Autophagy determines the fate of immune cells by regulating metabolic remodeling and PANoptosis (Review)

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Abstract. Autophagy, as a core mechanism for maintaining cellular homeostasis, influences differentiation and functional activation of immune cells by regulating metabolic reprogramming. Crucially, autophagy serves as a molecular switch that precisely modulates differentiation and subsequent cell fate decisions. It achieves this by eliminating intracellular danger signals or key complexes, thereby determining whether immune cells undergo PANoptosis, an inflammatory death mode that integrates features of pyroptosis, apoptosis and necroptosis. The present review systematically discusses the regulatory role of autophagy in the developmental, differentiation and metabolic pathways of various immune cells. Furthermore, it elucidates the mechanistic details by which autophagy, and particularly mitophagy, dampens excessive PANoptosis activation through the elimination of danger signals (such as mitochondrial DNA and reactive oxygen species) or the degradation of PANoptosome components. Additionally, it clarifies the molecular mechanism by which autophagy dysregulation, induced by specific pathological conditions, leads to inflammatory responses and immunopathological damage. Overall, this review establishes the significance of the autophagy-PANoptosis axis in the development and progression of autoimmune diseases and tumors, providing a solid theoretical foundation for the optimization and innovation of therapeutic strategies for these diseases.

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1. Introduction

When encountering infection or inflammatory signals, immune cells face a dilemma: They must precisely balance effective pathogen clearance against the prevention of excessive inflammatory damage. The ultimate manifestation of this balance is the cell's 'fate decision' -whether to survive and differentiate into effector cells to perform defense functions or to undergo programmed cell death (PCD) to terminate the response in a timely manner and prevent pathological damage. Studies have shown that in fatal influenza infections, the inflammatory damage caused by innate immunity is the main factor responsible for mortality, and merely limiting this immune damage is insufficient to maintain physiological functions (1). This finding indicates that when infectious or inflammatory signals exceed a critical threshold, the body must re-establish a balance between controlling pathogen spread and promoting tissue repair. Macrophages are highly plastic innate immune cells whose functional phenotypes

are regulated by signals from the tissue microenvironment, allowing them to alternate between pro-inflammatory (M1) and anti-inflammatory (M2) polarization states. Following antigen encounter, T cells undergo metabolic reprogramming and subsequently differentiate into effector cells, memory cells or an exhausted state. Their fate decisions are also precisely regulated by metabolic signals and inflammatory environments (2). Studies on cell death programs have shifted the perspective on the fate of immune cell survival. Upon completing their tasks, neutrophils must exit the inflammatory phase in a timely and orderly manner via apoptosis, after which they are recognized and cleared by macrophages, triggering the release of anti-inflammatory signals and terminating the inflammatory response (3). Conversely, if neutrophil death is excessive, such as through necroptosis, pyroptosis or NETosis, danger signals and pro-inflammatory factors will be released, leading to uncontrolled inflammation (4).

Traditionally, autophagy is considered a cellular 'scavenger' that maintains survival during nutrient deprivation by degrading cytoplasmic components in a non-selective manner. However, this function extends far beyond simple material recycling, as autophagy is also deeply involved in signal transduction and cell fate regulation. Contrary to this traditional view of indiscriminate degradation, autophagy can selectively eliminate ubiquitinated substrates through autophagy receptors. Specifically, selective autophagy recognizes ubiquitin signals on substrates via autophagy receptors such as p62/sequestosome-1 (SQSTM1) and nuclear dot protein 52 (NDP52), which then binds to light chain (LC)3 on the autophagosome membrane (5). Selective autophagy exerts diverse functions in governing cell fate: Mitophagy removes damaged mitochondria and regulates reactive oxygen species (ROS) levels, thereby determining cell survival or apoptosis (6); endoplasmic reticulum (ER)-phagy alleviates ER stress and maintains secretory homeostasis (7); and xenophagy removes invading pathogens, representing the first line of cellular autonomous immunity (8). Notably, autophagy also participates in non-degradative functions. In fibroblasts associated with head and neck squamous cell carcinoma, secretory autophagy mediated by tripartite motif-containing protein 16 releases cytokines such as IL-6 into the extracellular space, thereby promoting tumor progression (9). This secretory autophagy challenges the traditional view of autophagy merely as a lysosomal degradative process, revealing a novel role for autophagy in intercellular communication.

The development of molecular biology has gradually revealed that apoptosis, a non-inflammatory form of PCD mediated by the caspase family, plays a central role in the development and the maintenance of homeostasis. Its unique morphological features include cell shrinkage, nuclear pyknosis and apoptotic body formation. Subsequently, the discovery of necroptosis challenged the traditional view that necrosis is merely a passive form of cell death. Studies have confirmed that the cell death program executed by the receptor-interacting serine/threonine-protein kinase (RIPK)1, RIPK3, and mixed lineage kinase domain like pseudokinase (MLKL) signaling axis exhibits necrotic morphology but is precisely regulated. This process is characterized by plasma membrane disruption, leakage of intracellular contents and consequent induction of an inflammatory response (10). Pyroptosis is another form of regulated inflammatory cell death, initiated by inflammatory caspases (caspase-1/4/5/11)-mediated cleavage of gasdermin D. Its hallmarks include pore formation in the cell membrane, cell swelling and lysis, and secretion of inflammatory cytokines such as IL-1β and IL-18 (11).

As the understanding of PCD processes has deepened, PANoptosis integrates pyroptosis, apoptosis and necroptosis into a unified inflammatory cell death program. It coordinates diverse cell death pathways through the PANoptosome complex. In infections, cancer and cytokine storm syndrome, this program can not only serve as a powerful host defense mechanism but also become a driving force of pathological damage. Autophagy not only safeguards immune cell survival under stress conditions but is also essential for their differentiation and activation. Importantly, autophagy precisely determines whether immune cells commit to PANoptosis by eliminating danger signals and key protein complexes. The present review provides a systematic overview of the role of autophagy in immune cell survival, differentiation, development and metabolism. It aims to clarify the specific mechanisms through which autophagy functions as a core regulator of cell fate decisions, thereby supporting the development of improved therapeutic strategies for immune-mediated diseases.

2. Metabolic reprogramming during the activation of different immune cells

Immune cell activation involves complex metabolic reprogramming, a central tenet of immunometabolism. In the resting state, immune cells mainly depend on oxidative phosphorylation (OXPHOS) to produce ATP, thereby maintaining basal energy demands and cellular homeostasis. However, upon exposure to infectious or inflammatory stimuli, their metabolism shifts from OXPHOS to glycolysis, mirroring the Warburg effect (12).

T-cell receptor (TCR) stimulation can directly drive metabolic reprogramming. The traditional view holds that activated T cells shift away from OXPHOS toward glycolytic metabolism, which sustains their rapid proliferation and functional responses (13). However, recent evidence indicates that this model is overly simplistic. Activated T cells actually run two metabolic programs, glycolysis and OXPHOS, simultaneously, allocating distinct nutrients to specific anabolic and energetic demands (14). Following TCR activation, the PI3K/Akt/mTOR cascade induces Myc and hypoxia inducible factor (HIF)1α, which in turn prompts glucose transporter 1/solute carrier family 2 member 1 expression and facilitates glucose uptake (Fig. 1) (15). Concurrently, TCR signaling rapidly induces glycolysis via pyruvate dehydrogenase kinase 1 within minutes-a process that occurs independently of transcription and translation, yet directly supports cytokine synthesis (16). This metabolic remodeling provides biosynthetic precursors for T cells, underpinning the material demands required for their clonal expansion and acquisition of effector functions.

A study combining RNA sequencing and glucose isotope tracing confirmed that activation stimulation substantially upregulates OXPHOS, the tricarboxylic acid (TCA) cycle and nucleotide biosynthesis in B cells, but does not enhance

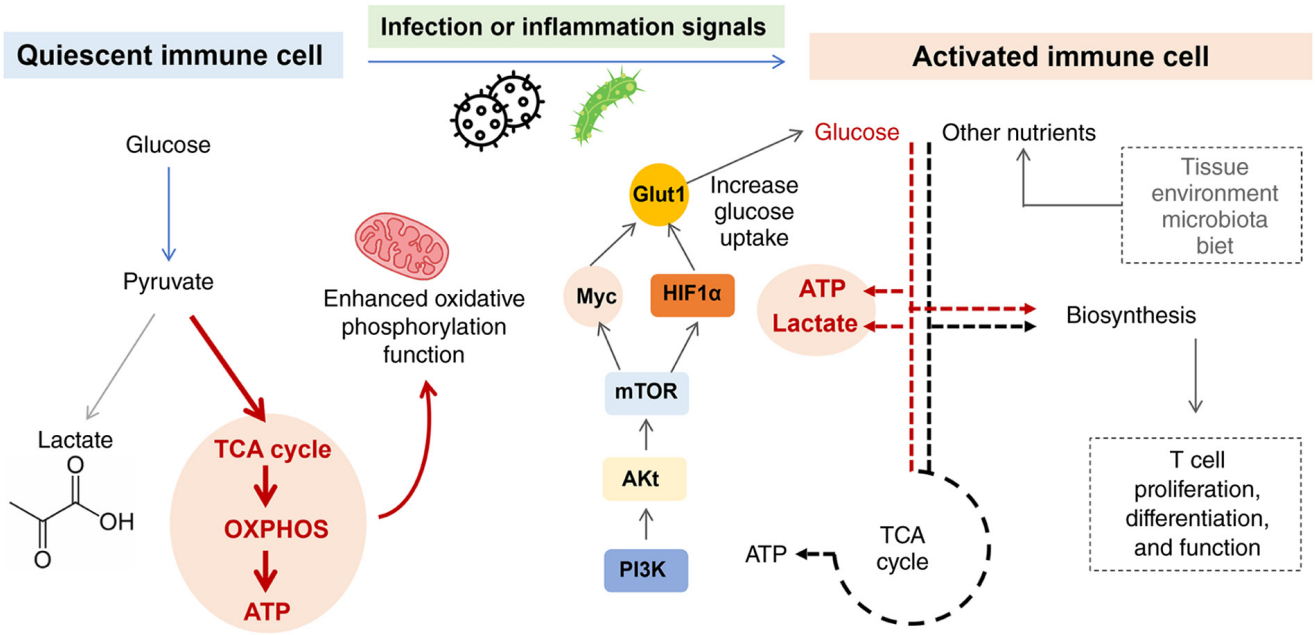

Figure 1. Metabolic reprogramming of T cells before and after activation. Quiescent T cells rely primarily on mitochondrial OXPHOS for energy supply; most glucose-derived pyruvate enters the TCA cycle to fuel OXPHOS for ATP production. Upon T-cell activation triggered by infection or inflammatory signals, the PI3K-Akt-mTOR signaling cascade upregulates Myc, HIF1α and Glut1 to boost glucose uptake. Cells then switch metabolism toward aerobic glycolysis, where the majority of pyruvate is converted into lactate. Glycolytic intermediates are diverted to biosynthetic pathways to support T-cell proliferation, differentiation and effector functions. TCA, tricarboxylic acid; HIF1α, hypoxia-inducible factor 1α; OXPHOS, oxidative phosphorylation; ATP, adenosine triphosphate; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; Myc, MYC proto-oncogene, bHLH transcription factor; Glut1, glucose transporter 1/solute carrier family 2 member 1.

the glycolytic flux (17). Metabolic regulation in B2 cells is primarily governed by the c-Myc and mTOR complex (mTORC) signaling pathways, with mTORC promoting protein synthesis and cell proliferation through glycolysis and OXPHOS (18). Resting naïve B cells maintain a hypometabolic homeostatic state that supports their long-term survival. These cells rely extensively on fatty acid oxidation for bioenergetic support, a metabolic pattern that is downregulated upon activation. B-cell receptor engagement mediates rapid glucose uptake via PI3K signaling (19). B-cell activation centers on the upregulation of mitochondrial metabolism, whereas glycolysis is not a key pathway for these cells. Glucose restriction does not impair B-cell physiological functions, whereas inhibition of OXPHOS or glutamine limitation markedly impairs B-cell growth and differentiation (17). Glutamine serves as the primary substrate for mitochondrial respiration after B-cell activation, with the AMPK signaling pathway maintaining mitochondrial respiratory function and homeostatic balance in activated B cells (17).

B cells exhibit remarkable metabolic heterogeneity across developmental stages, as summarized in Table I. Pre-B cells primarily rely on glycolysis, regulated by Fnip1, AMPK, and PI3K (20). B1a cells display a metabolically active phenotype engaging glycolysis, the pentose phosphate pathway, OXPHOS, and fatty acid metabolism, supported by Myc, perilipin-3, acetyl-CoA carboxylase 1, Acacb, Acsl1, Plin3, Srebp2, and Atg7 (21). Conventional B2 cells utilize both glycolysis and OXPHOS under the regulation of Myc and mTORC (18,22), whereas naïve B cells depend on glycolysis and fatty acid oxidation, driven by BCR, BAFF, PI3K and IL-4 (19,23). Germinal center B cells are highly glycolytic, with upregulated glycolytic enzymes (GLUT1, HK1, PFKM, GAPDH, LDHB, PDH) and transcriptional regulation by Myc and HIF1α (24). Regulatory B cells also rely on glycolysis, modulated by vitamin D3, aryl hydrocarbon receptor, SCFA butyrate, HIF1α, STAT3 and valerate (25). In contrast, memory B cells preferentially utilize OXPHOS for long-term survival, regulated by Bach2, mTORC1 and AMPK (26,27).

The metabolic differences between resting and activated T cells vs. B cells reflect the molecular adaptations that distinct lymphocyte lineages have evolved to execute their unique immunological functions. T-cell metabolism is geared toward supporting migration, proliferation and cytotoxic effector functions, whereas B-cell metabolism is preferentially directed toward antigen recognition, processing and presentation, as well as fulfilling the high biosynthetic demands required for immunoglobulin production. These distinct metabolic programs are integral to their functional specialization.

3. Autophagy and PANoptosis: The regulatory boundary of inflammatory death

Autophagy as a brake on PANoptosis. Inflammatory cell death is a form of PCD governed by precise molecular mechanisms and characterized by a robust inflammatory response. Unlike the immunologically silent clearance mediated by classical apoptosis, inflammatory cell death releases large amounts of damage-associated molecular patterns (DAMPs) and pro-inflammatory cytokines via membrane pore formation or rupture, thereby triggering immune activation and subsequent immune cell recruitment (28). The major forms of inflammatory cell death currently recognized include pyroptosis,

Table I. Metabolic pathways and regulatory factors of different types of B cells.

B cells	Metabolic pathways	Regulatory factors	(Refs.)
Pre-B	Glycolysis	Fnip1, AMPK, PI3K	(20)
B1a	Glycolysis, pentose phosphate pathway, OXPHOS, fatty acid metabolism	Myc, Perilipin-3, acetyl-CoA carboxylase 1, Acacb, Acsl1, Plin3, Srebf2, Atg7	(21)
B2	Glycolysis, OXPHOS	Myc, mTORC	(18,22)
Naïve B	Glycolysis, fatty acid oxidation	BCR, BAFF, PI3K, IL-4	(19,23)
GC B	Glycolysis	GLUT1, HK1, PFKM, GAPDH, LDHB, PDH, Myc, HIF1α	(24)
Breg	Glycolysis	Vitamin D3, aryl hydrocarbon receptor, SCFA butyrate, HIF1α, STAT3, short-chain fatty acid valerate	(25)
Memory B	OXPHOS	Bach2, mTORC1, AMPK	(26,27)

Fnip1, folliculin-interacting protein 1; AMPK, adenosine 5'-monophosphate-activated protein kinase; PI3K, phosphoinositide 3-kinase; Myc, MYC proto-oncogene, bHLH transcription factor; Acacb, acetyl-CoA carboxylase β; Acsl1, acyl-CoA synthetase long-chain family member 1; Plin3, perilipin 3; Srebf2, sterol regulatory element-binding protein 2; Atg7, autophagy related 7; mTORC, mechanistic target of rapamycin complex; BCR, B-cell receptor; BAFF, B-cell activating factor; IL-4, interleukin 4; GLUT1, glucose transporter type 1; HK1, hexokinase 1; PFKM, phosphofructokinase, muscle; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; LDHB, lactate dehydrogenase B; PDH, pyruvate dehydrogenase; HIF1α, hypoxia-inducible factor 1α; SCFA, short-chain fatty acid; STAT3, signal transducer and activator of transcription 3; Bach2, BTB domain and CNC homolog 2; mTORC1, mechanistic target of rapamycin complex 1.

necroptosis and PANoptosis-the latter integrating features of both pyroptosis and necroptosis. These cell death modalities serve as a cornerstone of anti-infection immunity and tumor immune regulation; however, their excessive activation can also precipitate autoimmune diseases and pathological tissue damage. Autophagy counteracts the initiation and progression of inflammatory cell death by eliminating intracellular danger signals, thereby constituting an important negative regulatory mechanism. This regulation operates through two interrelated pathways: First, mitophagy removes damaged mitochondria, preventing the release of pro-inflammatory mediators; second, autophagy-receptor-mediated selective autophagy degrades ubiquitinated protein aggregates and components of inflammatory complexes, thereby blocking the activation of PANoptosis signaling (29).

Selective autophagic degradation of ubiquitinated substrates is mediated by autophagy receptors, such as p62/SQSTM1, NDP52 and optineurin, a process instrumental in preventing PANoptosis initiation. Among these, p62-a canonical autophagy receptor-contains both the LC3-interaction domain and the ubiquitin-binding domain, enabling it to recognize ubiquitinated protein aggregates and deliver them to autophagosomes for degradation (30). This process not only maintains protein homeostasis but also clears aberrant proteins associated with inflammatory signaling activation, thereby indirectly constraining excessive inflammatory responses. Autophagy can selectively degrade the activated NLR family pyrin domain containing 3 (NLRP3) inflammasome, thereby limiting caspase-1 activation and its mediated pyroptosis (31). NLRP3 inflammasome activity is negatively regulated by autophagy, which mediates its lysosomal delivery and degradation (32). Furthermore, mitophagy deficiency-induced mitochondrial dysfunction markedly facilitates NLRP3 inflammasome assembly and activation, whereas restoration of mitophagy effectively alleviates the inflammatory response *in vivo* (33).

Autophagy and PANoptosis are functionally interdependent, forming a bidirectional regulatory network that involves both promotion and counterbalance (Fig. 2). Recent evidence indicates that autophagy can curb the initiation of PANoptosis at its source by degrading core components of PANoptosome, such as absent in melanoma 2 (AIM2), Z-DNA binding protein 1 (ZBP1) and pyrin. As a key PANoptosome component, absent in AIM2 is subject to p62-mediated selective autophagy. p62 recognizes ubiquitinated AIM2 and restricts its interaction with apoptosis-associated speck-like protein containing a CARD (ASC), thereby inhibiting PANoptosome assembly and activation (29). Additionally, autophagy suppresses PANoptosome formation by regulating the degradation of necroptosis effector molecules RIPK1, RIPK3 and MLKL, further restraining the inflammatory death process (34). Notably, the NLRP3 inflammasome-a critical upstream activation complex of PANoptosis-can be targeted for degradation by selective autophagy after activation, forming a negative feedback loop that prevents inflammatory response (35). The mitochondrial-associated ER membrane (MAM) serves as an important signaling integration platform and is pivotal for NLRP3 inflammasome assembly. Translocation of NLRP3 from the ER to the mitochondria and the MAM is a prerequisite for its activation (34). Cardiolipin, a unique phospholipid of the inner mitochondrial membrane, is exposed to the outer mitochondrial membrane under mitochondrial stress. Through a specific binding interface, cardiolipin couples NLRP3 with pro-caspase-1, thereby orchestrating NLRP3 inflammasome assembly. Furthermore, mitochondrial antiviral signaling protein and mitofusin 2 can form a complex that recruits NLRP3 to mitochondria during RNA virus infection, accelerating inflammasome activation (36). Autophagy also attenuates caspase-8 activity, indirectly inhibiting apoptosis (37). Collectively, autophagy functions as a homeostatic safeguard that suppresses aberrant PANoptosis activation under physiological conditions-an intrinsic brake that maintains immune equilibrium.

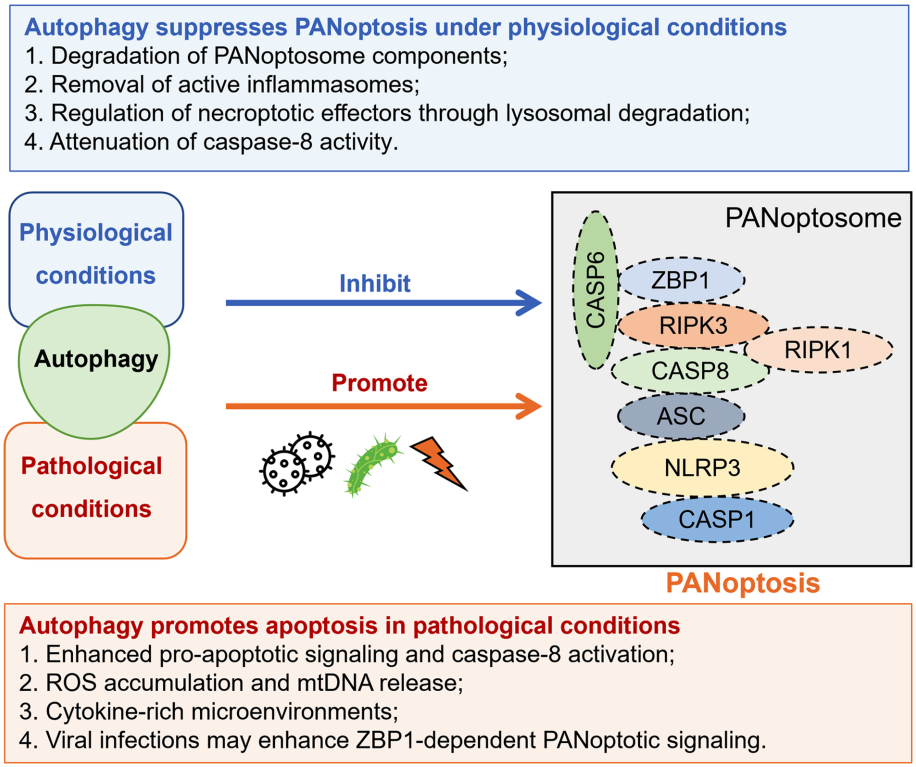

Figure 2. Role of autophagy in PANoptosis. Autophagy acts as the 'brake' for PANoptosis under physiological conditions; when autophagy function is insufficient or is pathologically over-activated, autophagy will shift the balance to the assembly of PANoptosome, triggering inflammatory cell death. ROS, reactive oxygen species; mtDNA, mitochondrial DNA; CASP1, caspase 1; ZBP1, Z-DNA binding protein 1; RIPK1, receptor interacting serine/threonine kinase 1; ASC, apoptosis-associated speck-like protein containing a CARD; NLRP3, NLR family pyrin domain containing 3.

In aged macrophages, mitophagy decline causes accumulation of damaged mitochondria and increased mitochondrial DNA (mtDNA) leakage, leading to persistent overactivation of the NLRP3 inflammasome and the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon response cGAMP interactor 1 (STING) pathway, ultimately disrupting inflammatory homeostasis (38). Autophagy indirectly inhibits PANoptosis by preserving mitochondrial functional integrity. In chondrocytes, sirtuin 3 restores mitochondrial function and suppresses excessive mitophagy, thereby blocking acidosis-induced PANoptosis (39). In a Parkinson's disease model, Parkin targets the NLRP3 inflammasomes for degradation via chaperone-mediated autophagy at the K353 site, effectively suppressing PANoptosis and protecting dopaminergic neurons (40). As a key upstream activator of PANoptosis, autophagic degradation of the NLRP3 inflammasomes potently blocks downstream inflammatory signaling cascades. Furthermore, ribophagy inhibits ZBP1-mediated PANoptosome formation by clearing damaged ribosomes, thereby alleviating PANoptosis in $CD4^+$ T lymphocytes during sepsis (41). Through clearing danger signals, degrading PANoptosome components and maintaining organelle homeostasis, autophagy acts as a negative regulator of PANoptosis across diverse physiological and pathological conditions, preserving immune homeostasis and preventing excessive inflammatory damage.

Interplay between autophagic cell death and PANoptosis. Autophagy plays a dual role in cell fate determination: On one hand, it acts as a core mechanism that maintains cellular homeostasis and ensures cell survival under stress conditions; on the other hand, under inflammatory or infectious conditions or upon dysregulation of autophagic flux, it can facilitate the propagation of PANoptotic signals by amplifying cellular stress responses and modulating cytokine secretion.

Deficiency of autophagy genes, lysosomal dysfunction or impaired autophagosome-lysosome fusion can all lead to abnormal accumulation of intracellular danger signals, thereby lowering the activation threshold of PANoptosis and creating favourable conditions for its initiation. Studies have shown that loss of autophagy-related genes such as autophagy-related 5 (ATG5), ATG7 or ATG16L1 triggers excessive inflammasome activation and aberrantly enhanced PANoptosis, accompanied by elevated release of pro-inflammatory cytokines including IL-1β and IL-18 (42-45). Mitophagy deficiency results in massive accumulation of damaged mitochondria, which subsequently releases mtDNA and mitochondrial ROS (mtROS), concurrently activating the NLRP3 inflammasome and the cGAS-STING pathway, and ultimately triggering PANoptotic inflammatory death (46,47). During viral infection, pathogens can exploit the autophagy pathway to enhance ZBP1-dependent PANoptotic signal transduction, accelerating the inflammatory death of host cells. Furthermore, autophagy dysfunction leads to substantially increased ZBP1 expression, which in turn potentiates PANoptosis sensitivity by activating RIPK3, caspase-8 and gasdermin D (GSDMD) (48,49).

Under certain stress conditions, autophagy can be aberrantly activated to excessive levels, leading to over-degradation of key organelles and metabolic enzymes, thereby triggering an energy crisis and metabolic collapse. When this 'self-digestion'

exceeds cellular tolerance, cells fail to maintain basic functions and may initiate inflammatory death programs, including PANoptosis. Shared regulatory molecules, including NLRP3, STING, RIPK, glutathione peroxidase 4 (GPX4) and nuclear receptor coactivator 4 (NCOA4), orchestrate a synergistic cell death network that connects autophagy-dependent ferroptosis and PANoptosis in myocardial and cerebral ischemia-reperfusion injury. These factors not only activate their respective pathways but also converge to drive PANoptosome assembly and consolidate death signals, thereby promoting signal propagation and cross-regulation (50). Induction of autophagy following ischemia-reperfusion aggravates oxidative injury and elicits marked ROS elevation. In parallel, ferritin is delivered to lysosomes via the autophagy adaptor NCOA4 for degradation, thereby releasing labile iron and precipitating autophagy-driven ferroptosis (51).

Persistent IFN signaling upregulates ZBP1 expression, whereas STING overactivation induces excessive autophagy, leading to massive autophagosome formation coupled with saturated lysosomal degradation capacity (52). This autophagic flux blockade shifts autophagy toward a pro-PANoptotic state through three mechanisms: i) Substantial accumulation of the autophagy substrate p62, which serves as a molecular scaffold that binds RIPK3 and caspase-8, stabilizing the PANoptosome complex; ii) direct binding of Beclin-1 to RIPK3, which enhances RHIM domain interactions and amplifies necroptotic signaling; and iii) release of cathepsins from damaged autolysosomes, which synergize with caspases to amplify pyroptotic and apoptotic signals. Together, these events establish an autophagy-PANoptosis positive feedback loop that drives extensive inflammatory cell death and a cytokine storm cascade (29).

Autophagy exhibits prominent cell-type specificity in regulating inflammatory cell death, with the autophagy-PANoptosis axis manifesting distinct patterns across diverse immune cells, including macrophages, dendritic cells (DCs), neutrophils and T cells. Macrophages represent the most extensively investigated cell type for this axis. In these cells, autophagy generally restrains PANoptosis through multiple mechanisms: i) Elimination of DAMPs and pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), mtROS and cytoplasmic DNA; ii) mitophagy curbs NLRP3 inflammasome activation through removing impaired mitochondria; iii) macroautophagy promotes the clearance of the NLRP3 inflammasome; and iv) suppression of the secretion of pro-inflammatory mediators such as IL-1β. Conversely, knockout of autophagy genes in macrophages triggers excessive inflammasome activation and PANoptosis, accompanied by elevated IL-1β and IL-18 levels. During influenza A virus infection, when autophagy fails to clear damaged organelles or viral components, macrophages assemble a ZBP1-NLRP3-caspase-8-RIPK3 complex to form the PANoptosome (29). In DCs, autophagy indirectly modulates susceptibility to PANoptosis by regulating Toll like receptor (TLR)-dependent priming and inflammasome activity. Notably, thyroid-resident DCs from patients with Hashimoto's thyroiditis exhibit concomitant activation of necroptosis, ferroptosis, pyroptosis, autophagy and PANoptosis, alongside differential expression of key PCD-related genes, including TNF-α-induced protein 3, cytochrome b-245 β chain, protein tyrosine phosphatase non-receptor type 6, signal transducer and enhancer of transcription (STAT)1, transforming growth factor β1 and NLRP3 (53). In neutrophils with high S100 calcium binding protein A8/A9 expression, nuclear respiratory factor 1 is downregulated, leading to repression of Nicotinamide Adenine Dinucleotide (NADH): ubiquinone oxidoreductase subunit A3-a component of mitochondrial complex I. This instigates mitochondrial dysfunction, characterized by hyper-fission and deficient mitophagy. Liberated mtDNA from compromised mitochondria ultimately drives ZBP1-mediated pan-pyroptosis in endothelial cells (54). In $CD4^+$ T lymphocytes during sepsis, nuclear FMR1 interacting protein 1 (NUFIP1)-dependent ribophagy eliminates damaged ribosomes through the cGAS-STING pathway and hinders ZBP1-driven PANoptosome assembly. Furthermore, mTOR depletion ameliorates pyroptosis in $CD4^+$ T cells from septic mice by boosting autophagic activity (55).

In summary, autophagy acts as a bidirectional regulator of PANoptosis. When autophagy effectively clears DAMPs and preserves mitochondrial homeostasis, it suppresses PANoptosis. Conversely, autophagy deficiency or pathological hyperactivation tilts the balance toward PANoptosome assembly, culminating in inflammatory cell death.

4. Interplay between autophagy, metabolic reprogramming and PANoptosis

Temporal and causal relationships among autophagy, metabolic reprogramming and PANoptosis. When immune cells encounter infection or inflammatory signals, they initially perceive shifts in metabolic status through energy sensors such as AMPK and mTOR. Under nutrient-sufficient conditions, mTORC1 is activated, which suppresses autophagy and promotes anabolic metabolism, thereby supporting cell proliferation and effector differentiation. Conversely, under nutrient deprivation or energy stress, AMPK becomes activated and phosphorylates unc-51 like autophagy activating kinase 1 (ULK1) to initiate autophagy (56). Upon initiation, autophagy eliminates damaged mitochondria via mitophagy, curbing mtROS and mtDNA release, while also degrading the NLRP3 inflammasomes and PANoptosome components through selective autophagy. This maintains inflammatory signals below the lethal threshold (57). At this stage, autophagy acts as a molecular brake to sustain cell survival and support the differentiation and effector functions of immune cells.

When inflammatory signals persist or exceed a critical threshold, autolysosomal function becomes saturated, resulting in autophagic flux blockade. Damaged mitochondria continuously release mtDNA, activating the cGAS-STING pathway and interferon signaling further upregulates ZBP1 expression. At this stage, autophagy transitions from a protective to a pro-death role: p62 accumulates extensively and serves as a molecular scaffold to stabilize the PANoptosome complex, whereas the autophagy protein Beclin-1 directly binds RIPK3 to enhance RHIM domain interactions, ultimately triggering the coordinated activation of pyroptosis, apoptosis and necroptosis (51). Following cell lysis, PANoptotic cells release large amounts of DAMPs and pro-inflammatory cytokines, which further activate neighboring immune cells and amplify inflammatory signals. This positive feedback loop sustains

and escalates inflammation, eventually leading to tissue destruction and systemic organ dysfunction.

Immune cells undergo profound metabolic reprogramming during activation, differentiation and execution of effector functions. T cells shift from OXPHOS dependence in the resting state to glycolysis dependence upon activation, while macrophages switch their metabolic profiles between M1 and M2 polarization (58). This metabolic plasticity far exceeds that of most non-immune cells, rendering autophagy regulation in immune cells more dynamic and precise.

Immune cells, ordinary somatic cells and tumor cells exhibit fundamentally distinct metabolic plasticity, reflecting their divergent biological objectives and survival strategies (Table II). Immune cells dynamically reprogram their metabolism in response to external signals (antigens, cytokines and microenvironmental cues), enabling reversible switching among resting, effector and memory states to support specific immune functions such as killing and cytokine secretion (59). By contrast, ordinary somatic cells maintain relatively stable metabolism to preserve homeostasis, with limited plasticity driven by systemic hormonal and nutritional changes, allowing only slow transitions between quiescence and proliferation. Tumor cells, however, adopt a 'selfish' metabolic reprogramming, driven by genetic mutations and microenvironmental stresses (hypoxia, acidosis), which unidirectionally locks them into the Warburg effect-aerobic glycolysis-to support unlimited proliferation and survival (60).

The coupling of autophagy with programmed cell death in immune cells exhibits high cell-type specificity. Autophagy exerts a dual influence on necroptosis, ferroptosis and pyroptosis. On the protective side, it eliminates RIPK proteins or the necrosome to prevent cell death; conversely, by targeting cellular inhibitor of apoptosis proteins (cIAPs) for degradation, it may potentiate necroptotic signaling (61). Autophagy-mediated cell death involves interaction between the autophagic machinery and other cell death molecules; alternatively, autophagy can directly activate apoptosis, ferroptosis or necroptosis to promote cell death. Recent studies have proposed that immune cells harbor a 'master molecular timer' composed of the ubiquitin-proteasome system, autophagy and translational control, which licenses or restricts the occurrence of pyroptosis, apoptosis, necroptosis and PANoptosis. Post-translational modifications provide a decisional framework that is co-opted by bacterial pathogens and viruses through effector deployment, enabling threshold modulation via host shutoff, ubiquitin/ISG15 ubiquitin like modifier editing and autophagy subversion. This dynamic proteostasis competition mechanism is particularly prominent in immune cells (62).

Metabolic reprogramming regulates autophagic-dependent cell death. When immune cells operate under nutrient-sufficient conditions with normal mitochondrial function, basal autophagy maintains cellular homeostasis through mitochondrial quality control, protecting cells from stress-induced damage. However, when metabolic reprogramming leads to mitochondrial dysfunction-such as enhanced glycolysis accompanied by impaired OXPHOS-damaged mitochondria release mtDNA and ROS. These danger signals not only activate the NLRP3 inflammasome and the cGAS-STING pathways, but also further disrupt autophagic flux via feedback loops, converting autophagy from a protector to a promoter of cell death. Meanwhile, autophagy deficiency (e.g., ATG5 deletion) impairs mitophagy, exacerbates mitochondrial damage and enhances GSDMD-mediated pore formation, promoting extracellular release of mtDNA, which in turn activates the cGAS-STING-NLRP3 signaling axis in macrophages (63). In myocardial and cerebral ischemia-reperfusion injury, autophagy-coupled ferroptosis and PANoptosis converge into a complex cell death circuitry governed by shared regulators, including NLRP3, STING, RIPK, GPX4 and NCOA4 (50).

TCA cycle intermediates such as succinate and itaconate not only function as energy metabolites but also act as signaling molecules that regulate inflammasome activation and cell death. Succinate primarily acts by inhibiting prolyl hydroxylases, thereby stabilizing HIF-1α, which in turn induces glycolysis and production of the pro-inflammatory cytokine IL-1β. Succinate accumulation also affects immune cells within the tumor microenvironment, participating in lymphocyte-mediated immunity and cytokine production. Furthermore, succinyl-CoA can modify key metabolic enzymes such as PKM2 through succinylation, enhancing HIF-1α activity and further promoting IL-1β production (64). Itaconate inhibits the NLRP3 inflammasome through multiple mechanisms: i) Alkylating cysteine residues of kelch-like ECH-associated protein 1 to activate the NRF2 antioxidant pathway; ii) inhibiting succinate dehydrogenase to reduce mtROS production; and iii) limiting oxidative stress and glycolytic flux. The itaconate derivative dimethyl itaconate inhibits LPS-induced NLRP3-dependent pyroptosis by inducing autophagy and regulating the Nrf2/heme oxygenase-1 signaling pathway (65). Another derivative, 4-octyl itaconate, enhances autophagy by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby protecting chondrocytes from IL-1β-induced inflammatory degradation and apoptosis (66). Changes in the concentrations of these metabolites directly influence autophagic flux and the threshold for PANoptosome assembly.

Mild metabolic stress induces adaptive autophagy that protects cell survival. However, under sustained or severe metabolic stress-such as in the tumor microenvironment or during chronic infection-autophagic function may become suppressed or overloaded. This leads to failure of mitochondrial quality control and continuous accumulation of danger signals, ultimately breaching the threshold for PANoptosis. Autophagy dictates the fate of $CD8^+$ T-cell progeny through asymmetric mitochondrial partitioning. Daughter cells that inherit aged mitochondria exhibit impaired memory potential, while those without aged mitochondria persist longer and mount robust expansion (67). These findings suggest that enhancing autophagy before or during T-cell division may promote the generation of daughter cells that avoid inheriting aged mitochondria, thereby augmenting the production of memory T cells-the cornerstone of long-term immunity and vaccine efficacy. This provides a novel framework for modulating autophagy to 'rejuvenate' memory T cells, with potential to improve vaccine responses and cancer immunotherapy.

Metabolic checkpoints that determine the survival and death of immune cells. Liver kinase B1 (LKB1) is a critical metabolic

Table II. Differences in metabolic plasticity between immune cells and other cells (59,60).

Item	Immune cells	Ordinary somatic cells	Tumor cells
Core objective	Carrying out specific immune functions (such as killing, secreting cytokines)	Maintenance of its own homeostasis and specific physiological functions. Metabolism is relatively stable.	Unlimited proliferation and survival. Metabolic reprogramming is 'selfish' and aims to hijack resources.
Plasticity driving factors	External signals (antigens, cytokines, microenvironment). The metabolic state is a reflection and driver of the functional state.	Systemic regulation such as hormones and nutritional status. The changes are relatively slow.	Genetic mutations and microenvironmental stress (such as hypoxia, acidosis).
Reprogramming direction	Dynamic and reversible switching among various functional states, such as from rest to effect, and then to memory.	Switching between different physiological states (such as rest and proliferation); the plasticity is limited.	Unidirectional locking occurs in the metabolic pattern that supports unlimited proliferation (the Warburg effect).
Adaptation to the environment method	Active integration of environmental signals (such as nutrients and oxygen) to adjust functions and being able to utilize the locally available fuels.	Passive adaptation to environmental changes in order to maintain survival.	Active modification of the microenvironment (such as producing lactic acid) to facilitate its own survival.

checkpoint in natural killer (NK) cells. LKB1 deficiency leads to mitochondrial dysfunction and impaired autophagic flux, triggering ROS-dependent cell death. LKB1 ablation also perturbs iron homeostasis, provoking iron deposition and cytotoxic lipid ROS production. Notably, these phenotypic changes are refractory to both AMPK agonism and mTORC1 antagonism, positioning LKB1 as a metabolic rheostat that operates independently of the canonical AMPK-mTOR circuitry. Furthermore, LKB1 deficiency upregulates programmed cell death-1 and T-cell immunoreceptor with Ig and ITIM domains expression, further compromising NK-cell immunosurveillance (68).

AMPK and mTOR are core metabolic checkpoints that respond to cellular energy and nutrient status. AMPK is activated under energy stress, promoting catabolism and autophagy, whereas mTOR is activated under nutrient-sufficient conditions, suppressing autophagy and promoting anabolism. The balance between these two kinases governs the direction and intensity of autophagic flux. The generation and maintenance of memory T cells are profoundly influenced by AMPKα1, which regulates autophagy and mitochondrial respiration-associated gene expression. Additionally, T-cell memory is sustained by low-grade IL-15/mTORC1 signals that activate the AMPKα1-ULK1-ATG7 metabolic axis (69). AMPKα1 stimulates mitochondrial biogenesis and fatty acid oxidation to support memory T-cell differentiation. Conversely, AMPKα1 deficiency abrogates these downstream responses, resulting in upregulation of mTORC1 and HIF-1α, which shifts metabolism from fatty acid oxidation toward glycolysis and reduces cell survival (70). When the AMPK-mTOR balance is disrupted-for example, by mTOR hyperactivation-autophagy is suppressed, damaged mitochondria accumulate and danger signals build up, rendering cells more susceptible to PANoptosis (59).

Mitochondrial health status constitutes a critical 'structural' metabolic checkpoint. When mitophagy efficiency is insufficient to clear damaged mitochondria, mtDNA leakage and excessive ROS production activate the NLRP3 inflammasome and the cGAS-STING pathways. The outcome of this checkpoint-'pass' or 'fail'-directly determines whether cells maintain homeostasis or proceed toward inflammatory cell death. In B cells, FIP200 governs cell fate by controlling mitophagy and metabolic reprogramming (71). In $CD8^+$ T cells, autophagy-regulated asymmetric mitochondrial inheritance dictates the fate divergence of daughter cells (67). Lipid metabolism represents another important metabolic checkpoint. Lipophagy, the selective autophagy of lipid droplets, modulates immune cell function and inflammatory responses by degrading these droplets. In the pancreatic cancer microenvironment, the ubiquitin-specific peptidase 20 (USP20)-regulated metabolic-autophagy axis directly drives $CD8^+$ T-cell exhaustion via cholesterol metabolic control (72). Thus, disrupting this USP20-cholesterol-autophagy circuit constitutes a rational strategy to reinvigorate antitumor immunity and enhance the efficacy of KRASG12D inhibitor therapy in pancreatic ductal adenocarcinoma.

Molecular switch connecting metabolism, autophagy and inflammatory death. The AMPK-mTOR pathway serves as the core hub linking cellular energy metabolism and autophagy. Dysregulation of this pathway, such as mTOR hyperactivation, leads to autophagy suppression, metabolic disruption

and a lowered threshold for PANoptosis. The underlying mechanisms include the following: i) Autophagy suppression and danger signal accumulation are driven by the following mechanisms: mTORC1 hyperactivation directly inhibits autophagy, preventing clearance of damaged mitochondria and protein aggregates; accumulation of these substrates triggers release of danger signals such as mtDNA and ROS; ii) activation of inflammatory pathways: Accumulated danger signals (e.g., mtDNA and ROS) activate the NLRP3 inflammasome and the cGAS-STING pathway; and iii) lowered PANoptosis threshold: Persistent inflammatory signals render cells more susceptible to PANoptosis, ultimately leading to inflammatory cell death (73). In autoimmune diseases such as systemic lupus erythematosus (SLE), mTORC1 hyperactivation is a key mechanism underlying T and B lymphocyte dysfunction. In SLE, T cells exhibit aberrant metabolic reprogramming. Activation of AMPK along with concomitant inhibition of mTOR signaling can effectively suppress glycolysis, restore the type 17 T-helper cell/regulatory T cell (Treg) balance, and thereby alleviate SLE symptoms (74). Aberrant activation of the AMPK-mTOR-STAT3 axis is associated with B-cell commitment to plasma cells and germinal center B cells, which in turn triggers autoantibody production. Pharmacological activation of AMPK, for instance with metformin, can inhibit this pathway, reduce B-cell differentiation and exert therapeutic benefits (75).

The cGAS-STING pathway represents a critical molecular connection between mitochondrial damage and inflammatory cell death. When mitophagy deficiency leads to mtDNA leakage into the cytosol, cGAS recognizes mtDNA and catalyzes cGAMP production, which activates STING and subsequently induces type I interferons and pro-inflammatory cytokines. Excessive STING activation further induces hyperautophagy, establishing a positive feedback loop. The cGAS-STING axis is also activated by sepsis-induced ribosome collision, which facilitates the recruitment of NUFIP1 to the STING complex. NUFIP1-mediated ribophagy clears damaged ribosomes, thereby inhibiting ZBP1-driven PANoptosome formation and alleviating PANoptosis in $CD4^+$ T lymphocytes (41). Blocking the cGAS pathway or deleting STING exerts protective effects, including suppression of PANoptosis and mitigation of subsequent pathological damage (52). At the metabolic level, STING hyperactivation induces excessive autophagy, while autophagic flux blockade further exacerbates mitochondrial damage and mtDNA release, forming a STING-autophagy-metabolism positive feedback amplification loop. Furthermore, ER cholesterol levels regulate ER-phagy and STING innate immunity through the complex comprising SREBF chaperone (SCAP) and reticulophagy regulator 1 (RETREG1) (76). Collectively, these findings establish the cGAS-STING pathway as a key molecular bridge connecting metabolism, autophagy and PANoptosis.

The ZBP1-RIPK3-caspase-8 axis serves as the core molecular switch for PANoptosome assembly and execution of inflammatory cell death. As a nucleic acid sensor, ZBP1 recruits RIPK3 and caspase-8 via its RHIM domain upon recognition of Z-form nucleic acids, thereby assembling the PANoptosome. Autophagy tightly regulates this axis by clearing mitochondrial DAMPs and cytosolic nucleic acids, thereby limiting ZBP1 activation. When autophagic function is impaired, ZBP1 expression is amplified and the threshold for PANoptosome assembly is lowered (77). In sepsis, ZBP1 promotes mitochondrial damage and glycolysis, thereby driving macrophage polarization toward a pro-inflammatory phenotype and enhancing NLRP3 inflammasome-mediated pyroptosis. ZBP1 knockout alleviates mitochondrial damage and suppresses glycolysis, shifting macrophage metabolism away from the pro-inflammatory state (78). In rheumatoid arthritis (RA), RIPK3 promotes the migration and invasion of fibroblast-like synoviocytes through malate shuttle-driven mitochondrial respiration (79). Thus, the ZBP1-RIPK3-caspase-8 axis not only serves as the core molecular switch for PANoptosome assembly and inflammatory death execution, but also functions as a critical node that integrates metabolic signals with cell fate determination. The crosstalk among autophagy, metabolic reprogramming and PANoptosis is illustrated in Fig. 3, which provides a framework for exploring the involvement of this axis in disease contexts.

5. Autophagy supports the metabolic reprogramming and survival of immune cells

Autophagy regulates the metabolic reprogramming and survival of T cells. Autophagy is a key regulator of T-cell survival, maintaining mitochondrial homeostasis and limiting accumulation of cytotoxic ROS. After specifically knocking out Atg3 in T cells, progressive expansion of mitochondria and ER occurs, and cell death is triggered within several weeks. This indicates that autophagy sustains T-cell longevity by modulating organellar balance (80). Upon TCR activation, T cells transition from a resting state to an activated stage and initiate a synthetic metabolic program, manifested as accelerated proliferation, increased mitochondrial biosynthesis and enhanced bioenergetic support for effector functions. During this process, PI3K-AKT-mTORC signaling drives metabolic rewiring in T cells, characterized by a core shift from fatty acid and pyruvate oxidation toward glycolysis and glutamine utilization, with concomitant generation of anabolic substrates, including nucleotides, amino acids and fatty acids (Fig. 4A) (81). T-cell functional specification is tightly coupled to glucose uptake and the ensuing metabolic rewiring is pivotal for orchestrating lineage polarization. The present review summarizes the energy metabolic pathways of T cells in distinct states (Fig. 4B).

After T-cell activation, autophagic activity increases substantially, as evidenced by rapid upregulation of LC3 synthesis accompanied by an accelerated degradation rate. This process is regulated at the post-transcriptional level (82) and is essential for accommodating the elevated bioenergetic demands of activated T cells (Fig. 4C). Loss of autophagy genes markedly impairs T-cell expansion and viability. Autophagy deficiency, whether induced by transplantation of autophagy-deficient fetal liver hematopoietic progenitor cells into lethally irradiated wild-type syngeneic recipient mice or by conditional knockout of autophagy-related genes in T cells, leads to severe disruption of T-cell homeostasis (83). Furthermore, autophagy selectively degrades the Bcl10 protein, thereby modulating the intensity of TCR-mediated NF-κB signaling and preventing excessive signal activation that would otherwise drive senescence. This mechanism

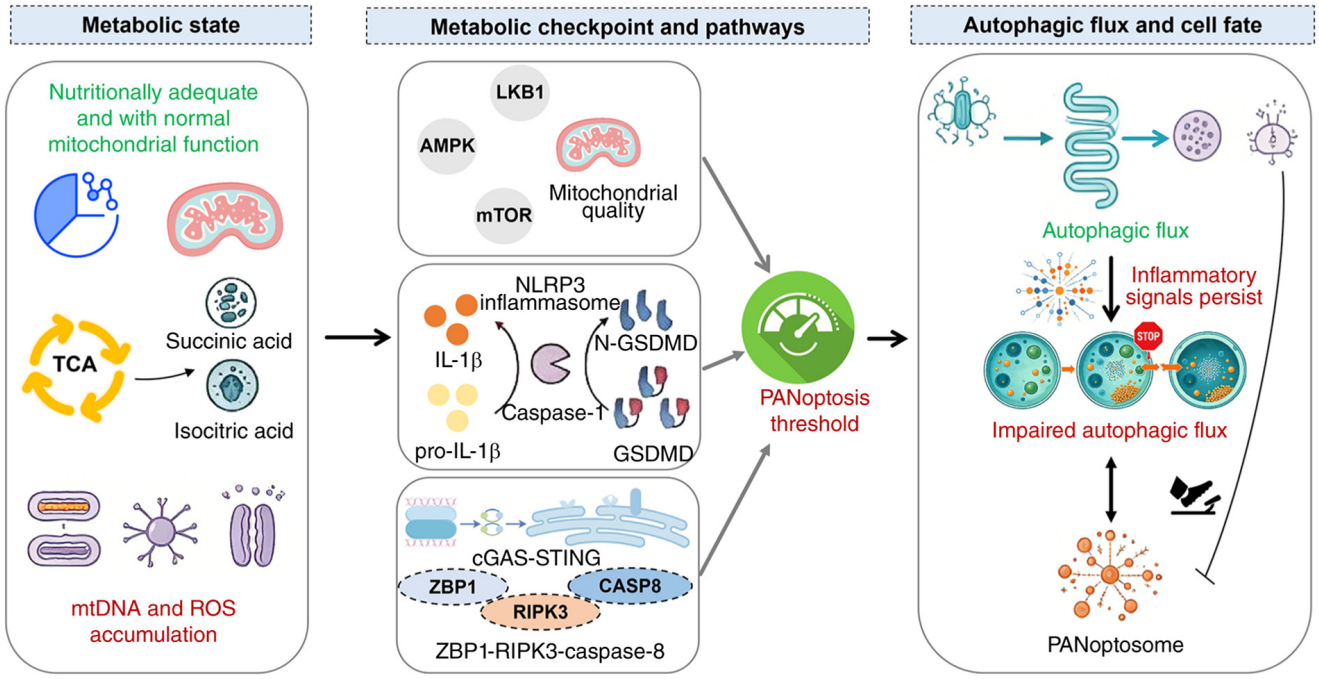

Figure 3. Metabolic status, metabolic checkpoints and associated pathways cooperatively regulate the activation threshold of PANoptosis. Cells shift from a nutritionally sufficient state with intact mitochondrial function to a state characterized by accumulation of succinic acid and isocitric acid, as well as extensive release of mtDNA and ROS. This metabolic transition modulates the activation of metabolic checkpoints and relevant signaling pathways, thus determining the threshold for PANoptosis induction. Persistent inflammatory signals block autophagic flux and defective autophagy further facilitates PANoptosome assembly, ultimately initiating PANoptosis. ROS, reactive oxygen species; mtDNA, mitochondrial DNA; TCA, tricarboxylic acid; LKB1, serine/threonine kinase 11; AMPK, adenosine 5'-monophosphate-activated protein kinase; mTOR, mechanistic target of rapamycin; NLRP3, NLR family pyrin domain containing 3; IL-1β, interleukin-1β; N-GSDMD, gasdermin D, N-terminal; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon response cGAMP interactor 1; CASP8, caspase 8; ZBP1, Z-DNA binding protein 1; RIPK3, receptor interacting serine/threonine kinase 3.

is crucial for the generation of $CD8^+$ memory T cells (84). Failure of T cells to adequately upregulate their metabolic rate results in immunosuppressive consequences, including reduced immune function, diminished cytokine secretion and impaired proliferation.

Autophagy-related genes play critical and diverse roles in modulating T-cell function, with their dysregulation being implicated in a wide spectrum of autoimmune, inflammatory and neurodegenerative diseases (Table III). Vacuolar protein sorting-associated protein 34 is essential for maintaining peripheral CD4+forkhead box P3+ Treg cells, and its T cell-specific deletion leads to intestinal inflammation and anemia (85). Similarly, phosphatidylinositol 3-kinase catalytic subunit type 3 regulates T-cell activation and promotes CD4+ T-cell differentiation into Th1 cells; its deficiency impairs cellular metabolism and Th1 differentiation, contributing to autoimmune diseases such as experimental autoimmune encephalomyelitis (86). Atg5 influences Th2 cell and cytokine levels, with polymorphisms linked to asthma, SLE and RA (87-90). Atg7 is crucial for CD8+ T-cell survival and memory formation, and its deficiency reduces CD4+ and CD8+ T-cell numbers while impairing secondary immune responses and atherosclerosis development (91,92). Atg16L1 regulates caspase-3 cleavage and Th2 responses while limiting Treg cell expansion in the intestine; its T cell-specific deletion triggers spontaneous intestinal inflammation and is associated with Crohn's disease and inflammatory bowel disease (93,94). Immunity-related GTPase family M member 1 (IRGM1), an IFN-γ-inducible GTPase, affects CD4+ T-cell survival and proliferation, and its human homolog IRGM is strongly linked to Crohn's disease (95). LC3-mediated endocytosis promotes β-amyloid clearance and alleviates neurodegeneration in Alzheimer's disease (96). Beclin-1 deficiency increases the expression of the pro-apoptotic protein Bim in Th1 cells, affecting T-cell survival and contributing to multiple sclerosis (97). Finally, C-type lectin domain containing 16A (CLEC16A) deficiency in thymic epithelial cells impairs autophagosome maturation and alters T-cell selection, leading to the generation of self-reactive lymphocytes associated with multiple sclerosis, SLE, rheumatoid arthritis, Crohn's disease and type 1 diabetes (98).

Autophagy regulates metabolic reprogramming and survival of B cells. The metabolic development and functional execution of B cells also depend on precise regulation by the autophagic pathway. During early B-cell development in the bone marrow, autophagy promotes the transition from progenitor B cells to pre-B lymphocytes. Fetal liver progenitor cells lacking Atg5 exhibit a notable developmental block at the pro-B to pre-B transition stage, with only a small number of pre-B cells surviving and entering peripheral lymphoid organs (99). In addition, phosphatase and tensin homolog serves as a key regulator of progenitor B-cell development, reducing their sensitivity to apoptosis (100). Autophagy also exerts specific regulatory functions in B1 cell subsets within mucosal-associated lymphoid tissues such as the peritoneal cavity. Loss of autophagic flux in mature B cells substantially reduces B1a cell counts but exerts minimal impact on B1b

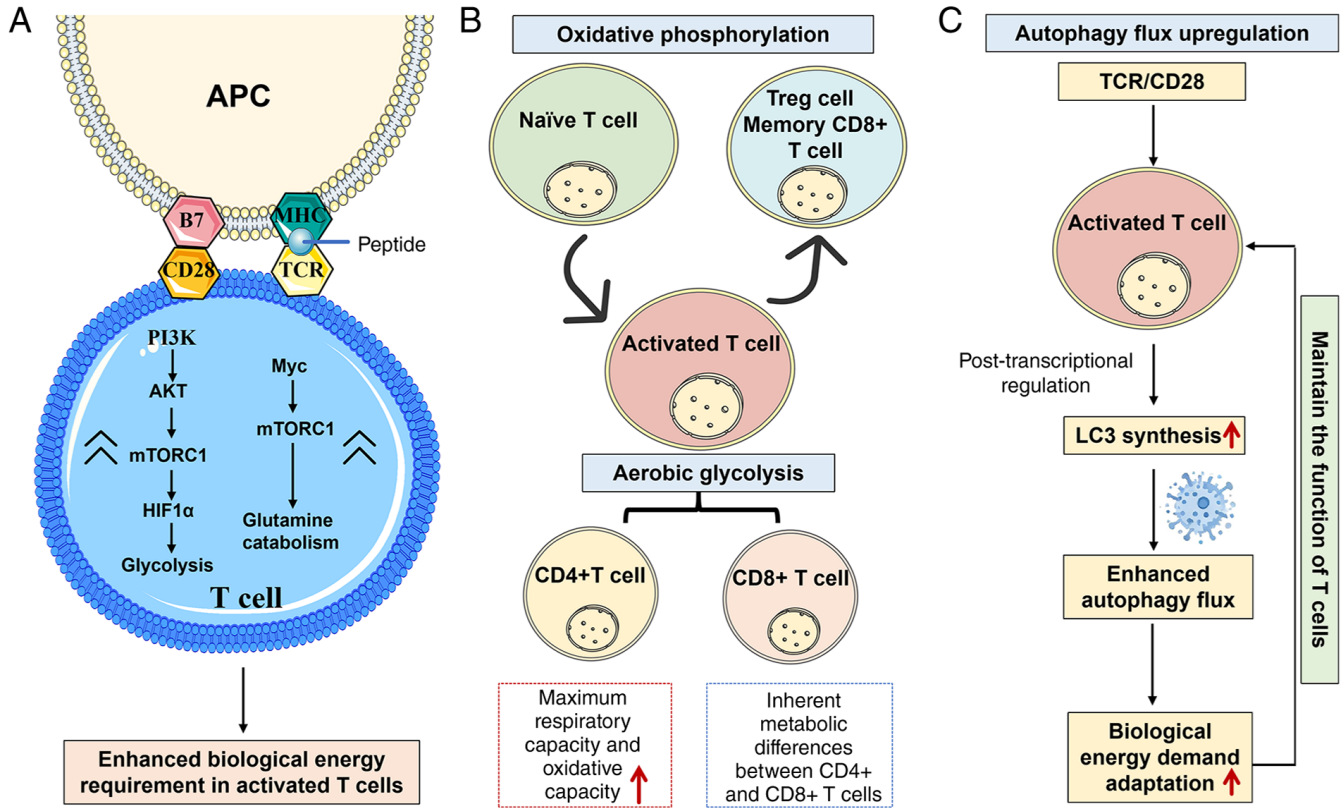

Figure 4. Differences in metabolic pathways utilized by T cells at different stages. (A) Metabolic pathways utilized by activated T cells. (B) Energy sources utilized by different types of T cells. (C) Upregulated autophagy flux upon T-cell activation. APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T cell receptor; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; mTORC1, mechanistic target of rapamycin complex 1; HIF1α, hypoxia-inducible factor 1α; Myc, MYC proto-oncogene, bHLH transcription factor; Treg cell, T-regulatory cell.

populations (99). Furthermore, early B1 progenitor development remains intact in autophagy-deficient mice, indicating that autophagy is not a prerequisite for B1-cell differentiation. These findings suggest a selective requirement for autophagy in peripheral self-renewal rather than in B1a cell differentiation. The role of autophagy in B2 cell development has also been investigated (101). Transplanting of Atg5-deficient fetal liver cells into recombination activating $1^{-/-}$ mice causes B-cell development to arrest at the pre-B stage. By contrast, specific knockout of Atg5 in mature B cells does not affect B-cell numbers in the spleen or lymph nodes. These observations indicate that autophagy is essential for early B2-cell development but dispensable for maintaining peripheral homeostasis of mature B2 cells (99).

In B cells that have matured and settled in peripheral lymphoid organs, autophagy orchestrates multiple aspects of plasma cell biology, including differentiation, antibody secretory capacity and long-term survival (Fig. 5). Loss of Atg5 leads to excessive ER expansion and heightened ER stress in differentiating plasma cells. Although PR/SET domain 1 expression and immunoglobulin secretion increase through a compensatory mechanism, intracellular ATP levels substantially decrease and cell death rises, suggesting that autophagy sustains plasma cell homeostasis via protective mechanisms (102). During influenza virus infection, memory B-cell generation does not rely on autophagy, whereas their persistence does. Loss of Atg7 causes abnormal accumulation of mitochondrial ROS, which drives progressive loss of memory B cells and ultimately impairs the establishment of effective antiviral immune memory and protective responses (103). Notably, during murine gammaherpesvirus 68 infection, germinal center B cells (GCB) exhibit the highest autophagy level among all B-cell populations, and high LC3-II expression correlates positively with enhanced autophagic flux. Further studies have confirmed that autophagy in GCB cells does not rely on the canonical mTORC1-mediated pathway but instead proceeds via non-canonical autophagy (104). B-cell receptor activation transiently inhibits canonical autophagy while initiating non-canonical autophagy. Conditional knockout of WD repeat domain phosphoinositide-interacting protein 2 (WIPI2) in B cells further enhances non-canonical autophagy, leading to mitochondrial homeostasis disruption, aberrant germinal center responses and altered antibody secretion (104). These findings suggest that B cells harbor a form of unconventional autophagy that is independent of ATG16L1 but dependent on WIPI2, which participates in regulating B-cell fate and function.

6. Involvement of the autophagy-PANoptosis axis in autoimmune disorders

Autoimmune diseases comprise a spectrum of disorders characterized by immune dysregulation, chronic inflammation and tissue damage, with pathogenesis involving aberrant innate immune sensing, cytokine imbalance and breakdown of immune tolerance. RA and SLE have been linked to the autophagy-PANoptosis axis.

Table III. Autophagy genes that affect T-cell function and association with disease.

Gene name	Function	Diseases or related symptoms	(Refs.)
Vps34	Maintenance of the function of CD4+FoxP3+ regulatory T cells at the periphery; influence on the development of NK T cells in the thymus.	Intestinal inflammation; anemia	(85)
Pik3c3	Regulation of the activation of T cells; promotion of the differentiation of CD4+ T cells into Th1 cells.	Autoimmune diseases	(86)
Atg5	Influence on the levels of Th2 cells and cytokines; reduction of autophagy and causing of ataxia.	Asthma, systemic lupus erythematosus, rheumatoid arthritis, ataxia	(87-90)
Atg7	Affecting the survival of CD8+ T cells and their differentiation into memory T cells; affecting the quantities of CD4+ T cells, CD8+ T cells and NK T cells, thereby reducing the occurrence of atherosclerosis.	The secondary immune response is reduced; atherosclerosis and hepatic steatosis	(91,92)
Atg16L1	Regulation of the cleavage of caspase-3, reduction of autophagy, inhibition of bacterial clearance and increase of the production of pro-inflammatory cytokines; regulation of the Th2 response and the number of Treg cells in the intestine.	Crohn's disease; inflammatory bowel disease	(93,94)
IRGM1	By regulating IFN-γ, the survival of CD4+ T cells and their proliferation in the peripheral circulation pool can be affected.	Crohn's disease	(95)
LC3	The LC3-mediated endocytosis promotes the clearance of β-amyloid protein and alleviates neurodegeneration in mice with Alzheimer's disease.	Alzheimer's disease	(96)
Beclin-1	The absence of Beclin-1 increases the expression of death proteins in Th1 cells, and affects the deletion of the Bim anti-apoptotic gene and the inhibition of caspases.	Multiple sclerosis	(97)
CLEC16A	The absence of CLEC16A in thymic epithelial cells inhibits the maturation of autophagosomes and alters the selection of T cells, resulting in the generation of self-reactive lymphocytes.	Multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, type 1 diabetes	(98)

NK, natural killer; Th1 cell, type 1 T-helper cell; Treg cell, regulatory T cell; Vps34, vacuolar protein sorting-associated protein 34 (the yeast homolog of mammalian Pik3c3); Pik3c3, phosphatidylinositol 3-kinase catalytic subunit type 3; Atg5, autophagy related 5; Atg16L1, autophagy related 16 like 1; IRGM1, immunity-related GTPase family M member 1; LC3, microtubule-associated protein 1A/1B light chain 3; IFN-γ, interferon γ; Bim, Bcl-2 interacting mediator of cell death; CLEC16A, C-type lectin domain containing 16A.

The autophagy-PANoptosis axis is critically involved in the pathogenesis of SLE and RA, with distinct gene signatures identified for each disease (Table IV). In SLE, five PANoptosis-related genes-ZBP1, MEFV, LCN2, IFI27 and HSP90AB1-have been identified as key dysregulated genes, while multiple autophagy-related susceptibility loci, including ATG5, ATG16L2, CDKN1B, DRAM1, CLEC16A, S100A8, MyD88, NCR3, DDIT3, GNB2L1, CTSD, HSPA8, ULK1, DNAJB1 and CANX, have been linked to disease risk (105-108). In RA, the PANoptosis-associated gene SPP1 serves as a biomarker to distinguish disease subtypes. Additionally, GWAS and Mendelian randomization studies have identified ATG16L1, ATG16L2, BCL2L1, RAF1 and MAPK3 as autophagy-related risk loci, with BCL2L1 and RAF1 showing causal relationships with RA risk (109,110).

SLE. SLE is a heterogeneous autoimmune disease characterized by breakdown of self-tolerance mechanisms. Its pathological process involves abnormal autoantibody production, excessive immune activation and immune complex deposition and damage in multiple tissues and organs. The pathogenesis of SLE arises from interactions among genetic, sex-related and environmental determinants. Among these, type I and type II IFN signaling pathways play a central regulatory role in disease development. Plasmacytoid DCs are the main source of type I IFN and a key driver of chronic inflammation, whereas macrophages and fibroblasts primarily produce IFN-β (111,112). Type II IFN also exerts a notable impact on SLE pathology. IFN-γ and IFN regulatory factor 1 expression is significantly elevated in peripheral blood mononuclear cells (PBMCs) from patients with SLE compared with healthy controls. Importantly, IFN-γ accumulation is already detectable at early disease stages, preceding autoantibody production or type I IFN responses (113). Sustained IFN production further amplifies the immune inflammatory cascade: It promotes immune cell proliferation and differentiation, while also accelerating immune complex formation and substantially increasing the risk of complications such as lupus

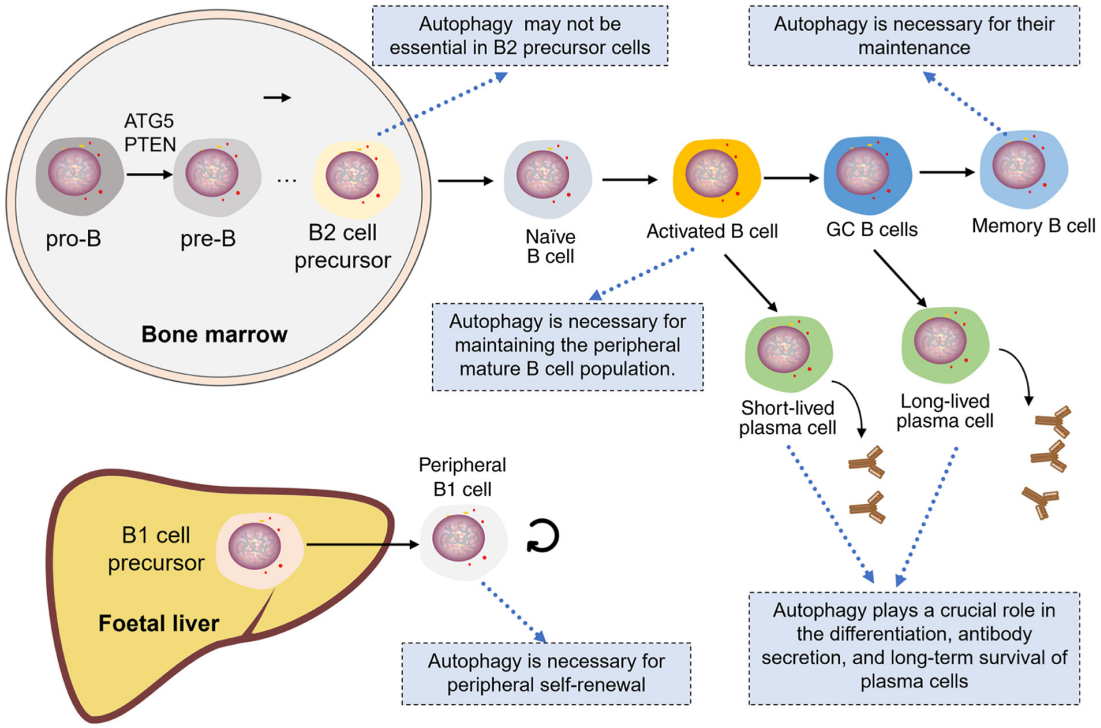

Figure 5. Role of autophagy in developing B cells and mature B cells. Autophagy plays a role in maintaining cellular homeostasis in various B cell subsets. Autophagy is not essential for the development of B1 cells and B2 cells, but it is necessary for the peripheral self-renewal of B1 cells. For B2 cells, autophagy also plays an important role in maintaining the production of immunoglobulins by plasma cells and ensuring the survival of memory B cells. PTEN, phosphatase and tensin homolog; ATG5, autophagy related 5; GC B cells, germinal center B cells.

nephritis and skin damage (114). Existing evidence indicates aberrant activation of multiple types of PCD in patients with SLE. NLRP3 inflammasome expression is upregulated in SLE macrophages and correlates with disease activity (115,116); neutrophil apoptosis is elevated and MLKL expression in PBMCs is also increased (117,118). Notably, multiple PCD modalities can coexist and act synergistically within the same cell. For instance, necroptosis and pyroptosis are concurrently activated in podocytes from patients with lupus nephritis and in renal tissue of lupus mice, as reported by Guo *et al* (119), suggesting a complex regulatory network among various cell death pathways.

As noted above, IFN signaling is a key regulator of PANoptosome assembly. In the context of SLE, chronic inflammation drives sustained mtROS accumulation, which promotes mtDNA translocation to the cytosol, where it is recognized as a DAMP. DNA sensors such as cGAS and ZBP1 detect these danger signals and trigger substantial IFN production. The released IFNs further upregulate ZBP1 transcription, thereby instigating PANoptosome assembly and culminating in PANoptosis. Transcriptomic analyses have identified PANoptosis-related gene signatures in PBMCs from patients with SLE, with ZBP1, MEFV innate immunity regulator, pyrin, lipocalin 2, IFN-α-inducible protein 27 and heat shock protein 90α family class B member 1 all showing elevated expression (108,120-123). At the cellular level, neutrophils and plasmacytoid DCs provided strong experimental evidence for PANoptosis activation, manifested as concurrent activation of key effector molecules including caspase-1, caspase-8 and RIPK3 (124). The autophagy-PANoptosis axis holds particular importance in SLE pathogenesis. Impairment of autophagic function amplifies type I IFN-mediated inflammation, increases mtROS production and upregulates ZBP1 expression, thereby lowering the threshold for PANoptotic activation in neutrophils and plasmacytoid dendritic cells.

RA. RA is a chronic autoimmune disease that can progressively affect multiple organs, including the heart, liver, kidneys and skin (125). RA onset is influenced by environmental, sex-related and genetic factors, with the core pathological mechanism involving aberrant recognition of self-antigens and mistaken attack on joint tissues, thereby triggering persistent inflammation and tissue damage (126,127). Emerging evidence has revealed a complex interplay between PCD and RA pathogenesis. Notably, RA fibroblast-like synoviocytes (FLSs) exhibit an intrinsic apoptosis-defective status, which leads to synovial hyperplasia and a concomitant inflammatory milieu (128). A cohort study demonstrated that the proportion of apoptotic and primary necrotic granulocytes in patients with RA is substantially higher than in healthy controls (129). Pyroptosis has also been detected in macrophages, monocytes and FLSs from patients with RA (130). Of note, RA involves the interaction and coordinated regulation of multiple PCD types across different cell populations, jointly modulating inflammation and immune function. Indeed, the pathological progression of RA cannot be fully explained by any single form of PCD.

The PANoptosis-autophagy axis in RA exhibits considerable complexity, with its functional outcome likely shaped by disease phase, inflammatory milieu and the recruited immune effector populations. In RA pathogenesis, PANoptosis occurs primarily in synovial macrophages and FLS, where TNF

Table IV. Role of the autophagy-PANoptosis axis in autoimmune diseases.

Autoimmune diseases	Disease-related core PANoptosis genes	Disease-related core autophagy genes	(Refs.)
SLE	ZBP1, MEFV, LCN2, IFI27, HSP90AB1	ATG5, ATG16L2, CDKN1B, DRAM1, CLEC16A, S100A8, MyD88, NCR3, DDIT3, GNB2L1, CTSD, HSPA8, ULK1, DNAJB1, CANX	(105-108)
RA	Identified the PANoptosis biomarker SPP1, distinguished between two different subtypes of RA and established a scoring model with the potential to differentiate the subtypes.	GWAS and Mendelian randomization studies have identified ATG16L1, ATG16L2, BCL2L1, RAF1 and MAPK3 as risk loci associated with rheumatoid arthritis.	(109,110)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ZBP1, Z-DNA binding protein 1; MEFV, MEFV innate immunity regulator, pyrin; LCN2, lipocalin 2; IFI27, interferon α inducible protein 27; HSP, heat shock protein; ATG5, autophagy related 5; ATG16L2, autophagy related 16 like 2; CDKN1B, cyclin dependent kinase inhibitor 1B; DRAM1, DNA damage regulated autophagy modulator 1; CLEC16A, C-type lectin domain containing 16A; S100A8, S100 calcium binding protein A8; MyD88, MYD88 innate immune signal transduction adaptor; NCR3, natural cytotoxicity triggering receptor 3; DDIT3, DNA damage inducible transcript 3; GNB2L1, guanine nucleotide binding protein (G protein), β polypeptide 2-like 1; CTSD, cathepsin D; ULK1, unc-51 like autophagy activating kinase 1; DNAJB1, DnaJ heat shock protein family (Hsp40) member B1; CANX, calnexin; SPP1, secreted phosphoprotein 1; BCL2L1, BCL2 like 1; RAF1, Raf-1 proto-oncogene, serine/threonine kinase; MAPK3, mitogen-activated protein kinase 3.

and IL-1β can trigger caspase-8-RIPK3-NLRP3-dependent inflammatory cell death (131,132). By contrast, PANoptosis in lymphocytes remains inferential and has yet to be unequivocally confirmed. Under physiological conditions, autophagy in RA synovial cells limits mitochondrial stress and inflammasome activation. However, protracted TNF-α stimulation suppresses autophagic flux, exacerbates ROS production, and sensitizes macrophages and FLS to PANoptosis (133). Thus, although autophagy restrains inflammation under homeostatic conditions, persistent inflammatory signaling drives cells towards PANoptotic death, forming a distinct 'autophagy exhaustion-PANoptosis amplification' pathological pattern in RA. Unlike the IFN-dominated environment in SLE, RA is characterized by TNF-α/IL-17-driven metabolic and mitochondrial stress. This unique inflammatory context modulates the autophagy-PANoptosis axis in synovial tissue in a disease-specific manner, generating a pathological feedback loop in which cytokine-driven autophagic dysfunction and PANoptosis synergistically exacerbate inflammation and tissue damage, thereby promoting RA progression.

7. Potential value of the autophagy-PANoptosis axis in tumor immunity

In the tumor microenvironment, the autophagy-PANoptosis axis also exerts dual and context-dependent functions. PCD can exert both pro- and anti-tumor effects in tumor immunity by modulating the recruitment of effector vs. regulatory immune cells, depending in part on the contents released upon cell death.

Dual role of autophagy in tumors. Autophagy serves as a multifaceted accomplice in tumor immune evasion. It sustains immunosuppressive cell functions while attenuating effector immune cell activity, collectively erecting a barrier to antitumor immunity. The function of Treg cells relies on autophagy to restrain tumor immunity. For example, Treg cells infiltrating human melanoma express high levels of arginase 2, which depletes intracellular arginine and inhibits arginine-mediated mTOR activation-a process that may induce autophagy (134). In autophagy-deficient Treg cells, the mTOR-MYC pathway is activated, resulting in enhanced glycolytic and loss of the lineage-specific transcription factor forkhead box protein P3, ultimately rendering cells more susceptible to apoptosis (135,136). Consistently, silencing key autophagy regulators (such as Beclin1, ATG5 or class III PI3K) substantially impairs Treg-cell function (85,137). Additionally, in hepatocellular carcinoma, TLR2 signaling selectively degrades NF-κB through an autophagy-dependent pathway, thereby inhibiting NF-κB signaling and driving macrophage polarization toward the M2 phenotype (138). Inhibition of autophagy restores NF-κB activity and induces polarized M2 macrophages to produce high levels of M1-like cytokines. The survival and development of myeloid-derived suppressor cells (MDSCs) also rely on autophagy. In triple-negative breast cancer, glycolytic metabolism attenuates liver-enriched activator protein expression via disruption of AMPK-ULK1 signaling and autophagosome biogenesis, consequently diminishing the release of granulocyte colony stimulating factor (CSF) and granulocyte-macrophage CSF and abrogating MDSC mobilization (139).

Autophagy plays an essential role in supporting the effector function and sustained survival of both T lymphocytes and NK cells. In $CD8^+$ tumor-infiltrating lymphocytes (TILs), mitophagy deficiency leads to abnormal accumulation of dysfunctional depolarized mitochondria, which predisposes cells to terminal exhaustion. Exogenous NAD^+ precursors, such as nicotinamide riboside, reduce the accumulation of dysfunctional mitochondria and ROS in T lymphocytes via a DNM1L (dynamin 1L, also known as Drp1)-mediated

mechanism, thereby enhancing the immunosurveillance capacity of TILs (29). These findings suggest that enhancing autophagy in immune cells, especially mitophagy, may represent an effective strategy to restore TIL function and improve antitumor immune responses.

DAMPs and PAMPs present in autophagy substrates can trigger innate immunity. Clearance of these substances through autophagy is essential for maintaining immune homeostasis and protecting cells from membrane damage and organellar stress (140). As an immunogenic form of cell death, autophagy enhances ATP secretion by promoting the migration of ATP-containing lysosomes to the plasma membrane (141). Given that ATP is a key chemoattractant for immune cells, loss of autophagic function in tumor cells substantially reduces the ability of chemotherapeutic agents to elicit a robust antitumor immune response *in vivo* (142).

Beyond ATP, the autophagy machinery can deliver a range of signaling molecules to professional antigen-presenting cells (APCs) (143). Following autophagic capture, pathogen-derived peptides are transported to APCs for major histocompatibility complex (MHC)II loading, thereby instigating $CD4^+$ T-cell responses. ATG5 ablation delays lysosomal-phagosomal fusion, which in turn impairs DC-mediated antigen cross-presentation and $CD4^+$ T-cell activation via the MHC I axis (144,145). Autophagy may also promote presentation of extracellular antigens to MHC I through ATG8/LC3-associated phagocytosis, a non-canonical autophagy pathway (146,147). This process is involved in macrophage clearance of dead cells and subsequent antigen presentation to immune effector cells. In the absence of ATG8/LC3-associated phagocytosis, dysregulation of pro- and anti-inflammatory cytokines can trigger inflammatory reactions (146,147). Furthermore, autophagy contributes to MHC I-mediated antigen presentation, providing important support for the initiation of antitumor immune responses (148,149).

PANoptosis serves as the core executor of immunogenic cell death. As a core PANoptosis adaptor, Fas-associated death domain protein (FADD) undergoes nucleocytoplasmic shuttling closely linked to lung cancer pathogenesis. Wei *et al* (150) reported that FADD is upregulated in lung adenocarcinoma relative to adjacent normal tissues and correlated this upregulation with worse survival. *In vitro* FADD knockdown not only suppressed cancer cell proliferation but also altered apoptosis/pyroptosis marker profiles, suggesting that targeting PANoptosis-associated factors may represent a promising therapeutic strategy. Gastric cancer is also intimately linked to PANoptosis, with aberrantly expressed long non-coding RNAs (lncRNAs) contributing to its pathogenesis. Hong *et al* (151) developed a prognostic signature based on PANoptosis-associated lncRNAs and identified candidate molecules correlated with patient prognosis, chemosensitivity and tumor immune infiltration, thereby offering potential biomarkers and actionable targets for clinical translation. In hepatocellular carcinoma, Shu *et al* (152) constructed a prognostic model using PANoptosis-related genes and found that lncRNA AC026412.3 exhibited superior predictive ability. Knockdown of AC026412.3 upregulated caspase-3, pro-apoptotic Bax, NLRP3 inflammasome and p-MLKL, mechanistically confirming the association between PANoptosis activation and tumor suppression. Adrenocortical carcinoma (ACC) is a rare, highly invasive malignancy closely associated with PANoptosis. Ren *et al* (153) identified cyclin-dependent kinase 1 (CDK1) as a predictor of poor prognosis in ACC. *In vitro* experiments showed that the CDK1 inhibitor cucurbitacin E upregulated markers of apoptosis, pyroptosis and necroptosis in ACC cells. Knockdown of ZBP1 abolished these effects, confirming that cucurbitacin E induces ZBP1-dependent PANoptosis.

The impact of PANoptosis on cancer is multifaceted and subject to diverse regulatory influences. On the one hand, it promotes organismal homeostasis by eliminating aberrant or neoplastic cells, thereby restraining malignant transformation. Mechanistically, the PANoptosome complex integrates sensors such as ZBP1, AIM2 and NLRP3, and can simultaneously activate the caspase-1 (pyroptosis), caspase-8 (apoptosis) and the RIPK3-MLKL (necroptotic apoptosis) signaling pathways. This confers a multi-pronged attack on tumor cells, effectively preventing escape via defects in any single death pathway (154). Such synergistic killing renders PANoptosis a potent antitumor weapon. On the other hand, excessive PANoptosis activation may lead to immune cell death, amplify inflammatory cascades and promote an immunosuppressive microenvironment, thereby facilitating tumor immune evasion and progression. In the tumor immune microenvironment, dysregulated PANoptosis can drive exhaustion and death of effector immune cells (such as $CD8^+$ T cells and NK cells), while releasing a large amount of pro-inflammatory factors (including IL-1β and IL-18). This creates a chronic inflammatory milieu that recruits and expands immunosuppressive populations including Tregs and MDSCs, establishing a pro-tumorigenic niche (28). This dual effect makes PANoptosis a double-edged sword. Moderate PANoptosis activation can remodel the tumor microenvironment, change immunologically 'cold' tumors into 'hot' tumors and enhance sensitivity to immunotherapy (155). Conversely, excessive PANoptosis may provoke immune exhaustion and tissue damage, accelerating tumor progression.

Microenvironmental metabolic signals regulate autophagy and PANoptosis in immune cells. The functional status and fate of immune cells are not determined autonomously, but are profoundly shaped by the surrounding microenvironment. Diverse pathological niches-including the tumor microenvironment, inflammatory lesions and autoimmune target organs-constitute a dynamic 'metabolic-immune regulatory network' through local gradients of metabolites, oxygen tension, cytokine profiles and intercellular contact signals, continuously transmitting fate cues to infiltrating immune cells (156).

In the tumor microenvironment, immune cells encounter a metabolically hostile niche characterized by hypoxia, nutrient deprivation, acidification and accumulation of immunosuppressive metabolites such as lactate and adenosine (157). The intense competition between tumor cells and immune cells for essential resources-including glucose and glutamine-profoundly affects the activation, differentiation and effector functions of infiltrating immune cells. Critically, microenvironmental metabolites not only serve as energy sources but also function as key signaling molecules that directly regulate PANoptosis.

Lactate enters macrophages via the MCT1 transporter, enhances ZBP1 lactylation and reduces ZBP1 interaction with RIPK1 and TRIF, thereby inhibiting ZBP1-mediated PANoptosis (158). This finding reveals a novel role for lactate-traditionally viewed as a metabolic waste product-as a brake signal for PANoptosis within the inflammatory microenvironment. Meanwhile, other metabolic intermediates such as succinate can upregulate PANoptosis-related gene expression, forming a bidirectional regulatory network.

In inflammatory and autoimmune diseases, microenvironmental metabolic signals also critically regulate cell fate. For instance, in acute lung injury, lactate exerts a protective effect by inhibiting ZBP1-mediated PANoptosis (158). In sepsis, PANoptosis-induced immunopathology directly contributes to T-cell exhaustion and cytokine storm, and targeted inhibition of PANoptosis signaling may represent a novel approach to restore T-cell immunity (41). These findings suggest that the same metabolite can exert opposing regulatory effects on PANoptosis in different pathological microenvironments through distinct mechanisms, including lactylation modification.

In autoimmune diseases, dysregulated microenvironmental metabolic signals similarly contribute to pathogenic immune cell transformation. In conditions such as RA, stromal cells sustain inflammatory responses by maintaining the metabolic niche of pathogenic immune cells (159). Furthermore, microenvironmental metabolites can act as epigenetic regulators, modulating immune-related gene expression through post-translational modifications such as lactylation and succinylation, thereby influencing immune cell activation, differentiation and propensity for PANoptosis.

8. Conclusions and prospects

Autophagy serves as a core molecular switch that determines immune cell fate, delineating a precise boundary between survival-differentiation and inflammatory death by eliminating intracellular danger signals and key protein complexes, thereby maintaining immune homeostasis. Under normal physiological conditions, autophagy (especially mitophagy) suppresses inflammatory signals below the lethal threshold by removing damaged mitochondria, controlling ROS levels and degrading PANoptosome components, thereby ensuring proper immune cell differentiation and functional execution. When autophagy is insufficient or pathologically over-activated, this 'braking' mechanism fails, leading to danger signal accumulation and reduced PANoptosome assembly threshold, ultimately triggering PANoptotic inflammatory death. Insufficient autophagy-resulting in danger signal accumulation and excessive PANoptosis activation-has emerged as a common pathological basis for various immune-related diseases, including autoimmune disorders, chronic inflammation and cancer.

Although notable progress has been made in understanding the autophagy-PANoptosis axis in recent years, this field still harbors many unanswered questions that merit further investigation: i) Technologies capable of monitoring the dynamic interplay between autophagy and PANoptosis in immune cells *in vivo* and in real time should be developed, to reveal spatiotemporal changes during disease initiation and progression; ii) the heterogeneous regulatory mechanisms of the autophagy-PANoptosis axis across distinct tissue microenvironments should be dissected to elucidate its functional divergence in specific cell types and pathological contexts; and iii) based on the 'autophagy-cell fate axis', drug screening may be conducted and precision intervention strategies may be developed to provide novel targeting opportunities for autoimmune diseases, chronic inflammation and tumor immunotherapy. A systematic understanding of the molecular mechanisms by which autophagy governs immune cell fate provides a theoretical basis for precise intervention of the autophagy-PANoptosis axis and for optimizing therapeutic strategies for related diseases.

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Authors' contributions

YG was involved in investigation, writing-original draft and writing-review and editing. XZ and YixT performed visualization and conceptualization. DC, XX and BZ contributed to writing-review and editing and visualization. YinT and YZ were involved in conceptualization and supervision. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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