HHS Public Access

Author manuscript

eGastroenterology. Author manuscript; available in PMC 2024 November 07.

Published in final edited form as:

eGastroenterology. 2024 October ; 2(3): . doi:10.1136/egastro-2024-100096.

Lysosomal physiology and pancreatic lysosomal stress in diabetes mellitus

Meihua Hao,

Sara C Sebag,

Qingwen Qian,

Ling Yang

Department of Anatomy and Cell Biology, Fraternal Order of Eagles Diabetes Research Center, Pappajohn Biomedical Institute, University of Iowa Carver College of Medicine, Iowa City, Iowa, USA

Abstract

Endocrine and exocrine functions of the pancreas control nutritional absorption, utilisation and systemic metabolic homeostasis. Under basal conditions, the lysosome is pivotal in regulating intracellular organelles and metabolite turnover. In response to acute or chronic stress, the lysosome senses metabolic flux and inflammatory challenges, thereby initiating the adaptive programme to re-establish cellular homeostasis. A growing body of evidence has demonstrated the pathophysiological relevance of the lysosomal stress response in metabolic diseases in diverse sets of tissues/organs, such as the liver and the heart. In this review, we discuss the pathological relevance of pancreatic lysosome stress in diabetes mellitus. We begin by summarising lysosomal biology, followed by exploring the immune and metabolic functions of lysosomes and finally discussing the interplay between lysosomal stress and the pathogenesis of pancreatic diseases. Ultimately, our review aims to enhance our understanding of lysosomal stress in disease pathogenesis, which could potentially lead to the discovery of innovative treatment methods for these conditions.

Correspondence to: Dr Ling Yang; ling-yang@uiowa.edu.

Contributors MH wrote and finalised the manuscript. SCS and QQ provided critical scientific suggestions and finalised the manuscript. LY conceived, wrote and supervised this manuscript.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

CELL BIOLOGY OF THE LYSOSOME

The identity of lysosomes

Discovered by Christian de Duve in the 1950s,[1] lysosomes are dynamic and heterogeneous organelles enclosed by a single lipid bilayer membrane. Lysosomes are found in all eukaryotic cells. However, their size, number, distribution, morphology and enzyme context vary greatly depending on different species, cell types and cell status. Ranging from 100 nm to 500 nm in diameter, on nutrient starvation, the size of the lysosome increases to 500–1500 nm as a result of membrane fusion.[2–5] In each mammalian cell, there are generally several hundred lysosomes, dramatically reduced to <50 per cell on acute nutrient starvation. However, when exposed to prolonged starvation, the lysosome number recovers.[3 6] Overall, lysosomes comprise about 0.5%–5% of the cell's mass. In phagocytes like the mammalian macrophage, lysosomes collectively take up 2%–10% of cell volume.[7]

There are four types of lysosomes depending on their morphology and function: primary, secondary, residual and auto-lysosomes.[8] Primary lysosomes are homologous, small, newly formed vesicles that originate from the Golgi apparatus which contain >60 acid hydrolytic enzymes but no substrate to act on. The secondary lysosomes contain large amounts of cargoes and substrates, which are subjected to digestion by lysosomal enzymes.[8] Residual lysosomes, also known as telolysosomes, contain indigestible substances that eventually move outwards and fuse with the plasma membrane in order to transport debris into the extracellular environment by exocytosis. Lastly, auto-lysosomes are created by the fusion of several primary lysosomes to remove intracellular cargoes, also known as autophagy.[8]

Lysosomal biogenesis

Lysosomal biogenesis is one of the most important mechanisms by which cells adapt to extracellular and intracellular demands. During starvation-induced autophagy, lysosome numbers increase. Furthermore, lysosomal reformation involves cargo-mediated degradation of lysosomes, resulting in regeneration and maintenance of the cellular lysosome pool. The process of lysosomal biogenesis requires mechanisms that rely on both lysosomal protein biosynthesis and endosome-lysosome trafficking. Lysosomal enzymes are synthesised and tagged with mannose-6-phosphate residues in the rough endoplasmic reticulum (RER), modified in the Golgi apparatus and delivered to the lysosomes.[9 10] Formation of lysosomal vesicles results from the fusion between vesicles originating from post-Golgi transport and those filled with cargo along the endocytic pathway.[11] For example, endocytic vesicles (EVs) from the plasma membrane mature into late endosomes that eventually become lysosomes. Lysosomes could also be formed through vesicular transport, 'kiss and run' events and fusion-fission processes.[12–15] Lastly, the intermediate forms of hybrid lysosomes are also observed in diverse sets of cells—for example, endocytic lysosome, autophagic lysosome and phagocytic lysosome reformation, which have been reviewed by Yang and Wang.[15]

Lysosome localisation and motility

Intracellularly, lysosomes can be found in a relatively immobile perinuclear cluster and a set of peripheral pools.[16] Lysosomes move bi-directionally in a stop-and-go manner due to

the alternating activities of kinesin and dynein motor proteins.[16] Depending on the cellular metabolic status or specific stimuli, lysosomes move to either the cell periphery or to the perinuclear region. The positioning of lysosomes is intimately associated with the activity of the mechanistic target of rapamycin complex 1 (mTORC1) and nutrient levels. For example, mTORC1 activation under nutrient-rich conditions causes scattering of lysosomes to the periphery.[16] During starvation, peripheral lysosomes move towards the perinuclear region where autophagosome-lysosome fusion occurs. Functionally, peripheral lysosomes are less acidic and have reduced vacuolar-type ATPase activity compared with perinuclear localised lysosomes.[17 18]

FUNCTIONS OF THE LYSOSOME

Catabolic role of the lysosome

Lysosomes are known for their terminal degradation function in eukaryotic cells. Their primary function is maintaining cellular health by processing and removing toxic components, damaged organelles and excess metabolites. Moreover, the lysosome plays a crucial role in breaking down and recycling a variety of biological macromolecules, such as proteins, lipids, carbohydrates and nucleic acids. To accomplish its functions, lysosomes use various enzymatic reactions that are activated in an acidic environment.[19] There are over 60 resident acid hydrolases, which are classified by substrate preference, including proteases, lipases, nucleases, sulfatases, phosphatases and glycosidases.[11] The end-products of lysosome-mediated digestion are then transported to the cytoplasm via specific lysosomal integral membrane proteins. These products play a vital role in various biosynthetic reactions essential for the cell's growth and development.[12]

The autophagy-lysosomal pathway

Autophagy, a fundamental cellular degradation process, serves a vital housekeeping function in maintaining cellular homeostasis. During the autophagic process, the autophagic cargoes are delivered to lysosomes for degradation and finally recycled to provide nutrients and building blocks for cells. Basal levels of autophagy occur naturally in most tissues to control protein and organelle quality.[20 21] Whereas, in response to various stimuli such as nutritional/cellular stress or infection, autophagy is induced above baseline levels to serve as an adaptive response to re-establish organ/tissue homeostasis and immunity.[22 23] Dysregulation of adaptive autophagy has been linked to the pathogenesis of many human diseases, including cancer, degenerative and immune disorders, metabolic disease and ageing.[24]

Role of the lysosome in ionic balancing

Lysosomes contain ions and harbour ion channels, which exert indispensable roles in regulating lysosomal pH and function.[25] Specifically, the lysosomal lumen comprises various ions including Fe^{2+}, Na^{+}, K^{+}, Zn^{2+}, H^{+} and Ca^{2+} (which is ~0.5 mM and 5000 times higher than cytosolic Ca^{2+} stores). Furthermore, the lysosome membrane contains more than six types of ion channels to balance the lysosomal ionic gradient.[26] These lysosomal ion channels and transporters mediate ion flux to regulate lysosomal ion homeostasis, membrane potential, catabolite export, membrane trafficking and nutrient sensing. Dysregulation of

lysosomal channels has been involved in the pathogenesis of many diseases, such as lysosomal storage diseases, metabolic diseases and neurodegenerative diseases,[3 27] all of which have been reviewed in detail elsewhere.[3 12]

The role of lysosome in immunity

The lysosome's function is not limited to cellular waste disposal and contributes significantly to the immune system.[28] The lysosome serves as a central hub for both innate and adaptive immunity, aiding the host's defence against harmful intruders such as bacteria and viruses.[28] In response to a diverse range of stimuli, dendritic cells (DCs) enhance the ability to form peptide-major histocompatibility complex (MHC) II class complexes in lysosomes to initiate antigen-specific immune responses.[29 30] Regarding T cells, virus-induced autophagy plays a critical role in MHC class antigen presentation and $CD8^+$ T cell responses.[31] Due to their phagocytic nature, macrophages are abundant in lysosomes for degrading dead cells and foreign substances.[32] On infection, macrophages undergo significant alterations in the quantity and composition of the lysosomal proteome, respectively.[33] In addition to local lysosomal events, the immune cells' autophagy-lysosome pathway aids pathogen detection, thus enhancing the immune system's effectiveness.[31 34] Lastly, autophagy regulators mediate innate immunity by directly modulating inflammasomes in macrophages.[35]

The metabolic function of lysosome

The lysosome modulates extracellular nutritional sensing by degrading or recycling plasma membrane receptors, such as transferrin (Tf)-Tf receptor complex and low-density lipoprotein (LDL) receptor.[36–40] Motile and primary cilia are microtubule-based structures located at the cell surface which modulate cellular functions ranging from motility to sensing nutritional signalling from the environment.[41] Notably, recent studies highlight the interplay between autophagy and ciliogenesis during nutritional stress.[42 43] Intracellularly, in mammalian and yeast cells, activation of the mTORC1 protein kinase and AMP-activated protein kinase (AMPK), two essential anabolic and catabolic regulators, respectively, occur at the lysosome.[44–47]

In addition to sensing nutritional status, lysosomes play a crucial role in maintaining intracellular metabolic balancing by degrading both internal and external substances for cellular energy fuel resources.[3 11 48 49] Furthermore, lysosome-mediated signalling pathways and transcriptional programmes are responsible for controlling the switch between anabolism and catabolism. This is achieved by regulating the transcription factor EB (TFEB)-mediated lysosomal biogenesis and the autophagy programme.[50 51] Lysosomes also control intracellular metabolic status by modulating other organelles' functions through interorganelle communication. This organellar direct communication is crucial for lysosomal function, positioning and repair of damaged lysosomal membranes,[52] and for fine-tuning intracellular calcium transfer, lipid transport, signal transduction, glucose metabolism and mitochondrial respiration.[12 53–60] Together, the lysosome plays a vital role in detecting nutrients, transmitting metabolic signals and regulating both cellular anabolic and catabolic processes. The functions of the lysosome are summarised in figure 1.

LYSOSOMAL STRESS AND ITS RELEVANCE TO DISEASES

Under acute and chronic stress, such as pathogens, toxins, nutrient alteration or disruption of the endolysosome system, lysosomal homeostasis is disrupted, leading to stressed lysosomes.[61–65] Different criteria have been suggested to assess lysosomal stress, including changes in the intralysosomal pH (eg, lysosome de-acidification), lysosome enlargement, membrane permeabilisation, cationic efflux, intracellular repositioning, misfolded protein aggregation, LDL cholesterol accumulation, redox catastrophe and bioenergetic crisis.[65] Cells respond to the stressed-out lysosome by initiating the lysosome stress response (LSR) to restore lysosomal homeostasis. Proper initiation of the LSR to re-establish lysosomal homeostasis is critical for maintaining cellular function, and maladaptive LSR can contribute to the development of a variety of diseases.

Transcriptional control of lysosomal genes and selective autophagy is an essential regulatory mechanism of LSR.[65 66] Specifically, in response to lysosome stress, the release of lysosome localised mTORC1 results in dephosphorylation and activation of TFEB and the resultant induction of lysosome-related genes and the LSR.[66 67] Zinc finger protein with Kruppel-associated box (KRAB) and SCAN domains 3 (ZKSCAN3) is a zinc-finger transcription factor that harbours a KRAB and a SCAN domain occupying the promoter regions of various lysosomal genes. However, in contrast to TFEB, ZKSCAN3 is a strong inhibitor of these lysosomal genes.[68 69] Moreover, lysosomal Ca^{2+} signaling is an essential process that enables adaptive lysosomal response to ensure the body responds appropriately to environmental changes.[70] While the endoplasmic reticulum (ER) and mitochondrial stress responses have been extensively studied in relation to disease pathologies, LSRs have been largely overlooked. Recently, studies have implicated the relevance of the LSR to various tumourigenesis[71 72] and neurodegenerative diseases.[73] However, the functional significance of the LSR in the context of pancreatic diseases is not well established.

LYSOSOMAL STRESS IN PANCREATIC ENDOCRINE TISSUE IN THE CONTEXT OF DIABETES MELLITUS

Physiological pancreatic lysosomal function

The pancreas consists of endocrine and exocrine glands. The exocrine compartment of pancreas consists of acinar and ductal cells to produce and drain the digestive enzymes. The endocrine compartment, islets of Langerhans, include α, β, δ, ε and pancreatic polypeptide (PP) cells which secrete glucagon, insulin, somatostatin, ghrelin and pancreatic polypeptide, respectively.[74] Mounting studies have demonstrated that β-cell lysosome-autophagy process plays an important role in insulin biosynthesis, secretion and degradation.[75–78] Moreover, β-cell autophagy plays an important role in fine-tuning organelle homeostasis, such as the ER function, to ensure a functional β-cell.[79] In addition to serving as the terminal site of the autophagy pathway, lysosomes are responsible for monitoring and sensing nutritional flux in β-cells. It has been demonstrated that β-cell mTORC1 signalling controls systemic glucose homeostasis by regulating β-cell mass, proliferation, apoptosis, insulin secretion and insulin secretory granule degradation.[80] Moreover, the inactivation of β-cell AMPK elevates insulin secretion while the overactivation of β-cell AMPK prevents insulin secretion.[67 81 82] Taken

together, these studies demonstrated that basal lysosome-autophagy process is essential for maintaining β-cell cellular and insulin homeostasis (figure 2). However, thus far there are limited studies investigating lysosomal function in other cell types of the pancreas.

Pancreatic β-cell lysosomal stress in type 1 diabetes and type 2 diabetes

Diabetes mellitus (DM) is a common disease that is increasing worldwide. Type 2 diabetes (T2D) is characterised by hyperglycaemia due to insulin resistance and impaired insulin secretion.[83] Mounting studies have shown that autophagy is essential for maintaining the structure, mass, survival and cellular homeostasis of β-cells in response to cellular stress,[84–87] and dysregulation of autophagy in β-cells has been linked to an increased incidence of T2D.[86 88 89] Although numerous studies have demonstrated the pathophysiological relevance of dysfunctional autophagy in T2D, less evidence has been provided to support this link in the context of type 1 diabetes (T1D). T1D is an autoimmune disease attributed to the autoimmune mechanism-induced destruction of β-cells in pancreatic islets.[90] Of note, several T1D susceptibility genes are known to play critical roles in autophagic degradation pathways. For example, in mouse models of T1D, Clec16a, a T1D disease susceptibility gene, has been demonstrated to play a critical role in regulating mitophagy, glucose-stimulated insulin secretion[91] and protection of β-cells against cytokine-induced apoptosis.[92 93] Recently, a study by Muralidharan *et al* further supported the translational relevance of lysosomal dysfunction in T1D pathogenesis, demonstrating a blocked autophagic flux in the islets of non-obese diabetic (NOD) mice as well as in residual β cells of human donors with T1D.[94]

Cathepsins (CTS) are the most abundant lysosomal proteases with a broad spectrum of functions, such as intracellular protein degradation, energy metabolism and immune response.[95] Increasing evidence suggests that dysregulation of several lysosomal CTS are genetically associated with T1D. For example, *CTSC* has been identified as a causal risk gene in T1D,[96] and *CTSC* has been shown to positively regulate cytokine-induced β-cell apoptosis in the context of T1D.[97] Moreover, it has been demonstrated that deletion of CTSS, CTSB and CTSL ameliorates T1D development and diabetes incidence in mice.[98] In terms of T2D, reduced transcription of CTSB and CTSD has been linked to β-cell dysfunction and cell death in patients with T2D.[99] Lastly, abnormal lysosomal glycohydrolase activities, such as β-N-acetylhexosaminidase, β-galactosidase and α-glucosidase, have been revealed in patients with juvenile DM.[100]

In addition to serving as a central site of proteostasis, the lysosome plays an important role in modulating intracellular calcium flux.[101] For example, lysosomal calcium release via transient receptor potential mucolipin 1 (TRPML1) is known to play a key role in inducing the nuclear translocation of TFEB, autophagosome fusion, mitophagy and lysosomal adaptation during starvation.[102] Recent studies have begun to reveal the functional relevance of these lysosomal calcium channels in disease progression.[103 104] Of note, Park *et al* identified a lysosomal Ca^{2+}-mediated TFEB activation in mitophagy and functional adaptation in pancreatic β-cell adaptation to metabolic stress.[105 106]

Lysosome stress of pancreatic α cells in DM

It is proposed that one key cause of DM's hyperglycaemia is the excessive production of glucagon (or hyperglucagonaemia), which reflects dysregulated glucagon secretion from pancreatic α cells.[107] Impaired intracellular trafficking of glucagon has been recognised as a mechanism underlying defective glucagon secretion in diabetes.[108] Notably, altered lysosomal trafficking of glucagon has been proposed as a new pathway for glucagon hypersecretion in diabetes.[109 110] This is caused by a switch from trafficking lysosome (Lamp 2A+) to autophagic lysosomes to secretory lysosomes (Lamp 1+), as well as an increase in glucagon trafficking through secretory granules.[109]

Lysosome stress of immune cells in DM

The pancreas's endocrine unit comprises a diverse cell population including immune cells.[111] During T1D progression, immune cells infiltrate the pancreas creating an inflammatory environment characteristic of insulitis. In turn, insulitis accelerates T1D development by increasing exposure of islet antigens and attacking β-cell.[112 113] Both adaptive and innate immune systems are involved in the onset and progression of T1D.[114 115] Although the lysosome-autophagy axis plays a crucial role in modulating immunity,[116] the immune cell-lysosomal function in T1D is poorly studied. It has been shown that autophagy regulates T cell metabolic flexibility and survival to prevent autoimmune attacks on pancreatic β-cells.[94] Furthermore, autophagy-deficient DCs display accelerated expression of MHC I leading to $CD8^+$ T cell activation.[117] It is proposed that B cells autophagy might impact intracellular MHC I presentation by reducing the amount of neoantigens formed in β-cells.[118] At the site of the lysosome, it is reported that T1D elevates CTSL expression in peripheral $CD8^+$ T in NOD mice.[119] Moreover, it is shown that the CTSL-processed granule proteins create chimeric epitopes for diabetogenic $CD4^+$ T cells augmenting impairment of peripheral self-tolerance in T1D.[120]

Another key feature of T1D and T2D immunity is the elevation of islet macrophage infiltration. It has been shown that in mice with STZ-induced T1D diabetes, macrophages make up to 0.9% of total islet cells compared with 0.5% in normal mice.[121] In T2D, it is estimated that the average number of islet macrophages is around 1.34 macrophage/islet compared with 0.52 macrophage/islet under normal condition.[121] In mice with diabetes, the elevation of mitochondrial reactive oxygen species (ROS) promotes macrophage polarisation towards the proinflammatory M1 phenotype.[122] Of note, this process is mediated by impairing lysosomal function and autophagic flux in peritoneal macrophages of mice with diabetes.[122] Sterile stimuli, such as damage-associated molecular patterns, sterile particulates and intracellular cytokines released from necrotic cells can trigger sterile inflammation by activating the host immune system.[123 124] It is well recognised that the NLR family pyrin domain containing 3 inflammasomes is the key regulator for sterile inflammatory responses.[125–127] Aberrant macrophage polarisation and inflammasome activation coexist in the pathogenesis and progression of diabetes and its complications.[128–130] Notably, the lysosome plays a crucial role in both the priming and assembly phases of the lipotoxic inflammasome in peritoneal macrophages.[131] Although it is largely unknown to what extent islet macrophage lysosome-modulated inflammasome activity contributes

to DM pathologies, lysosomes may be potential targets for therapies to address the hyperinflammatory phenotypes observed in patients with diabetes.[131]

Functional relevance of lysosomal stress in other types of DM

Gestational diabetes mellitus (GDM) occurs when the body cannot respond properly to pregnancy-related metabolic challenges and insulin resistance.[132] After giving birth, blood glucose levels return to normal in most individuals with gestational diabetes. However, these patients have a considerable risk of developing T2D in the future.[133] Of note, a recent human study has identified an inversed correlation between fetal pancreas-autophagic markers and GDM-associated maternal metabolic risk.[134] Furthermore, using a humanised islet amyloid polypeptide transgenic mouse line, Gurlo *et al* found a compromised β-cell autophagy in female mice with GDM.[135] However, the pathophysiological relevance of pancreatic lysosomal function in the context of GDM has not been explored. Another distinct type of DM is cystic fibrosis-related diabetes (CFRD), which is characterised by decreased islet mass, β-cell dysfunction, hypoinsulinaemia and systemic insulin resistance.[136–138] Thus far, there are only a few published studies on lysosomal stress in CFRD. High-mobility group box 1 protein (HMGB1) is a non-histone nuclear factor which regulates diverse biological processes depending on its subcellular or extracellular localization.[139] During inflammation, HMGB1 is actively secreted into the extracellular space by lysosome-mediated exocytosis.[140] Notably, patients with CFRD have elevated circulating levels of HMGB1 due to loss of function of cystic fibrosis transmembrane conductance regulator.[141] However, what are the cell resources for the lysosome-mediated HMGB1 secretion and how lysosome stress affects the CFRD pathogenesis remain largely unknown.

THE ROLE OF LYSOSOMAL STRESS IN THE EXOCRINE OF THE PANCREAS

Pancreatitis is defined by inflammation of the pancreas accompanied by damaged exocrine acinar cells, with the postpancreatitis diabetes as the most frequent complication.[142] Autophagy-lysosomal dysfunction is unequivocally the primary initiating event in pancreatitis and serves as the convergence point for multiple pathological pathways (figure 2).[143] Defects in various phases of autophagy, including lysosomal biogenesis, autophagosome formation and closure of fusion with lysosomes, can all lead to pancreatitis.[144] For instance, deletion of the autophagy gene *Atg5* led to spontaneous pancreatitis.[145] Moreover, loss of LAMP2 in mice resulted in spontaneous pancreatitis characterised by acinar cell vacuolation, progressive inflammation in the pancreas and acinar cell necrosis resulting from lysosomal and autophagic dysfunction.[146] In addition to acinar cell vacuolation, lysosomal/autophagic dysfunction leads to the accumulation of active trypsin in acinar cells, another hallmark response of pancreatitis.[147 148] Lastly, recent research suggests that pancreatitis impairs lysosomal function through deficient proteolytic activity and altered membrane proteins, which has already been reviewed extensively by others.[143 144]

PERSPECTIVES

The regulatory role of lysosomes in β-cell autophagy in health and diseases has been largely studied in the pathogenesis of diabetes. However, our understanding of cell type-specific lysosome biogenesis, dynamics and autophagy-independent role of lysosomes in the pancreas is largely uncovered. Furthermore, the pancreatic islet is composed of multiple parenchymal cell types and a diverse set of immune cells. It is essential to determine whether a lysosome-related organelles communication exists between parenchymal cells and immune cells within the pancreatic microenvironment. Dissecting the roles of lysosomes in immunity, inflammation processes and metabolic regulation in diverse sets of DMs will advance our understanding of the molecular mechanisms of autophagy in inflammation in DM. With recent advances in understanding of lysosomal dysfunction in pathogenesis of human diseases, there has been considerable attention in therapeutically targeting the lysosome-depended pathways including autophagy.[149–151] However, so far there is a limited number of lysosome-targeted therapeutics that have progressed towards clinical development. Developing cell type-specific and subtype-specific lysosomal activators or inhibitors for safely treating diverse types of DM is needed.

Acknowledgements

We thank the Yang lab members for their scientific insights.

Funding

This study was funded by National Institute of Health Sciences (R01 DK126817).

REFERENCES

1. DE DUVE C, PRESSMAN BC, GIANETTO R, et al. Tissue fractionation studies. 6. Intracellular distribution patterns of enzymes in rat-liver tissue. Biochem J 1955;60:604–17. [PubMed: 13249955]
2. Bandyopadhyay D, Cyphersmith A, Zapata JA, et al. Lysosome transport as a function of lysosome diameter. PLoS One 2014;9:e86847. [PubMed: 24497985]
3. Xu H, Ren D. Lysosomal physiology. Annu Rev Physiol 2015;77:57–80. [PubMed: 25668017]
4. Steinman RM, Brodie SE, Cohn ZA. Membrane flow during pinocytosis. A stereologic analysis. J Cell Biol 1976;68:665–87. [PubMed: 1030706]
5. Bakker AC, Webster P Jacob WA, et al. Homotypic fusion between aggregated lysosomes triggered by elevated [Ca2+]i in fibroblasts. J Cell Sci 1997;110 (Pt 18):2227–38. [PubMed: 9378772]
6. Yu L, McPhee CK, Zheng L, et al. Termination of autophagy and reformation of lysosomes regulated by mTOR. Nat New Biol 2010;465:942–6.
7. Holtzmann E. Lysosomes New York: Plenum Press, 1989.
8. Ghadially FN. Lysosomes: ultrastructural pathology of the cell and matrix. 3rd edn. 1988.
9. Woychik NA, Cardelli JA, Dimond RL. A conformationally altered precursor to the lysosomal enzyme alpha-mannosidase accumulates in the endoplasmic reticulum in a mutant strain of Dictyostelium discoideum. J Biol Chem 1986;261:9595–602. [PubMed: 3090024]
10. Seaman MNJ. Cargo-selective endosomal sorting for retrieval to the Golgi requires retromer. J Cell Biol 2004;165:111–22. [PubMed: 15078902]
11. Perera RM, Zoncu R. The Lysosome as a Regulatory Hub. Annu Rev Cell Dev Biol 2016;32:223–53. [PubMed: 27501449]
12. Trivedi PC, Bartlett JJ, Pulinilkunnil T. Lysosomal Biology and Function: Modern View of Cellular Debris Bin. Cells 2020;9:1131. [PubMed: 32375321]

13. Luzio JP, Pryor PR, Bright NA. Lysosomes: fusion and function. Nat Rev Mol Cell Biol 2007;8:622–32. [PubMed: 17637737]
14. Luzio JP, Pryor PR, Gray SR, et al. Membrane traffic to and from lysosomes. Biochem Soc Symp 2005;2005:77–86.
15. Yang C, Wang X. Lysosome biogenesis: regulation and functions. J Cell Biol 2021;220:e202102001. [PubMed: 33950241]
16. Cabukusta B, Neefjes J. Mechanisms of lysosomal positioning and movement. Traffic 2018;19:761–9. [PubMed: 29900632]
17. Johnson DE, Ostrowski P, Jaumouillé V, et al. The position of lysosomes within the cell determines their luminal pH. J Cell Biol 2016;212:677–92. [PubMed: 26975849]
18. Heuser J. Changes in lysosome shape and distribution correlated with changes in cytoplasmic pH. J Cell Biol 1989;108:855–64. [PubMed: 2921284]
19. Saftig P, Klumperman J. Lysosome biogenesis and lysosomal membrane proteins: trafficking meets function. Nat Rev Mol Cell Biol 2009;10:623–35. [PubMed: 19672277]
20. Mizushima N, Komatsu M. Autophagy: renovation of cells and tissues. Cell 2011;147:728–41. [PubMed: 22078875]
21. Hara T, Nakamura K, Matsui M, et al. Suppression of basal autophagy in neural cells causes neurodegenerative disease in mice. Nature New Biol 2006;441:885–9.
22. Shang L, Chen S, Du F, et al. Nutrient starvation elicits an acute autophagic response mediated by Ulk1 dephosphorylation and its subsequent dissociation from AMPK. Proc Natl Acad Sci U S A 2011;108:4788–93. [PubMed: 21383122]
23. Gutierrez MG, Master SS, Singh SB, et al. Autophagy is a defense mechanism inhibiting BCG and Mycobacterium tuberculosis survival in infected macrophages. Cell 2004;119:753–66. [PubMed: 15607973]
24. Levine B, Kroemer G. Autophagy in the pathogenesis of disease. Cell 2008;132:27–42. [PubMed: 18191218]
25. Xiong J, Zhu MX. Regulation of lysosomal ion homeostasis by channels and transporters. Sci China Life Sci 2016;59:777–91. [PubMed: 27430889]
26. Riederer E, Cang C, Ren D. Lysosomal Ion Channels: What Are They Good For and Are They Druggable Targets? Annu Rev Pharmacol Toxicol 2023;63:19–41. [PubMed: 36151054]
27. Kolter T, Sandhoff K. Principles of lysosomal membrane digestion: stimulation of sphingolipid degradation by sphingolipid activator proteins and anionic lysosomal lipids. Annu Rev Cell Dev Biol 2005;21:81–103. [PubMed: 16212488]
28. Watts C Lysosomes and lysosome-related organelles in immune responses. FEBS Open Bio 2022;12:678–93.
29. Trombetta ES, Ebersold M, Garrett W, et al. Activation of lysosomal function during dendritic cell maturation. Science 2003;299:1400–3. [PubMed: 12610307]
30. Bretou M, Sáez PJ, Sanséau D, et al. Lysosome signaling controls the migration of dendritic cells. Sci Immunol 2017;2:eaak9573. [PubMed: 29079589]
31. Crotzer VL, Blum JS. Autophagy and adaptive immunity. Immunology 2010;131:9–17. [PubMed: 20586810]
32. Hirayama D, Iida T, Nakase H. The Phagocytic Function of Macrophage-Enforcing Innate Immunity and Tissue Homeostasis. Int J Mol Sci 2017;19:92. [PubMed: 29286292]
33. Gao Y, Chen Y, Zhan S, et al. Comprehensive proteome analysis of lysosomes reveals the diverse function of macrophages in immune responses. Oncotarget 2017;8:7420–40. [PubMed: 28088779]
34. Deretic V Autophagy as an immune defense mechanism. Curr Opin Immunol 2006;18:375–82. [PubMed: 16782319]
35. Nakahira K, Haspel JA, Rathinam VAK, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. Nat Immunol 2011;12:222–30. [PubMed: 21151103]
36. Sigismund S, Lanzetti L, Scita G, et al. Endocytosis in the context-dependent regulation of individual and collective cell properties. Nat Rev Mol Cell Biol 2021;22:625–43. [PubMed: 34075221]

37. Goh LK, Sorkin A. Endocytosis of receptor tyrosine kinases. Cold Spring Harb Perspect Biol 2013;5:a017459. [PubMed: 23637288]
38. Irannejad R, Tsvetanova NG, Lobingier BT, et al. Effects of endocytosis on receptor-mediated signaling. Curr Opin Cell Biol 2015;35:137–43. [PubMed: 26057614]
39. Mayle KM, Le AM, Kamei DT. The intracellular trafficking pathway of transferrin. Biochim Biophys Acta 2012;1820:264–81. [PubMed: 21968002]
40. Beglova N, Blacklow SC. The LDL receptor: how acid pulls the trigger. Trends Biochem Sci 2005;30:309–17. [PubMed: 15950875]
41. Satir P, Pedersen LB, Christensen ST. The primary cilium at a glance. J Cell Sci 2010;123:499–503. [PubMed: 20144997]
42. Pampliega O, Orhon I, Patel B, et al. Functional interaction between autophagy and ciliogenesis. Nature New Biol 2013;502:194–200.
43. Liu Z-Q, Lee JN, Son M, et al. Ciliogenesis is reciprocally regulated by PPARA and NR1H4/FXR through controlling autophagy in vitro and in vivo. Autophagy 2018;14:1011–27. [PubMed: 29771182]
44. Lawrence RE, Zoncu R. The lysosome as a cellular centre for signalling, metabolism and quality control. Nat Cell Biol 2019;21:133–42. [PubMed: 30602725]
45. Menon S, Dibble CC, Talbott G, et al. Spatial control of the TSC complex integrates insulin and nutrient regulation of mTORC1 at the lysosome. Cell 2014;156:771–85. [PubMed: 24529379]
46. Hawley SA, Boudeau J, Reid JL, et al. Complexes between the LKB1 tumor suppressor, STRAD alpha/beta and MO25 alpha/beta are upstream kinases in the AMP-activated protein kinase cascade. J Biol 2003;2:28. [PubMed: 14511394]
47. Zhang C-S, Jiang B, Li M, et al. The lysosomal v-ATPase-Ragulator complex is a common activator for AMPK and mTORC1, acting as a switch between catabolism and anabolism. Cell Metab 2014;20:526–40. [PubMed: 25002183]
48. He C, Klionsky DJ. Regulation mechanisms and signaling pathways of autophagy. Annu Rev Genet 2009;43:67–93. [PubMed: 19653858]
49. Settembre C, Fraldi A, Medina DL, et al. Signals from the lysosome: a control centre for cellular clearance and energy metabolism. Nat Rev Mol Cell Biol 2013;14:283–96. [PubMed: 23609508]
50. Ballabio A, Bonifacino JS. Lysosomes as dynamic regulators of cell and organismal homeostasis. Nat Rev Mol Cell Biol 2020;21:101–18. [PubMed: 31768005]
51. Settembre C, Di Malta C, Polito VA, et al. TFEB links autophagy to lysosomal biogenesis. Science 2011;332:1429–33. [PubMed: 21617040]
52. Radulovic M, Wenzel EM, Gilani S, et al. Cholesterol transfer via endoplasmic reticulum contacts mediates lysosome damage repair. EMBO J 2022;41:e112677. [PubMed: 36408828]
53. Hong Z, Pedersen NM, Wang L, et al. PtdIns3P controls mTORC1 signaling through lysosomal positioning. J Cell Biol 2017;216:4217–33. [PubMed: 29030394]
54. Morgan AJ, Davis LC, Wagner SKTY, et al. Bidirectional Ca(2)(+) signaling occurs between the endoplasmic reticulum and acidic organelles. J Cell Biol 2013;200:789–805. [PubMed: 23479744]
55. Friedman JR, DiBenedetto JR, West M, et al. Endoplasmic reticulum-–endosome contact increases as endosomes traffic and mature. MBoC 2013;24:1030–40. [PubMed: 23389631]
56. Peng W, Wong YC, Krainc D. Mitochondria-lysosome contacts regulate mitochondrial Ca^{2+} dynamics via lysosomal TRPML1. Proc Natl Acad Sci U S A 2020;117:19266–75. [PubMed: 32703809]
57. Cai W, Li P, GU M, et al. Lysosomal Ion Channels and Lysosome-Organelle Interactions. Handb Exp Pharmacol 2023;278:93–108. [PubMed: 36882602]
58. Luo J, Jiang L, Yang H, et al. Routes and mechanisms of post-endosomal cholesterol trafficking: a story that never ends. Traffic 2017;18:209–17. [PubMed: 28191915]
59. Atakpa P, Thillaiappan NB, Mataragka S, et al. IP3 Receptors Preferentially Associate with ER-Lysosome Contact Sites and Selectively Deliver Ca2+ to Lysosomes. Cell Rep 2018;25:3180–93. [PubMed: 30540949]
60. Garrity AG, Wang W, Collier CM, et al. The endoplasmic reticulum, not the pH gradient, drives calcium refilling of lysosomes. Elife 2016;5:e15887. [PubMed: 27213518]

61. Lin J, Shi S, Zhang J, et al. Giant Cellular Vacuoles Induced by Rare Earth Oxide Nanoparticles are Abnormally Enlarged Endo/Lysosomes and Promote mTOR-Dependent TFEB Nucleus Translocation. Small 2016;12:5759–68. [PubMed: 27593892]
62. Yogalingam G, Lee AR, Mackenzie DS, et al. Cellular Uptake and Delivery of Myeloperoxidase to Lysosomes Promote Lipofuscin Degradation and Lysosomal Stress in Retinal Cells. J Biol Chem 2017;292:4255–65. [PubMed: 28115520]
63. Pan HY, Alamri AH, Valapala M. Nutrient deprivation and lysosomal stress induce activation of TFEB in retinal pigment epithelial cells. Cell Mol Biol Lett 2019;24:33. [PubMed: 31160892]
64. Papadopoulos C, Meyer H. Detection and Clearance of Damaged Lysosomes bythe Endo-Lysosomal Damage Response andLysophagy. Curr Biol 2017;27:R1330–41. [PubMed: 29257971]
65. Lakpa KL, Khan N, Afghah Z, et al. Lysosomal Stress Response (LSR): Physiological Importance and Pathological Relevance. J Neuroimmune Pharmacol 2021 ;16:219–37. [PubMed: 33751445]
66. Sasaki K, Yoshida H. Organelle autoregulation-stress responses in the ER, Golgi, mitochondria and lysosome. J Biochem 2015;157:185–95. [PubMed: 25657091]
67. Mészáros G, Pasquier A, Vivot K, et al. Lysosomes in nutrient signalling: a focus on pancreatic β-cells. Diabetes Obes Metab 2018;20 Suppl 2:104–15. [PubMed: 30230186]
68. Chauhan S, Goodwin JG, Chauhan S, et al. ZKSCAN3 is a master transcriptional repressor of autophagy. Mol Cell 2013;50:16–28. [PubMed: 23434374]
69. Pan HY, Valapala M. Role of the Transcriptional Repressor Zinc Finger with KRAB and SCAN Domains 3 (ZKSCAN3) in Retinal Pigment Epithelial Cells. Cells 2021 ;10:2504:10:. [PubMed: 34685484]
70. Lloyd-Evans E, Waller-Evans H. Lysosomal Ca(2+) Homeostasis and Signaling in Health and Disease. Cold Spring Harb Perspect Biol 2020;12.
71. Kirkegaard T, Jäättelä M. Lysosomal involvement in cell death and cancer. Biochim Biophys Acta 2009;1793:746–54. [PubMed: 18948147]
72. Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 2011 ;144:646–74. [PubMed: 21376230]
73. Lie PPY, Nixon RA. Lysosome trafficking and signaling in health and neurodegenerative diseases. Neurobiol Dis 2019;122:94–105. [PubMed: 29859318]
74. Da Silva Xavier G. The Cells of the Islets of Langerhans. J Clin Med 2018;7:54. [PubMed: 29534517]
75. Riahi Y, Wikstrom JD, Bachar-Wikstrom E, et al. Autophagy is a major regulator of beta cell insulin homeostasis. Diabetologia 2016;59:1480–91. [PubMed: 26831301]
76. Orci L, Ravazzola M, Amherdt M, et al. Insulin, not C-peptide (proinsulin), is present in crinophagic bodies of the pancreatic B-cell. J Cell Biol 1984;98:222–8. [PubMed: 6368567]
77. Landström AH, Westman J, Borg LA. Lysosomes and pancreatic islet function. Time course of insulin biosynthesis, insulin secretion, and lysosomal transformation after rapid changes in glucose concentration. Diabetes 1988;37:309–16. [PubMed: 3286331]
78. Pasquier A, Vivot K, Erbs E, et al. Lysosomal degradation of newly formed insulin granules contributes to β cell failure in diabetes. Nat Commun 2019;10:3312. [PubMed: 31346174]
79. Bachar-Wikstrom E, Wikstrom JD, Ariav Y, et al. Stimulation of autophagy improves endoplasmic reticulum stress-induced diabetes. Diabetes 2013;62:1227–37. [PubMed: 23274896]
80. Blandino-Rosano M, Barbaresso R, Jimenez-Palomares M, et al. Loss of mTORC1 signalling impairs β-cell homeostasis and insulin processing. Nat Commun 2017;8:16014. [PubMed: 28699639]
81. Granot Z, Swisa A, Magenheim J, et al. LKB1 regulates pancreatic beta cell size, polarity, and function. Cell Metab 2009;10:296–308. [PubMed: 19808022]
82. Fu A, Eberhard CE, Screaton RA. Role of AMPK in pancreatic beta cell function. Mol Cell Endocrinol 2013;366:127–34. [PubMed: 22766107]
83. American Diabetes Association Professional Practice Committee. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes—2022*. Diabetes Care 2022;45:S17–38. [PubMed: 34964875]

84. Kang HJ, Yoo EJ, Lee HH, et al. TonEBP Promotes β-Cell Survival under ER Stress by Enhancing Autophagy. Cells 2020;9:1928. [PubMed: 32825390]
85. Lee Y-H, Kim J, Park K, et al. β-cell autophagy: mechanism and role in β-cell dysfunction. Mol Metab 2019;27S:S92–103. [PubMed: 31500836]
86. Hur KY, Jung HS, Lee MS. Role of autophagy in β-cell function and mass. Diabetes Obes Metab 2010;12 Suppl 2:20–6.
87. Marasco MR, Linnemann AK. β-Cell Autophagy in Diabetes Pathogenesis. Endocrinology 2018;159:2127–41. [PubMed: 29617763]
88. Jung HS, Chung KW, Won Kim J, et al. Loss of autophagy diminishes pancreatic beta cell mass and function with resultant hyperglycemia. Cell Metab 2008;8:318–24. [PubMed: 18840362]
89. Wang Y, Li Y, Yin J, et al. Autophagy regulates inflammation following oxidative injury in diabetes. Autophagy 2013;9:272–7. [PubMed: 23343748]
90. Roep BO, Thomaidou S, van Tienhoven R, et al. Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?). Nat Rev Endocrinol 2021 ;17:150–61. [PubMed: 33293704]
91. Soleimanpour SA, Gupta A, Bakay M, et al. The diabetes susceptibility gene Clec16a regulates mitophagy. Cell 2014;157:1577–90. [PubMed: 24949970]
92. Sidarala V, Pearson GL, Parekh VS, et al. Mitophagy protects β cells from inflammatory damage in diabetes. JCI Insight 2020;5:e141138. [PubMed: 33232298]
93. Soleimanpour SA, Ferrari AM, Raum JC, et al. Diabetes Susceptibility Genes Pdx1 and Clec16a Function in a Pathway Regulating Mitophagy in β-Cells. Diabetes 2015;64:3475–84. [PubMed: 26085571]
94. Muralidharan C, Conteh AM, Marasco MR, et al. Pancreatic beta cell autophagy is impaired in type 1 diabetes. Diabetologia 2021 ;64:865–77. [PubMed: 33515072]
95. Yadati T, Houben T, Bitorina A, et al. The Ins and Outs of Cathepsins Physiological Function and Role in Disease Management. Cells 2020;9:1679. [PubMed: 32668602]
96. Fløyel T, Brorsson C, Nielsen LB, et al. CTSH regulates β-cell function and disease progression in newly diagnosed type 1 diabetes patients. Proc Natl Acad Sci U S A 2014;111:10305–10. [PubMed: 24982147]
97. Fløyel T, Frørup C, Størling J, et al. Cathepsin C Regulates Cytokine-Induced Apoptosis in β-Cell Model Systems. Genes (Basel) 2021:12:1694. [PubMed: 34828301]
98. Hsing LC, Kirk EA, McMillen TS, et al. Roles for cathepsins S, L, and B in insulitis and diabetes in the NOD mouse. J Autoimmun 2010;34:96–104. [PubMed: 19664906]
99. Masini M, Bugliani M, Lupi R, et al. Autophagy in human type 2 diabetes pancreatic beta cells. Diabetologia 2009;52:1083–6. [PubMed: 19367387]
100. Bomback FM, Nakagawa S, Kumin S, et al. Altered Lysosomal Glycohydrolase Activities in Juvenile Diabetes Mellitus. Diabetes 1976;25:420–7. [PubMed: 1269840]
101. Raffaello A, Mammucari C, Gherardi G, et al. Calcium at the Center of Cell Signaling: Interplay between Endoplasmic Reticulum, Mitochondria, and Lysosomes. Trends Biochem Sci 2016;41:1035–19. [PubMed: 27692849]
102. Wang W, Gao Q, Yang M, et al. Up-regulation of lysosomal TRPML1 channels is essential for lysosomal adaptation to nutrient starvation. Proc Natl Acad Sci USA 2015;112:E1373–81. [PubMed: 25733853]
103. Qi J, Li Q, Xin T, et al. MCOLN1/TRPML1 in the lysosome: a promising target for autophagy modulation in diverse diseases. Autophagy 2024 ;20:1712–22. [PubMed: 38522082]
104. Li G, Li PL. Lysosomal TRPML1 Channel: Implications in Cardiovascular and Kidney Diseases. Adv Exp Med Biol 2021;1349:275–301. [PubMed: 35138619]
105. Park K, Lim H, Kim J, et al. Lysosomal Ca2+-mediated TFEB activation modulates mitophagy and functional adaptation of pancreatic β-cells to metabolic stress. Nat Commun 2022;13:1300. [PubMed: 35288580]
106. Park K, Lee MS. Essential role of lysosomal Ca2+-mediated TFEB activation in mitophagy and functional adaptation of pancreatic β-cells to metabolic stress. Autophagy 2022;18:3043–5. [PubMed: 35468040]

107. Wewer Albrechtsen NJ, Kuhre RE, Pedersen J, et al. The biology of glucagon and the consequences of hyperglucagonemia. Biomark Med 2016;10:1141–51. [PubMed: 27611762]
108. Asadi F, Dhanvantari S. Pathways of Glucagon Secretion and Trafficking in the Pancreatic Alpha Cell: Novel Pathways, Proteins, and Targets for Hyperglucagonemia. Front Endocrinol (Lausanne) 2021;12:726368. [PubMed: 34659118]
109. Asadi F, Dhanvantari S. Misrouting of glucagon and stathmin-2 towards lysosomal system of α-cells in glucagon hypersecretion of diabetes. Islets 2022;14:40–57. [PubMed: 34923907]
110. Amherdt M, Patel YC, Orci L. Binding and internalization of somatostatin, insulin, and glucagon by cultured rat islet cells. J Clin Invest 1989;84:412–7. [PubMed: 2569474]
111. Guo J, Fu W. Immune regulation of islet homeostasis and adaptation. J Mol Cell Biol 2020;12:764–74. [PubMed: 32236479]
112. Willcox A, Richardson SJ, Bone AJ, et al. Analysis of islet inflammation in human type 1 diabetes. Clin Exp Immunol 2009;155:173–81. [PubMed: 19128359]
113. Coppieters KT, Dotta F, Amirian N, et al. Demonstration of islet-autoreactive CD8 T cells in insulitic lesions from recent onset and long-term type 1 diabetes patients. J Exp Med 2012;209:51–60. [PubMed: 22213807]
114. Lehuen A, Diana J, Zaccone P, et al. Immune cell crosstalk in type 1 diabetes. Nat Rev Immunol 2010;10:501–13. [PubMed: 20577267]
115. Sun L, Xi S, He G, et al. Two to Tango: Dialogue between Adaptive and Innate Immunity in Type 1 Diabetes. J Diabetes Res 2020;2020:1–9.
116. Pradel B, Robert-Hebmann V, Espert L. Regulation of Innate Immune Responses by Autophagy: A Goldmine for Viruses. Front Immunol 2020;11:578038. [PubMed: 33123162]
117. Yamamoto K, Venida A, Perera RM, et al. Selective autophagy of MHC-I promotes immune evasion of pancreatic cancer. Autophagy 2020;16:1524–5. [PubMed: 32459143]
118. Liu Q-R, Aseer KR, Yao Q, et al. Anti-Inflammatory and Pro-Autophagy Effects of the Cannabinoid Receptor CB2R: Possibility of Modulation in Type 1 Diabetes. Front Pharmacol 2021;12:809965. [PubMed: 35115945]
119. Yamada A, Ishimaru N, Arakaki R, et al. Cathepsin L Inhibition Prevents Murine Autoimmune Diabetes via Suppression of CD8+ T Cell Activity. PLoS One 2010;5:e12894. [PubMed: 20877570]
120. Reed B, Crawford F, Hill RC, et al. Lysosomal cathepsin creates chimeric epitopes for diabetogenic CD4 T cells via transpeptidation. J Exp Med 2021;218:e20192135. [PubMed: 33095259]
121. Richardson SJ, Willcox A, Bone AJ, et al. Islet-associated macrophages in type 2 diabetes. Diabetologia 2009;52:1686–8. [PubMed: 19504085]
122. Yuan Y, Chen Y, Peng T, et al. Mitochondrial ROS-induced lysosomal dysfunction impairs autophagic flux and contributes to M1 macrophage polarization in a diabetic condition. Clin Sci 2019;133:1759–77.
123. Gong T, Liu L, Jiang W, et al. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. Nat Rev Immunol 2020;20:95–112. [PubMed: 31558839]
124. Sarhan M, Land WG, Tonnus W, et al. Origin and Consequences of Necroinflammation. Physiol Rev 2018;98:727–80. [PubMed: 29465288]
125. Hornung V, Bauernfeind F, Halle A, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol 2008;9:847–56. [PubMed: 18604214]
126. Halle A, Hornung V, Petzold GC, et al. The NALP3 inflammasome is involved in the innate immune response to amyloid-β. Nat Immunol 2008;9:857–65. [PubMed: 18604209]
127. Li N, Zhou H, Wu H, et al. STING-IRF3 contributes to lipopolysaccharide-induced cardiac dysfunction, inflammation, apoptosis and pyroptosis by activating NLRP3. Redox Biol 2019:24:101215. [PubMed: 31121492]
128. Eguchi K, Nagai R. Islet inflammation in type 2 diabetes and physiology. J Clin Invest 2017 ;127:14–23. [PubMed: 28045399]

129. Goossens GH, Blaak EE, Theunissen R, et al. Expression of NLRP3 inflammasome and T cell population markers in adipose tissue are associated with insulin resistance and impaired glucose metabolism in humans. Mol Immunol 2012;50:142–9. [PubMed: 22325453]
130. Lee H-M, Kim J-J, Kim HJ, et al. Upregulated NLRP3 Inflammasome Activation in Patients With Type 2 Diabetes. Diabetes 2013;62:194–204. [PubMed: 23086037]
131. Weber K, Schilling JD. Lysosomes integrate metabolic-inflammatory cross-talk in primary macrophage inflammasome activation. J Biol Chem 2014;289:9158–71. [PubMed: 24532802]
132. Nakshine VS, Jogdand SD. A Comprehensive Review of Gestational Diabetes Mellitus: Impacts on Maternal Health, Fetal Development, Childhood Outcomes, and Long-Term Treatment Strategies. Cureus 2023;15:e47500. [PubMed: 38021940]
133. Li M, Rahman ML, Wu J, et al. Genetic factors and risk of type 2 diabetes among women with a history of gestational diabetes: findings from two independent populations. BMJ Open Diabetes Res Care 2020;8:e000850.
134. Avagliano L, Massa V, Terraneo L, et al. Gestational diabetes affects fetal autophagy. Placenta 2017;55:90–3. [PubMed: 28623978]
135. Gurlo T, Kim S, Butler AE, et al. Pregnancy in human IAPP transgenic mice recapitulates beta cell stress in type 2 diabetes. Diabetologia 2019;62:1000–10. [PubMed: 30852627]
136. Barrio R Management of endocrine disease: cystic fibrosis-related diabetes: novel pathogenic insights opening new therapeutic avenues. Eur J Endocrinol 2015;172:R131–41. [PubMed: 25336504]
137. Moran A, Dunitz J, Nathan B, et al. Cystic Fibrosis–Related Diabetes: Current Trends in Prevalence, Incidence, and Mortality. Diabetes Care 2009;32:1626–31. [PubMed: 19542209]
138. Moran A, Hardin D, Rodman D, et al. Diagnosis, screening and management of cystic fibrosis related diabetes mellitus. Diabetes Res Clin Pract 1999;45:61–73. [PubMed: 10499886]
139. Tang D, Kang R, Zeh HJ, et al. The multifunctional protein HMGB1: 50 years of discovery. Nat Rev Immunol 2023;23:824–41. [PubMed: 37322174]
140. Gardella S, Andrei C, Ferrera D, et al. The nuclear protein HMGB1 is secreted by monocytes via a non-classical, vesicle-mediated secretory pathway. EMBO Rep 2002;3:995–1001. [PubMed: 12231511]
141. Montanini L, Cirillo F, Smerieri A, et al. HMGB1 Is Increased by CFTR Loss of Function, Is Lowered by Insulin, and Increases In Vivo at Onset of CFRD. J Clin Endocrinol Metab 2016;101:1274–81. [PubMed: 26760176]
142. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. Nat Rev Gastroenterol Hepatol 2019;16:175–84. [PubMed: 30482911]
143. Gukovskaya AS, Gukovsky I. Autophagy and pancreatitis. Am J Physiol Gastrointest Liver Physiol 2012;303:G993–1003. [PubMed: 22961802]
144. Ding W-X, Ma X, Kim S, et al. Recent insights about autophagy in pancreatitis, e Gastroenterol 2024;2:e100057.
145. Diakopoulos KN, Lesina M, Wörmann S, et al. Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes. Gastroenterology 2015;148:626–38. [PubMed: 25497209]
146. Mareninova OA, Sendler M, Malla SR, et al. Lysosome-Associated Membrane Proteins (LAMP) Maintain Pancreatic Acinar Cell Homeostasis: LAMP-2–Deficient Mice Develop Pancreatitis. Cell Mol Gastroenterol Hepatol 2015;1:678–94. [PubMed: 26693174]
147. Hashimoto D, Ohmuraya M, Hirota M, et al. Involvement of autophagy in trypsinogen activation within the pancreatic acinar cells. J Cell Biol 2008;181:1065–72. [PubMed: 18591426]
148. Mareninova OA, Hermann K, French SW, et al. Impaired autophagic flux mediates acinar cell vacuole formation and trypsinogen activation in rodent models of acute pancreatitis. J Clin Invest 2009;119:3340–55. [PubMed: 19805911]
149. Bonam SR, Wang F, Muller S. Lysosomes as a therapeutic target. Nat Rev Drug Discov 2019;18:923–18. [PubMed: 31477883]
150. Platt FM. Emptying the stores: lysosomal diseases and therapeutic strategies. Nat Rev Drug Discov 2018;17:133–50. [PubMed: 29147032]

151. Vakifahmetoglu-Norberg H, Xia H, Yuan J. Pharmacologic agents targeting autophagy. J Clin Invest 2015;125:5–13. [PubMed: 25654545]

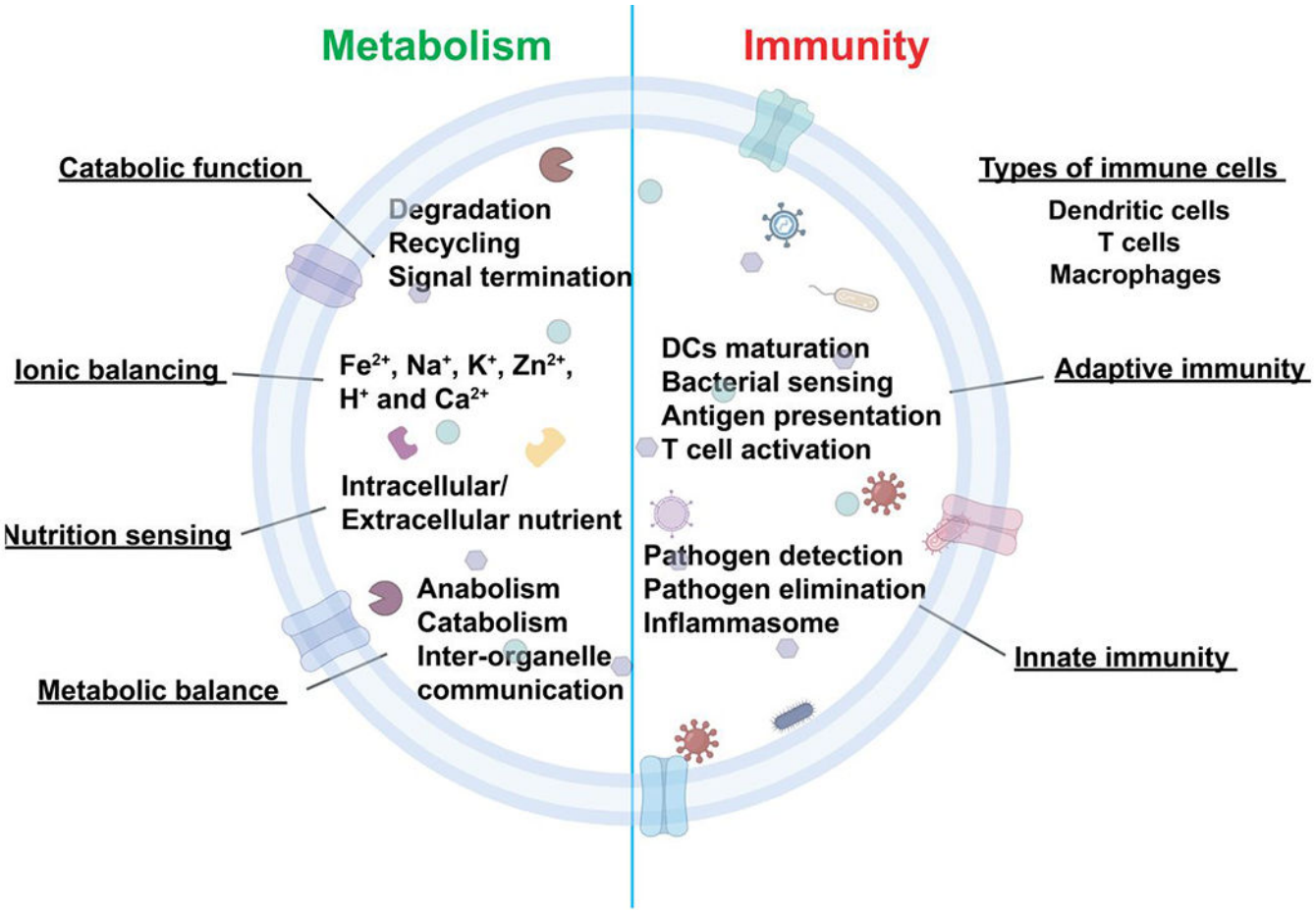

Figure 1.

The lysosomal function in metabolism and immunity. The lysosome is a critical site for maintaining cellular catabolic function, ionic balance, nutrition sensing, metabolic balance and immunity balance. DC, dendritic cell.

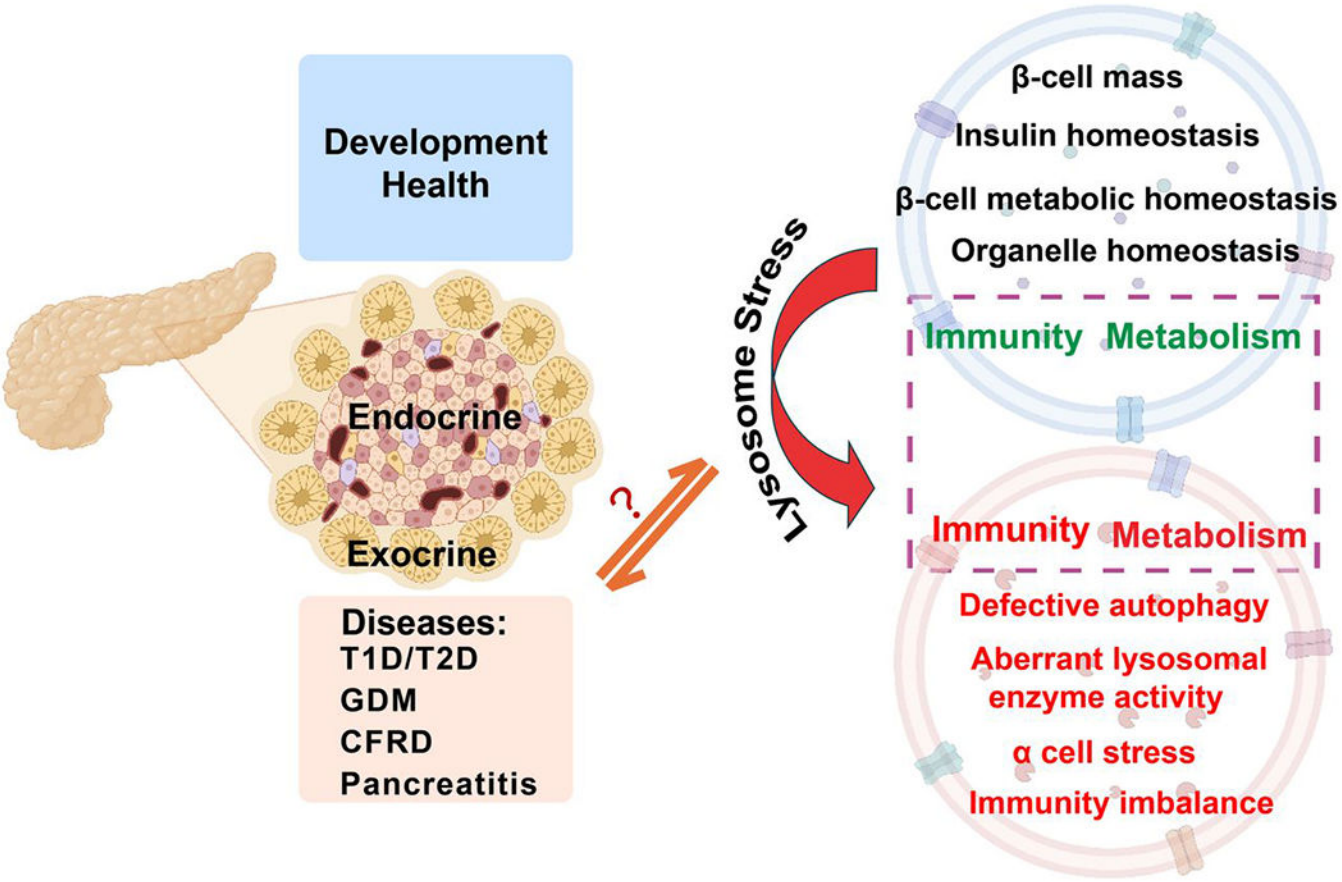

Figure 2.

The pancreatic lysosomal function in health and disease. The lysosome plays a critical role in maintaining cellular proteostasis, organelle function, ion balance, immunity as well as metabolic sensing and homeostasis in the pancreas. Disruption of the lysosomal stress response contributes to immuno-metabolic imbalance in diabetes mellitus. CFRD, cystic fibrosis-related diabetes; GDM, gestational diabetes mellitus; T1D, type 1 diabetes; T2D, type 2 diabetes.