DOI: 10.66069/ojspub.27451020

Lysosomal Acidification Reserve in Diabetic Encephalopathy: From Adaptive Homeostasis to Functional Failure

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Abstract: ***Diabetic encephalopathy (DE) is a complex neurological disorder arising from chronic metabolic dysregulation and involving synaptic dysfunction, neuroinflammation, impaired proteostasis and neurodegenerative changes. The autophagy–lysosomal pathway (ALP) is a central network for maintaining intracellular homeostasis in neurons and glial cells. However, studies of lysosomal dysfunction in diabetes have largely relied on endpoint measures, including lysosomal abundance, membrane markers, lysosomal enzyme activity, autophagic flux and steady-state luminal acidity. Although these parameters can identify lysosomal dysfunction, they provide limited insight into the capacity of lysosomes to maintain or restore function when challenged by sustained metabolic stress. Here, we propose lysosomal acidification reserve capacity (LARC) as a conceptual framework for understanding lysosomal acidification as a dynamic functional property governed by proton transport, ion homeostasis, membrane integrity, organelle interactions and degradative demand. Integrating mechanistic evidence from diabetes and neurodegenerative disorders, we propose that chronic metabolic stress may initially increase or redistribute lysosomal degradative demand, while compensatory mechanisms preserve apparent homeostasis. With persistent stress, however, the capacity to sustain or recover an acidic lumen may progressively decline, increasing the fraction of lysosomes with limited recovery capacity and predisposing cells to impaired ALP-dependent quality control and downstream injury. This framework further suggests that lysosomal heterogeneity may reflect dynamic functional states rather than simply the coexistence of fixed subpopulations. A key, experimentally testable prediction is that impaired lysosomal re-acidification may emerge before overt abnormalities in steady-state luminal acidity. We discuss how metabolic sensing and transcriptional regulation, membrane and ion homeostasis, lysosomal damage repair and ALP-mediated quality control could shape this reserve, and propose experimental strategies to directly test whether LARC represents a functional link between chronic metabolic stress and neuronal homeostatic failure in DE.***

Keywords: Diabetic encephalopathy, Lysosomes, Lysosomal acidification, Acidification reserve, Lysosomal heterogeneity, Autophagy–lysosome pathway, Cellular homeostasis**.**

1. Introduction

Diabetic encephalopathy (DE) is associated with chronic metabolic dysregulation, neuroinflammation, synaptic dysfunction and cognitive decline. Lysosomes integrate nutrient sensing, interorganelle signalling and cellular quality control through autophagy, membrane trafficking and transcriptional regulation [1, 2], potentially linking metabolic stress to neuronal dysfunction.

Evidence implicates lysosomal dysfunction in diabetes-associated neuropathology. In db/db mice, reduced brain lysosomal stability and abnormalities in hexosaminidase A and cathepsin D have been linked to altered cholesterol homeostasis [3]. High glucose has been associated with neuronal lysosomal membrane damage, impaired lysophagy (LP) and the accumulation of amyloid-β (Aβ) and phosphorylated tau (p-Tau) [4]. Furthermore, TFEB-mediated autophagy–lysosomal pathway (ALP) regulation is implicated in NLRP3 degradation and neuroinflammation [5], while impaired microglial lysophagy promotes lipid droplet accumulation and increased TREM1 abundance [6]. Activation of the AMPK–TFEB axis has also been reported to ameliorate diabetes-associated cognitive impairment and tau hyperphosphorylation [7]. Collectively, these findings suggest that diabetes disrupts lysosomal stability, degradation and lipid handling, although the underlying functional changes remain incompletely characterised.

Importantly, lysosomal dysfunction does not necessarily entail impaired acidification. Lysosomal pH depends on V-ATPase-mediated proton transport, ion homeostasis and membrane integrity, while lysosomes differ in composition, localisation and functional state [1, 2]. Metabolic stress may therefore alter lysosomal functional states before producing a uniform increase in steady-state pH. We propose lysosomal acidification reserve capacity (LARC) as a testable framework describing the ability of lysosomes to maintain an appropriate acidic lumen and restore acidification and degradative function following metabolic, oxidative or membrane-damaging challenges. We hypothesise that chronic metabolic stress progressively depletes this reserve, reducing lysosomal resilience even when basal pH remains relatively normal. Establishing LARC as a distinct functional property will require dynamic measurements of re-acidification, single-lysosome profiling and longitudinal analyses during disease progression (Figure 1).

The figure illustrates a continuous mechanistic pathway through which diabetes-associated metabolic stress may reshape lysosomal functional heterogeneity, deplete LARC, and impair compensatory mechanisms, progressively driving lysosomes toward a low-function state and compromising cellular quality control. These changes may ultimately contribute to proteostasis disruption, neuroinflammation, synaptic dysfunction, and neurodegenerative changes. The dashed pathway below depicts the conventional model, which attributes lysosomal dysfunction to impaired V-ATPase activity and elevated luminal pH. In contrast, the proposed dynamic model suggests that lysosomal reacidification

kinetics, membrane integrity, and degradative function may be impaired even when basal pH remains relatively preserved. LARC depletion and the collapse of lysosomal heterogeneity remain mechanistic hypotheses requiring validation through time-resolved analyses, single-lysosome measurements, and causal interventions; they are not yet established pathological hallmarks of DE.

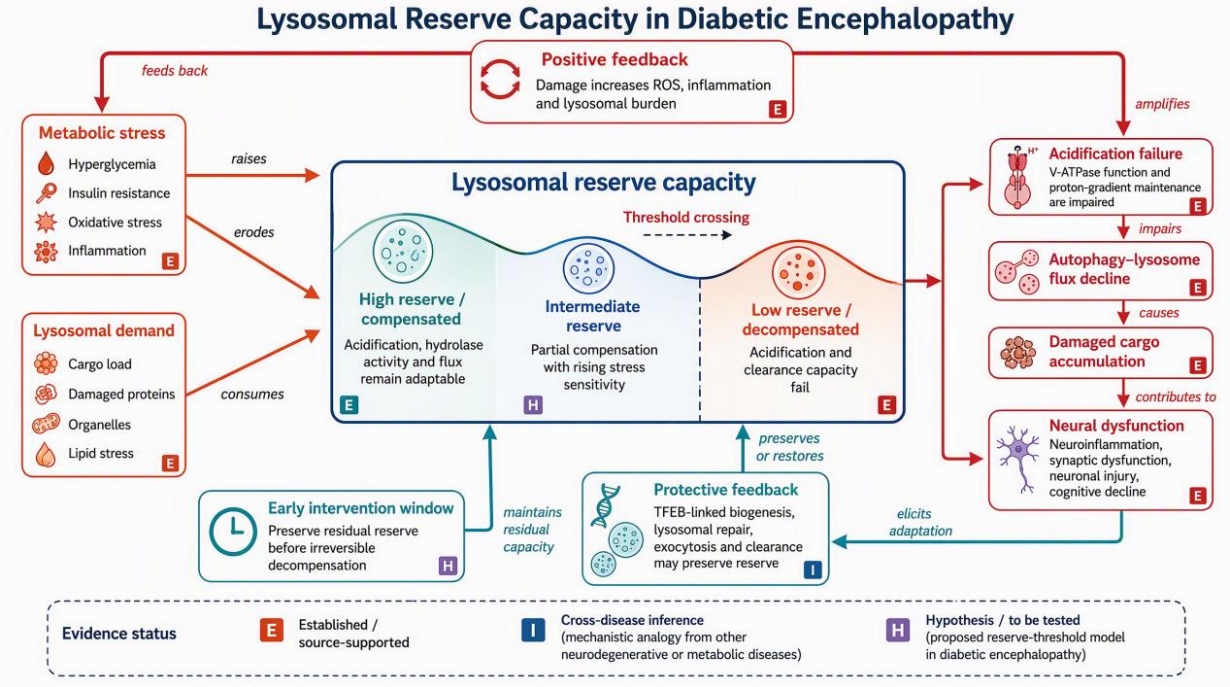


Figure 1: Lysosomal Acidification Reserve Capacity in Diabetic Encephalopathy

2. Lysosomal Heterogeneity

Lysosomes are heterogeneous organelles that differ in membrane protein composition, subcellular localisation, trafficking routes and substrate-processing capacity, with their functional states adapting to cellular demands [1, 2]. Their positioning influences substrate access, fusion, exocytosis and membrane repair. In particular, endoplasmic reticulum (ER)–lysosome contacts facilitate lipid exchange, while interactions with mitochondria, lipid droplets and other organelles support lipid handling, ion signalling and organelle quality control [1, 9, 10]. Thus, lysosomal function depends not only on individual organelle composition but also on the surrounding interorganelle network.

Lysosomal acidification is driven by the vacuolar H^+-ATPase (V-ATPase), while ClC-7/OSTM1 contributes to chloride conductance and charge compensation [11, 12]. TMEM175 regulates lysosomal ion fluxes and pH, whereas TRPML1-mediated Ca^{2+} release contributes to lysosomal signalling and membrane trafficking [13]. Accordingly, lysosomal pH reflects the balance between proton pumping, counter-ion transport, membrane potential and proton leakage. Interorganelle contacts and fusion events further regulate lipid exchange, substrate delivery and organelle renewal [1]. Variations in membrane proteins, including CD63, TMEM192 and NPC1, may also contribute to differences in lysosomal trafficking, fusion and metabolic functions [8, 9].

Diabetic encephalopathy (DE), lysosomal abundance should therefore be distinguished from degradative capacity. If metabolic stress preferentially affects specific lysosomal subpopulations, population-averaged measurements may mask differences in their functional resilience and capacity to maintain homeostasis.

3. Current Evidence for Lysosomal Acidification Dysfunction in Diabetic Encephalopathy

Existing studies indicate that diabetes-associated metabolic stress can disrupt the autophagy–lysosomal pathway (ALP), increase lysosomal membrane damage and impair protein and lipid clearance [2, 3]. These findings are therefore best interpreted as evidence of compromised lysosomal adaptive capacity in diabetes, rather than as definitive proof of sustained lysosomal acidification failure.

3.1 Evidence Supports Disruption of Lysosomal Quality Control

Studies of diabetic encephalopathy (DE) have reported abnormalities in lysosomal stability, hydrolase function and lipid handling in the brain [14]. Collectively, these findings support the notion that the diabetes-associated metabolic environment affects the lysosomal system. However, the models, cell types and outcome measures differ across studies, and the reported abnormalities cannot be reduced to a uniform failure of lysosomal acidification.

The recognition and clearance of damaged lysosomes constitute an additional, distinct component of lysosomal quality control. Under high-glucose conditions, TRIM16-associated lysophagy has been linked to aberrant amyloid-β (Aβ) accumulation in neurons [4]; In microglia, impaired lipophagy has been associated with lipid droplet accumulation and TREM1-related inflammatory processes [6]. In addition, TFEB-mediated autophagic processes have been reported to promote NLRP3 clearance and attenuate DE-associated

neuroinflammation [5]. These findings implicate distinct aspects of lysosomal quality control, lipid turnover and inflammatory regulation, collectively supporting a role for the ALP in diabetes-associated pathology.

3.2 Lysosomal Dysfunction Does Not Necessarily Imply Impaired Basal Acidification

Lysosomal acidification is a dynamic process governed by the coordinated activities of proton pumps, ion fluxes and mechanisms that preserve membrane integrity [12]. A lysosomal pH measurement obtained at a single time point reflects the steady-state acidity at that moment but cannot fully capture the organelle's capacity to respond to metabolic stress or membrane damage. Lysosomes can recover function through membrane repair, compositional remodelling and lysosomal biogenesis [2]. Such adaptive capacity is particularly important in neurons, which rely heavily on lysosomal function to maintain intracellular homeostasis.

This raises a key question: does DE impair the capacity of lysosomes to maintain and restore an acidic lumen, rendering them more susceptible to functional decompensation under sustained metabolic stress? Although studies in DE have documented abnormalities in lysosomal membrane stability, hydrolase activity and ALP function [4, 6], these findings alone do not establish a primary defect in lysosomal acidification. The dynamics of acidification and subsequent re-acidification therefore remain important unresolved questions in the study of lysosomal dysfunction in DE.

3.3 From Existing Evidence to the LARC Hypothesis

Building on these observations, we propose lysosomal acidification reserve capacity (LARC) as a functional framework for interpreting lysosomal abnormalities in DE. LARC is defined as the integrated capacity of lysosomes to maintain an effective acidic lumen under basal conditions and to restore acidification and degradative function following metabolic, oxidative or membrane-damaging stress. Mechanistically, LARC depends on several interconnected processes, including V-ATPase-mediated proton influx; transmembrane ion homeostasis and charge compensation; preservation of membrane integrity and control of proton leakage; maintenance of lysosomal hydrolase maturation and activity; and the capacity for re-acidification and functional recovery following injury [12, 13].

The available evidence is consistent with a progressive model in which diabetes-associated hyperglycaemia, oxidative stress and dyslipidaemia increase lysosomal substrate burden and membrane damage while potentially compromising TFEB-mediated biogenesis and quality control. If these stresses persist, the capacity of lysosomes to maintain an acidic lumen and recover function may decline further, ultimately contributing to insufficient degradative flux, the accumulation of aberrant proteins and lipids, and enhanced neuroinflammation [4, 6]. This model therefore provides a framework for integrating existing findings while generating testable hypotheses for future investigation.

Table 1: Evidence hierarchy for lysosomal dysfunction in diabetic encephalopathy.

Evidence	Representative mechanism	Interpretation of the evidence	References
Direct evidence in DE	Lysosomal destabilization and lysosomal enzyme dysfunction	Reduced lysosomal stability in db/db mouse brains is associated with altered HexA and CTSD function and cholesterol accumulation.	[3]
Diabetes-associated evidence	TFEB–ALP dysfunction	TFEB-associated ALP dysfunction occurs in T2DM models; TFEB activation ameliorates diabetes-related neuropathology.	[15]
	TFEB–NLRP3 coupling	TFEB-dependent autophagy promotes NLRP3 clearance, linking lysosomal function to neuroinflammation in T2DM.	[5]
	TRIM16-mediated lysophagy	Impaired lysophagy compromises damaged lysosome clearance; TRIM16-associated lysophagy also contributes to Aβ clearance.	[4, 6]
	Impaired lipophagy	Impaired microglial lipophagy promotes lipid droplet accumulation and TREM1-related inflammation in diabetes.	[6]
	AMPK–TFEB signaling	AMPK–TFEB signalling links metabolic stress to lysosomal biogenesis and ALP regulation in DE.	[7]
	mTOR–TFEB signaling	The mTOR–TFEB axis regulates ALP in DE; TFEB activation may alleviate AD-like pathology.	[14]
	Oxidized cholesterol and lipid stress	Diabetes-associated cholesterol dysregulation may destabilise brain lysosomes.	[3]
Evidence from neurodegenerative disease models	V-ATPase-mediated proton pumping	V-ATPase drives lysosomal acidification; reduced activity is associated with impaired acidification in AD models.	[15-18]
	ClC-7/OSTM1	ClC-7-mediated Cl^-/H^+ exchange supports lysosomal ion balance and acidification.	[12, 19]
	TMEM175	TMEM175 regulates lysosomal H^+ permeability, pH homeostasis and proteolytic capacity.	[12, 19]
	Lysosomal membrane repair and LMP	Lysosomal membrane repair, ESCRT and lysophagy cooperate in membrane quality control; failure may cause cathepsin release and cell death.	[17, 18, 21-23]
Evidence from neurodegenerative disease models → hypothesis	Lysosomal acidification reserve	Lysosomal acidification is dynamically measurable and potentially reversible, but acidification reserve remains unvalidated in DE; deficits may precede Aβ plaques in AD models.	[17, 18, 21-23]

4. Multilevel Regulatory Networks Sustaining Lysosomal Acidification Reserve

In diabetic encephalopathy (DE), hyperglycemia, dysregulated lipid metabolism, oxidative stress, and inflammation may not initially cause structural defects in the vacuolar H^+-ATPase (V-ATPase) itself. Instead, these stressors may progressively compromise lysosomal acidification by increasing substrate-processing demands, altering the membrane lipid environment, disrupting energy supply, and exacerbating lysosomal damage. As compensatory mechanisms become insufficient to meet these demands, the capacity to maintain lysosomal acidification may gradually be exceeded. Lysosomal acidification dysfunction should therefore be understood as a consequence of dynamic homeostatic imbalance rather than necessarily as a

primary defect in the proton pump.

4.1 Metabolic Stress Increases the Functional Burden on the Acidification System

Among the available evidence directly relevant to DE, functional findings from hyperglycemic neuronal models are particularly informative. Human induced pluripotent stem cell (iPSC)-derived neurons and mouse hippocampal neurons exposed to high glucose exhibit elevated lysosomal pH, accompanied by reduced LysoTracker signals and decreased colocalization of cathepsins B and D (CTSB and CTSD) with lysosome-associated membrane protein 1 (LAMP1). These findings suggest that disruption of the acidic lysosomal environment coincides with impaired proteolytic function [4]. By contrast, studies in db/db mice have primarily identified reduced lysosomal membrane stability, cholesterol accumulation, and abnormalities involving lysosomal enzymes such as hexosaminidase A (HexA) and CTSD, whereas baseline lysosomal pH in the cortex and hippocampus remains largely unchanged [3]. This apparent discrepancy suggests that diabetes-associated lysosomal dysfunction may not invariably manifest as a measurable increase in basal lysosomal pH. Rather, metabolic stress may increase the overall burden on the mechanisms required to sustain an effective proton gradient and a functional degradative environment, thereby rendering lysosomal acidification more vulnerable to perturbations in energy metabolism, ion homeostasis, and membrane integrity.

4.2 The mTOR–TFEB and AMPK–TFEB Signal in Metabolic Adaptation

Under sustained metabolic stress, the capacity of the lysosomal system to compensate through biogenesis, functional renewal, and maintenance of autophagic flux is likely to be a key determinant of long-term homeostasis. In type 2 diabetes mellitus (T2DM) mouse models and high-glucose-treated HT22 hippocampal neuronal cells, reduced nuclear translocation of transcription factor EB (TFEB) is accompanied by impaired autophagy–lysosomal function. Inhibition of mechanistic target of rapamycin (mTOR) or enhancement of TFEB activity improves the clearance of aberrant proteins, supporting a role for the mTOR–TFEB axis in diabetes-associated impairment of lysosomal adaptation [14]. Collectively, these findings suggest that dysregulation of mTOR–TFEB signaling may compromise the capacity of the lysosomal system to maintain an effective acidic degradative environment.

In diabetic models, tomatidine activates the AMP-activated protein kinase (AMPK)–TFEB pathway and ameliorates cognitive deficits and Tau pathology, whereas AMPK inhibition attenuates these protective effects [7]. Thus, mTOR- and AMPK-dependent signaling can be viewed as upstream regulatory pathways linking metabolic status to lysosomal renewal capacity. Studies in T2DM models and high-glucose-treated BV2 microglial cells further indicate that TFEB promotes NLRP3 degradation and attenuates neuroinflammation [5]. This finding links lysosomal functional capacity to downstream inflammatory responses, although the extent to which this relationship depends specifically on the maintenance of lysosomal acidification remains to be established.

4.3 Lipid Homeostasis and the Lysosomal Membrane Environment

The lysosomal membrane provides both the structural basis for establishing a proton gradient and the platform required to maintain membrane protein function and ion homeostasis. Accordingly, alterations in membrane lipid composition may compromise the stability of the acidification system. Studies in db/db mice have demonstrated cholesterol accumulation in brain lysosomes alongside reduced membrane stability, while oxidized cholesterol can further exacerbate lysosomal membrane damage [5]. A separate study in cynomolgus monkeys with T2DM identified increased cholesterol levels in brain membranes and provided evidence that cholesterol dysregulation can disrupt lysosomal degradation [26]. Together, these findings support an association between diabetes-related alterations in the lipid environment and lysosomal dysfunction. However, they do not establish that cholesterol accumulation directly causes impaired lysosomal acidification. Endoplasmic reticulum (ER)–lysosome contact sites may provide an additional interface linking lipid transfer and nutrient sensing to lysosomal homeostasis [27, 28], At present, therefore, lipid dysregulation is best regarded as a structural and metabolic context that may influence the stability of lysosomal acidification, rather than as an established direct cause of acidification failure.

4.4 ROS, Lysosomal Membrane Permeabilization, and Impaired Lysophagy

In hyperglycemic neuronal models and streptozotocin (STZ)-induced diabetic models, increased reactive oxygen species (ROS)-associated lysosomal membrane permeabilization has been observed alongside elevated lysosomal pH, impaired lysophagy, and the accumulation of aberrant proteins. Impaired TRIM16-mediated lysophagy further contributes to neuronal amyloid-β (Aβ) accumulation under these conditions [4]. These findings place lysosomal damage, acidification abnormalities, and defective organelle quality control within a shared pathological context, implicating their interplay as a potential mechanism linking metabolic stress to progressive lysosomal dysfunction.

Within this framework, lysosomal acidification reserve capacity (LARC) can be defined as the integrated capacity of the lysosomal system to maintain, replenish, and restore effective acidification and degradative function under sustained metabolic and damage-related stress. When this capacity becomes insufficient to accommodate persistently increased substrate-processing demands, lysosomal dysfunction may progress to impaired clearance of proteins, lipids, and damaged organelles, thereby contributing to downstream inflammatory responses and increased neuronal vulnerability.

5. From Lysosomal Reserve Decompensation to Neurodegenerative Pathology

As lysosomal recovery capacity and substrate-processing efficiency progressively decline, organelle-level dysfunction may propagate across biological scales, ultimately

manifesting as neuronal dysfunction, glial inflammation, and neurodegenerative pathology. Importantly, the proposition that LARC depletion serves as an upstream integrative mechanism linking metabolic stress to neurodegeneration in diabetic encephalopathy (DE) remains a conceptual model proposed in this review. Current evidence supports several downstream components of this proposed pathway, but the model as a whole has yet to be experimentally validated.

5.1 From Impaired Degradation to Proteostasis Imbalance

A decline in lysosomal processing capacity may first compromise the cell's ability to accommodate sustained degradative demands. Neurons rely heavily on the autophagy–lysosomal pathway (ALP) to clear long-lived proteins, aggregation-prone species, and damaged organelles [18]. When the effective processing capacity of this system declines, the balance between substrate generation and clearance may progressively deteriorate. Diabetes-associated lysosomal dysfunction has been linked to abnormalities in amyloid-β (Aβ), tau, and phosphorylated tau, whereas enhancement of the ALP can alleviate some aspects of the associated pathological burden [14].

5.2 Synapses as a Critical Interface Between Declining Organelle Reserve and Neuronal Dysfunction

Synapses and axons require continuous membrane trafficking, protein turnover, and organelle renewal. Their spatial separation from the neuronal soma further increases their dependence on efficient intracellular transport and organelle quality control for the removal of damaged components [29]. Consequently, reduced organelle turnover efficiency may render synapses and distal axons particularly susceptible to an early decline in functional reserve.

In the diabetic context, autophagy inhibition can further exacerbate learning and memory deficits and impair hippocampal synaptic plasticity [30], supporting a functional link between the ALP and diabetes-associated neurological dysfunction. Within the proposed framework of lysosomal decompensation, reduced organelle-processing capacity may initially diminish neuronal tolerance to sustained metabolic and transport demands, subsequently increase synaptic and axonal vulnerability, and ultimately elevate the risk of neuronal degeneration under prolonged conditions of homeostatic imbalance.

5.3 Glial Cells Convert Local Quality-Control Failure into Sustained Inflammatory Signaling

Microglia continuously perform phagocytosis and process membrane-derived material and cellular debris, making their functional state closely coupled to lysosomal workload. When quality-control capacity becomes insufficient to accommodate persistent metabolic and organelle stress, intracellular damage-associated signals may be translated into inflammatory responses. Studies in DE have shown that intervention in the AKAP8L–mTORC1 axis can improve autophagic flux, attenuate microglial activation and inflammatory responses, and ameliorate diabetes-associated cognitive impairment [31]. In addition, microglial lipid droplet accumulation in diabetes-associated cognitive impairment has been linked to impaired lipophagy and TREM1-associated inflammatory signaling [6].

These findings suggest that reduced ALP processing capacity may alter the ability of microglia to handle aberrant lipids and inflammation-associated substrates, thereby contributing to persistent inflammatory phenotypes. Inflammation may thus represent an amplifying layer of pathology downstream of lysosomal decompensation. In turn, inflammatory mediators and oxidative stress may further increase organelle stress in neurons and glial cells, perpetuating the burden on cellular quality-control systems.

5.4 Cell-Type-Specific Vulnerability Determines Tissue-Level Outcomes

Neurons sustain continuous electrical activity and axonal transport, whereas microglia are responsible for substantial phagocytic and lipid-processing demands. Astrocytes and neurovascular cells, in turn, contribute to metabolic support, ionic homeostasis, and barrier integrity [23]. Accordingly, the same diabetic metabolic environment may produce distinct pathological consequences across cell types, depending on their physiological demands and organelle quality-control requirements.

Neurodegenerative pathology in DE should therefore not be interpreted solely on the basis of measurements averaged across whole-brain tissue, which may obscure cell-type-specific functional impairments. In this context, LARC is best regarded as a conceptual framework for describing differences in functional reserve across cell types and their potential contributions to divergent pathological outcomes.

5.5 From Organelle Dysfunction to Neurodegenerative Pathology

Current evidence supports the view that lysosomal dysfunction may constitute an important organelle-level node linking metabolic stress to pathological changes across multiple levels of the nervous system. However, whether LARC depletion represents a causally decisive upstream state in this process remains to be established experimentally.

Studies in several mouse models of Alzheimer's disease (AD) have identified impaired acidification of neuronal autophagic and lysosomal compartments before extracellular Aβ deposition, accompanied by subsequent autophagic accumulation, alterations in lysosomal membrane permeability, and neuronal injury [23]. These findings support the possibility that impaired acidification can arise at an early stage of neurodegenerative pathology. Accordingly, a key question in DE is whether a decline in lysosomal acidification reserve occurs sufficiently early and exerts sufficiently robust causal effects to predict and modify subsequent pathological outcomes across multiple biological levels.

6. Challenges and Future Directions

LARC is a falsifiable functional model proposing that metabolic stress initially impairs lysosomal recovery from

transient perturbations, followed by persistent defects in acidification, degradation, and membrane integrity. This hypothesis reflects the dynamic nature of lysosomes, whose functions vary with cellular state; therefore, single-time-point measurements of mean lysosomal pH or abundance may not adequately capture their functional reserve [1].

To validate LARC as a distinct functional state, future studies should measure baseline lysosomal pH, re-acidification kinetics, and recovery capacity alongside V-ATPase-dependent H^+ flux, hydrolase activity, and membrane integrity. Reversible perturbation and real-time imaging could quantify recovery kinetics. Impaired recovery preceding overt lysosomal dysfunction would support LARC as an early state; concurrent changes would weaken its distinction from established lysosomal damage.

LARC may also arise in specific lysosomal subpopulations rather than uniformly across the lysosomal pool. Given the distinct metabolic demands and cargo-processing functions of neurons, astrocytes, and microglia [1]. studies should integrate single-lysosome dynamics with cellular identity, spatial localization, cargo burden, and membrane status to determine whether low-reserve lysosomes accumulate during disease progression.

Crucially, current evidence does not establish whether reduced acidification reserve precedes impaired lysosomal quality control and neuroinflammation. TFEB-mediated autophagic clearance of NLRP3 ameliorates neuroinflammation in DE, while impaired neuronal lysophagy under high-glucose conditions is associated with increased lysosomal membrane permeability and Aβ and phosphorylated tau accumulation [5]. However, these findings do not demonstrate a causal role for LARC. Future studies should determine whether selectively impairing re-acidification before overt lysosomal damage disrupts cargo processing, and whether restoring dynamic acidification capacity alleviates subsequent neuronal pathology. Such evidence would establish whether LARC is a causal mechanism rather than an integrative explanatory model.

References

[1] Ballabio A, Bonifacino J S. Lysosomes as dynamic regulators of cell and organismal homeostasis. [J]. Nature reviews. Molecular cell biology, 2020, 21(2): 101-118.

[2] Zoncu R, Perera R M. Built to last: lysosome remodeling and repair in health and disease. [J]. Trends in cell biology, 2022, 32(7): 597-610.

[3] Sims-Robinson C, Bakeman A, Rosko A, et al. The Role of Oxidized Cholesterol in Diabetes-Induced Lysosomal Dysfunction in the Brain [J]. Molecular Neurobiology, 2016, 53(4): 2287-2296.

[4] Chae C W, Yoon J H, Lim J R, et al. TRIM16-mediated lysophagy suppresses high-glucose-accumulated neuronal Aβ [J]. Autophagy, 2023, 19(10): 2752-2768.

[5] Lin Y, Cheng L, Chen Y, et al. TFEB signaling promotes autophagic degradation of NLRP3 to attenuate neuroinflammation in diabetic encephalopathy [J]. American Journal of Physiology-Cell Physiology, 2024, 327(6): C1481-C1496.

[6] Li Q, Zhao Y, Guo H, et al. Impaired lipophagy induced-microglial lipid droplets accumulation contributes to the buildup of TREM1 in diabetes-associated cognitive impairment. [J]. Autophagy, 2023, 19(10): 2639-2656.

[7] Zhang W G, Ding J, Wang L, et al. Tomatidine Ameliorates Diabetes-Induced Cognitive Impairment and Tau Hyperphosphorylation Through theAMPK - TFEB Pathway [J]. Journal of Neurochemistry, 2025, 169(5): e70087.

[8] Bond C, Hugelier S, Xing J, et al. Heterogeneity of late endosome/lysosomes shown by multiplexed DNA-PAINT imaging. [J]. The Journal of cell biology, 2025, 224(1).

[9] Chavan I, Bhattacharjee A. Lysosome heterogeneity and diversity mapped through its distinct cellular functions. [J]. Cellular and molecular life sciences: CMLS, 2025, 82(1): 380.

[10] Ebner M, Fröhlich F, Haucke V. Mechanisms and functions of lysosomal lipid homeostasis. [J]. Cell chemical biology, 2025, 32(3): 392-407.

[11] Xu H, Ren D. Lysosomal physiology. [J]. Annual review of physiology, 2015, 77: 57-80.

[12] Graves A R, Curran P K, Smith C L, et al. The Cl-/H+ antiporter ClC-7 is the primary chloride permeation pathway in lysosomes [J]. Nature, 2008, 453(7196): 788-792.

[13] Hu M, Li P, Wang C, et al. Parkinson's disease-risk protein TMEM175 is a proton-activated proton channel in lysosomes. [J]. Cell, 2022, 185(13): 2292-2308.

[14] Cheng L, Chen Y, Guo D, et al. mTOR-dependent TFEB activation and TFEB overexpression enhance autophagy-lysosome pathway and ameliorate Alzheimer's disease-like pathology in diabetic encephalopathy [J]. Cell Communication and Signaling, 2023, 21(1): 91.

[15] Mindell J A. Lysosomal acidification mechanisms. [J]. Annual review of physiology, 2012, 74(10): 69-86.

[16] Forgac M. Vacuolar ATPases: rotary proton pumps in physiology and pathophysiology [J]. Nature reviews. Molecular cell biology, 2007, 8(11): 917-929.

[17] Lee J, Yang D, Goulbourne C N, et al. Faulty autolysosome acidification in Alzheimer's disease mouse models induces autophagic build-up of Aβ in neurons, yielding senile plaques. [J]. Nature neuroscience, 2022, 25(6): 688-701.

[18] Nixon R A, Rubinsztein D C. Mechanisms of autophagy-lysosome dysfunction in neurodegenerative diseases. [J]. Nature reviews. Molecular cell biology, 2024, 25(11): 926-946.

[19] Di Zanni E, Palagano E, Lagostena L, et al. Pathobiologic Mechanisms of Neurodegeneration in Osteopetrosis Derived From Structural and Functional Analysis of 14 ClC-7 Mutants. [J]. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research, 2021, 36(3): 531-545.

[20] Tang T, Jian B, Liu Z. Transmembrane Protein 175, a Lysosomal Ion Channel Related to Parkinson's Disease. [J]. Biomolecules, 2023, 13(5).

[21] Skowyra M L, Schlesinger P H, Naismith T V, et al. Triggered recruitment of ESCRT machinery promotes

endolysosomal repair. [J]. Science (New York, N.Y.), 2018, 360(6384).
[22] Radulovic M, Schink K O, Wenzel E M, et al. ESCRT-mediated lysosome repair precedes lysophagy and promotes cell survival. [J]. The EMBO journal, 2018, 37(21).
[23] Kampmann M. Molecular and cellular mechanisms of selective vulnerability in neurodegenerative diseases. [J]. Nature reviews. Neuroscience, 2024, 25(5): 351-371.
[24] Lo C H, O'Connor L M, Loi G W Z, et al. Acidic Nanoparticles Restore Lysosomal Acidification and Rescue Metabolic Dysfunction in Pancreatic β-Cells under Lipotoxic Conditions. [J]. ACS nano, 2024, 18(24): 15452-15467.
[25] Bourdenx M, Daniel J, Genin E, et al. Nanoparticles restore lysosomal acidification defects: Implications for Parkinson and other lysosomal-related diseases. [J]. Autophagy, 2016, 12(3): 472-483.
[26] Takeuchi S, Ueda N, Suzuki K, et al. Elevated Membrane Cholesterol Disrupts Lysosomal Degradation to Induce β-Amyloid Accumulation: The Potential Mechanism Underlying Augmentation of β-Amyloid Pathology by Type 2 Diabetes Mellitus. [J]. The American journal of pathology, 2019, 189(2): 391-404.
[27] Wong Y C, Kim S, Peng W, et al. Regulation and Function of Mitochondria-Lysosome Membrane Contact Sites in Cellular Homeostasis. [J]. Trends in cell biology, 2019, 29(6): 500-513.
[28] Kleniuk J, Nadadhur A G, Rodger C, et al. Protrudin acts at ER-endosome contacts to promote KIF5-mediated endosomal tubule fission. [J]. Neurobiology of disease, 2026, 218: 107231.
[29] Dejanovic B, Sheng M, Hanson J E. Targeting synapse function and loss for treatment of neurodegenerative diseases. [J]. Nature reviews. Drug discovery, 2024, 23(1): 23-42.
[30] Li Z, Hao S, Yin H, et al. Autophagy ameliorates cognitive impairment through activation of PVT1 and apoptosis in diabetes mice. [J]. Behavioural brain research, 2016, 305: 265-277.
[31] Zhang W, Wei Q, Zhang T, et al. Microglial AKAP8L: a key mediator in diabetes-associated cognitive impairment via autophagy inhibition and neuroinflammation triggering. [J]. Journal of neuroinflammation, 2024, 21(1): 177.