du decoction (HLJDD)	Autophagy, neuroinflammation	Enhances autophagy activity, clears inflammatory complexes, and inhibits microglial activation	[102]
Nao-Fu-Cong	Epigenetic regulation, core signaling pathways	Downregulates HK2 and PDK2, reduces lactate production, lowers H4K8la levels, and relieves transcriptional repression of Hrh4; simultaneously inhibits the JNK/CHOP/Bcl-2 pathway and reduces hippocampal neuronal apoptosis	[74,121]
Polygonum multiflorum **(emodin)**	Epigenetic regulation, core signaling pathways	Inhibits HDAC4, blocks the JNK pathway, and reduces hippocampal neuronal apoptosis	[123]
Other Interventions			
Electroacupuncture	Autophagy, ferroptosis	Upregulates netrin-1, inhibits mTOR, and activates autophagy; upregulates GPX4 and inhibits ferroptosis; activates DISC1-mediated mitophagy	[67,117]
High-intensity interval training	Epigenetic regulation, neuroinflammation	Upregulates miR-146a, inhibits the IRAK1/TRAF6/NF-κB pathway, and alleviates neuroinflammation	[142]

DACD patients may present with distinct dominant pathological mechanism subtypes, such as oxidative stress-dominant, neuroinflammation-dominant, dysbiosis-dominant, and epigenetic dysregulation-dominant types. Through integrated analysis of multi-omics data (genome, epigenome, metabolome, microbiome), combined with clinical phenotypes and imaging features, a basis is provided for identifying specific molecular subtypes and formulating personalized intervention strategies.[73,111,168,171,176] For example, for patients with dysbiosis-dominant subtypes, fecal microbiota transplantation or specific probiotic supplementation may be the optimal choice;[76,85] for patients with epigenetic dysregulation-dominant subtypes, HDAC inhibitors or DNA methylation modulators may be more targeted.[117,119,141]

However, transitioning from network-based pathological models to clinical application still faces significant challenges. Currently, the vast majority of studies are based on animal models, with interventions largely in the preclinical stage. Future efforts require large-scale, multi-center, rigorously designed randomized controlled trials, integrating liquid biopsy and multi-omics analysis, to validate the efficacy and safety of combined intervention strategies based on network-based pathological models.[4,23,73] At the same time, key nodes in the network (such as autophagy and NF-κB) often have dual roles, necessitating careful selection of intervention timing and intensity.[55,96] Additionally, the pathological mechanisms in DACD patients exhibit individual differences, highlighting the need to develop biomarker-based subtype classification tools to achieve truly personalized medicine.[70,111]

Conclusion

Type 2 diabetes–associated cognitive dysfunction is driven by complex mechanisms involving energy metabolism disorders, the oxidative stress–mitochondrial damage–neuroinflammation axis, ferroptosis, autophagy dysregulation, microbiota–gut–brain axis disruption, and epigenetic regulation.[3,67,125] This review integrates these mechanisms to outline an overall pathological pathway from peripheral metabolic disturbances to central neuronal damage, while highlighting the critical roles of emerging epigenetic mechanisms (such as non-CpG methylation and histone lactylation) and novel non-coding RNAs in linking different pathological processes.[53,114,131,138]

Based on this integrated perspective, future research should focus on mechanistic subtyping: utilizing multi-omics and imaging technologies to identify molecular subtypes of DACD, providing a basis for patient stratification;[73] multi-target combined intervention: developing novel drugs or combination therapies that can simultaneously act on key network nodes, such as GLP-1 receptor agonists combined with HDAC inhibitors;[56,107,117,119] and precision intervention strategies: exploring personalized pharmacological treatments, natural products, lifestyle interventions, and non-pharmacological solutions such as fecal microbiota transplantation tailored to different mechanistic subtypes.[2,85] Ultimately, this will achieve a shift from "symptomatic treatment" to "precision prevention and control," effectively improving the cognitive function and quality of life for patients with DACD.

Data Sharing Statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Author Contributions

All authors have made substantial contributions to the reported work, including in the conception, design, execution, acquisition of data, analysis, and interpretation of the study; participated in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; agreed to submit the article to the target journal; and agreed to be accountable for all aspects of the work. The specific contributions are as follows: Zhou Huan and Ran Yili were responsible for literature search and investigation; Zhou Huan and Ran Yili were responsible for drafting the initial manuscript; Jiang Yi and Li Ruoqing were responsible for manuscript review and revision; Jiang Yi and Li Ruoqing were

responsible for research guidance and supervision; Li Ruoqing was responsible for funding acquisition. All authors have read and agreed to the publication of this manuscript.

Disclosure

The authors report no conflicts of interest in this work.

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