

Autophagy dictates metabolism and differentiation of inflammatory immune cells

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ABSTRACT

The role of macroautophagy/autophagy, a conserved lysosomal degradation pathway, during cellular differentiation has been well studied over the last decade. In particular, evidence for its role during immune cell differentiation is growing. Despite the description of a variety of dramatic immune phenotypes in tissue-specific autophagy knockout models, the underlying mechanisms are still under debate. One of the proposed mechanisms is the impact of autophagy on the altered metabolic states during immune cell differentiation. This concept is strengthened through novel molecular insights into how AMPK and mTOR signaling cascades affect both autophagy and metabolism. In this review, we discuss direct and indirect evidence linking autophagy, metabolic pathways and immune cell differentiation including T, B, and innate lymphocytes as well as in myeloid cells that are direct mediators of inflammation. Herein, we propose a model for autophagy-driven immunometabolism controlling immune cell differentiation.

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How autophagy can shape immune cell differentiation

Macroautophagy (hereafter referred to as autophagy) is a conserved cellular degradation pathway that recycles cellular content. Degradation of cytoplasmic content in turn frees up metabolites required for anabolic processes, such as cell growth and proliferation as well as the remodeling that occurs during differentiation. Particularly during terminal immune cell differentiation, committed hematopoietic precursor cells undergo extensive remodeling to form specialized immune effector cells. Perhaps not surprisingly, many studies found that this process is highly dependent on functional autophagy, but the mechanistic roles of autophagy during differentiation remain incompletely understood.^{1,2} In the past decade, a multifaceted picture emerged in which autophagy can drive distinct effects according to the type of immune cell differentiation. We have recently classified these mechanisms into 4 categories exemplified in 4 cell types.³

First, during monocyte-to-macrophage differentiation, it is crucial to avoid caspase activation and apoptosis, which is mediated by stage-specific autophagy induction.^{4,5} Secondly, autophagy regulates mitochondrial quality and quantity as well as other organelle content during differentiation. Examples include thymic natural killer T (NK-T) cell differentiation, natural killer (NK) cell maturation and NK memory formation.^{6,7} Third, a switch in energy-metabolism has recently emerged as a critical pathway that can be rate-limiting during differentiation. Such is the case in long-lived regulatory T cell (Treg) and memory T cell (Tmem) generation where this switch is controlled by autophagy.^{8–11} And finally, maintenance of proteostasis and removal of bulk or specific proteins may require

autophagy to establish new protein translation associated with differentiation. Although there is no direct evidence for this, sustained immunoglobulin production in plasma cells requires autophagy for cellular survival and to balance the ER stress during immunoglobulin translation.¹² Importantly, a combination of these categories is likely to be mediated by autophagy in most cases of immune cell differentiation, but the context dictates which effect becomes limiting. For example, preliminary evidence suggests that in CD8⁺ Tmem generation, the switch from glycolytic to oxidative metabolism is disturbed in the absence of autophagy, which may be due to defective mitochondrial maintenance and organelle homeostasis, with the final outcome of increased apoptosis and lost maintenance of the memory T cell compartment.^{8,9} In this review, we will summarize in more detail the interactions of autophagy and metabolism controlling immune cell differentiation, using myeloid cell and T cell lineages as examples.

Metabolism in the control of immune cell differentiation

A major task of metabolic pathways in the context of differentiation is to produce molecules, metabolites and energy necessary for the events associated with a new cellular state. Autophagy in this view may have similar and overlapping roles with other metabolic pathways to adapt the cellular availability of biomolecules for differentiation. Because the metabolome of immune cells is highly complex and flexible, it is difficult to deduce general principles that may explain or predict interactions between metabolic states and differentiation. However, one common

feature in hematopoietic differentiation is enhanced cellular proliferation before cells settle down to become quiescent (cell cycle exit). For example, hematopoietic progenitors undergo rapid proliferation and expansion but eventually terminally differentiate to form mostly post-mitotic blood cells. Similarly, effector T cells rapidly expand and proliferate in response to antigen while long-lived antigen-experienced populations such as Tmem or Treg are in a quiescent state. In both cases, a hallmark of the proliferative state is aerobic glycolysis, a metabolic state originally described for cancer cells used to sustain proliferation and anabolism even in the presence of oxygen (Warburg metabolism).

Metabolic changes during differentiation of healthy cells may be controlled by similar mechanisms as cellular proliferation and differentiation of transformed cells. In line with this, defective differentiation is a hallmark of some cancers, and targeting cancer cell-specific anabolic metabolism can be an effective way to treat cancer by inducing differentiation.¹³ A remaining major challenge, however, is to establish whether metabolic changes are causative for differentiation dynamics, an unrelated bystander, or rather a consequence, downstream of the signaling that controls differentiation. It is also unclear how these metabolic changes link in with the more established transcriptional control of differentiation. In this respect, other tissues and basic model organisms have elucidated remarkable and definitive causative links between metabolism and differentiation.¹⁴ Evidence for this is now also emerging in the field of immunometabolism, with several examples showing that extensive metabolic remodeling may actively control lineage specification, activation and effector functions of immune cells. Particularly in myeloid cells and T cells, the balance between mitochondrial and glycolytic metabolism has recently been identified as a central determinant of differentiation and phenotype, rather than merely being a bystander of differentiation.¹⁵ The link with autophagy has only been investigated in a few pioneering studies. We will discuss here how autophagy may be closely linked to metabolic regulation and differentiation in inflammatory cells and then discuss the supporting literature in different immune lineages.

Autophagy and metabolism are integrated by common nutrient-sensing pathways

When autophagy captures cytoplasmic content for degradation, the resulting breakdown products directly feed into cellular metabolic pathways, thus intimately linking autophagy with metabolism. The recycled metabolites can either be used for biosynthesis or harnessed for energy production. The amino acids resulting from autophagic proteolysis can serve for translation, but over two-thirds of amino acids are either glucogenic or ketogenic and thereby can directly feed into central metabolism. Furthermore, by selectively degrading key metabolic organelles/compartments such as mitochondria (mitophagy), peroxisomes (pexophagy) and lipid droplets (lipophagy), autophagy has the capability to rapidly redirect cellular metabolite flow. Finally, both MTOR (mechanistic target of rapamycin) and 5' adenosine monophosphate-activated protein kinase (AMPK) signaling, the 2 key integrators for environmental status and nutrient availability, directly control and coordinate

autophagy together with metabolic pathways.¹⁶ MTOR complex1 (MTORC1) activation is well established as a potent initiator of protein translation and ribosome biogenesis through phosphorylation of RPS6KB1/S6K1 (ribosomal S6 protein kinase B1) and EIF4EBP1/4E-BP1 (eukaryotic translation initiation factor 4E binding protein 1).¹⁷ Stimulation of MTORC1 activates further transcription factors, such as HIF1A (hypoxia inducible factor 1 α subunit) and SREBF/SREBP (sterol regulatory element binding transcription factor), resulting in the expression of genes controlling glycolysis, inflammation and de novo lipid synthesis.¹⁸ While supporting cell growth and downstream metabolic pathways, MTOR signaling negatively regulates autophagy by phosphorylation of ATG13 (autophagy related 13) and ULK1 (unc-51 like autophagy activating kinase 1) as well as through its interaction with the master regulator of autophagosomal and lysosomal biogenesis, TFEB (transcription factor EB) on the surface of lysosomes, thereby preventing TFEB nuclear translocation and autophagy gene program activation.¹⁹

Conversely, AMPK is a positive regulator of autophagy by suppressing MTOR activity and through direct phosphorylation of ULK1 as well as via controlling the PIK3C3/VPS34-containing phosphatidylinositol 3-kinase complex during glucose starvation.²⁰ When ATP synthesis is outweighed by its consumption, ADP and AMP accumulate and activate AMPK. Among its downstream targets are lipolysis and fatty acid oxidation for ATP synthesis; at the same time it negatively regulates ATP-consuming biosynthetic pathways including gluconeogenesis, and lipid and protein synthesis.²¹

Because the cellular energy-metabolic balance, autophagy, and their regulation via AMPK and MTOR signaling are so intimately linked (summarized in Fig. 1), it is not surprising that several are crucially involved in immune cell differentiation. Particularly in effector, Treg and Tmem differentiation as well as myeloid differentiation, recent discoveries start to reveal common principles that link interactions between these pathways to cellular differentiation, which we discuss in the following sections.

Differentiation, autophagy and metabolism in innate immune cells

Under inflammatory conditions, myeloid progenitor cells undergo drastic transcriptional and cellular changes to drive rapid immune activation and proliferation. This highly energy-consuming process calls for a well-coordinated metabolic adaptation in monocyte and granulocyte progenitors. The short-lived requirement of high levels of free ATP forces progenitors of pro-inflammatory cells to enter into glycolysis. Interestingly, loss of autophagy in hematopoietic stem cells (HSCs) through *Atg7* knockout (*atg7*-KO) results in severe myeloproliferation with large accumulation of mostly immature myeloid cells in bone marrow, blood and tissues.²² This phenotype is accompanied by a metabolic shift toward glycolysis, which facilitates proliferation in a model of acute myeloid leukemia.²³ Monocyte-to-macrophage differentiation is biphasic with a first commitment into the macrophage lineage and terminal differentiation into pro-inflammatory M1 or anti-inflammatory M2 phenotypes upon lipopolysaccharide, IFNG (interferon

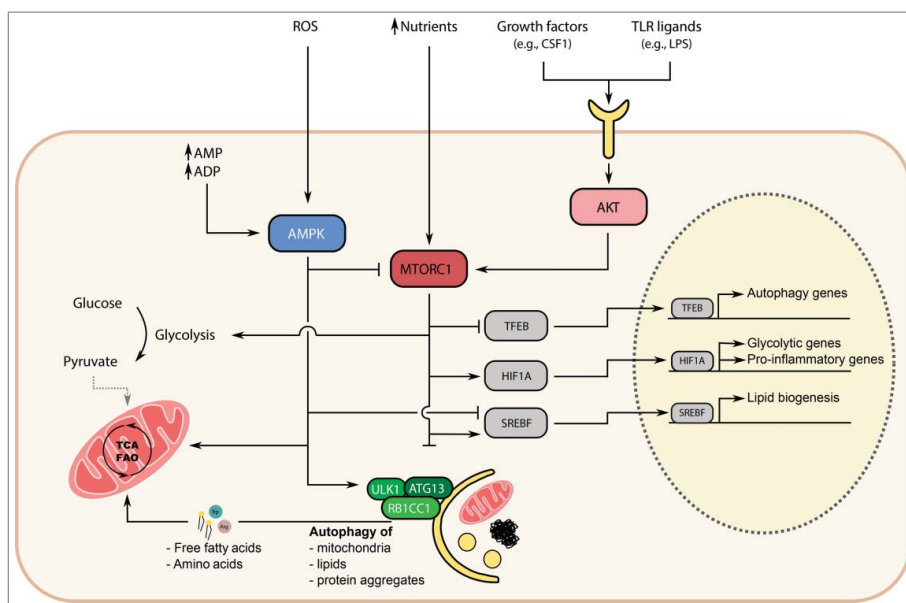


Figure 1. Molecular links between metabolism and autophagy in inflammatory cells. High nutrient state, growth factors and pro-inflammatory signaling converge in the activation of MTORC1, a master regulator controlling a variety of transcription factors (e.g., TFEB, HIF1 A and SREBF) to promote glycolytic metabolism to ensure rapid cell activation. Furthermore, the activation in MTORC1 downregulates autophagic flux and consequently promotes anabolic processes. In contrast, high ADP or AMP levels (equivalent to low ATP levels) and ROS lead to the activation of AMPK, which inhibits MTORC1 rendering it inactive. AMPK directly stimulates autophagy induction by phosphorylation of ULK1 and ATG13 and hence shifts the cells toward a catabolic metabolism. This is further strengthened by AMPK-mediated activation of OXPHOS and the repression of SREBF leading to reduced lipid biogenesis.

gamma) and IL4 stimulation, respectively. Using *Atg*-deficient mouse models, numerous studies show the role of ATG proteins in limiting inflammation in macrophages by a variety of processes including LC3-associated phagocytosis (LAP)²⁴ and alterations of cytokine release.²⁵ A general pro-inflammatory milieu caused by the absence of LAP and altered cytokine balance may also affect lineage specification of immune cells indirectly. The findings with LAP also indicate that *Atg* deficiencies might affect additional processes than autophagy itself.

Further support for a direct link of autophagy-dependent metabolism and cellular differentiation is provided by decreased potential of monocytes to differentiate into M2 macrophages in *atg7*-KO mice²⁶ along with increased glycolytic activity, M1 inflammatory cytokine and reactive oxygen species production.²⁷ In support of this, another study found increased M1 polarization and inflammation in the liver of high-fat diet fed *atg5*-KO mice.²⁸ The differentiation of monocytes into macrophages upon CSF1 (colony stimulating factor 1) stimulation is dependent on induction of ULK1-mediated autophagy, which is cytoprotective and thereby promotes differentiation.⁴ Further differentiation into M2 macrophages requires increased fatty acid oxidation (FAO) metabolism.²⁹ The latter study also reveals that M2 differentiation requires LIPA/LAL (lipase A, lysosomal acid type)-mediated degradation of exogenous fatty acids taken up by the scavenger receptor CD36, which is necessary to fuel FAO metabolism. It is an intriguing possibility that the requirement of autophagy for M2 differentiation stems from its role to support FAO by providing free fatty acids through lipophagy, a metabolic pathway recently described to be essential for neutrophil differentiation.³⁰

The fate of macrophages toward the M1 or M2 phenotype is dependent on the activation of the MTOR complexes 1 and 2, which decides whether autophagy is induced and on the type of

metabolic switch. This is supported by the fact that constitutive activation of MTORC1 in mice results in impaired M2 differentiation upon IL4 stimulation,³¹ suggesting that autophagy's role in FAO metabolism may be contributing to this differentiation step. Controversially, abrogation of the MTORC2 signaling pathway also decreases levels of M2 macrophages, whereas the M1 macrophage level remains unchanged suggesting the necessity of MTORC2 signaling specifically in M2 differentiation.³² The activation of MTORC1 is a well-established inhibitor of autophagy, whereas the link between MTORC2 and autophagy is less clear.

The largest fraction of inflammatory cells in the blood are granulocytes, in particular neutrophils. CSF3/G-CSF drives neutrophil differentiation in the bone marrow from myeloid progenitors. Autophagy is activated upon CSF3 treatment and is indispensable for the mobilization of neutrophils and HSCs by increasing cell-intrinsic survival in the peripheral circulation.³³ Peripheral neutrophils that reside in low-oxygen tissues are classically associated with a predominantly glycolytic metabolism, which is further supported by the requirement of functional MTORC1 signaling during granulocyte maturation.³⁴ Yet, uncoupling granulocyte progenitors from mitochondrial respiration impairs the frequency of mature neutrophils, indicating the necessity of oxidative phosphorylation (OXPHOS) in terminal neutrophil differentiation.³⁵ Granulopoiesis also requires NAMPT, an enzyme essential for NAD⁺ biosynthesis and maintaining a variety of metabolic pathways including the tricarboxylic acid cycle and FAO.³⁶ Indeed, a recent study by Riffelmacher et al. identified an autophagy-dependent pathway of lipid breakdown for FAO and OXPHOS that generates ATP to support neutrophil differentiation.³⁰ Whether the lysosomal lipolysis previously described for M2 macrophage polarization is similarly dependent on

autophagy to enforce the metabolic switch remains to be established.²⁹

The role of autophagy in dendritic cells (DCs) has mainly focused on its capacity to promote antigen presentation. Autophagy's influence on early DC differentiation has not been studied, which is not surprising as DC progenitors have only recently been identified.³⁷ However, a handful of studies have addressed the link between autophagy and metabolism in late DC activation. The metabolism of DCs shifts toward glycolysis, mitochondrial respiration and lipid synthesis in a MTORC1-dependent, but MTORC2-independent manner, presumably to satisfy energy demands of an activated DC for migration, cytokine production and antigen presentation.³⁸ In contrast, stimulation of AMPK activity enhances autophagic flux and promotes tolerogenic DC differentiation.^{39,40} In concordance with this, AMPK activation in DCs antagonizes their ability to switch from OXPHOS to glycolysis in response to TLR (toll like receptor).⁴¹ Taken together, both MTOR and AMPK are crucial for DC activation through affecting their metabolism,⁴¹ but direct evidence for the role of autophagy in mediating the metabolic transition in DC activation is still lacking.

Besides a role for autophagy in myeloid cell differentiation, it is also important for lymphoid cell development including innate lymphocytes, such as iNK-T, NK subsets and innate lymphoid cells (ILCs). Using a tissue-specific autophagy deletion model, 2 studies show an arrest of iNK-T differentiation at the thymic stage, and increased apoptosis possibly due to increased reactive oxygen species production in comparison to autophagy-competent cells, underlying autophagy's central function in the development of invariant NK-T cell development.^{7,42} Yet another link to a metabolic switch is given by the fact that iNK-T cell development is impaired in cells deficient in the metabolic regulator FNIP1 (folliculin interacting protein 1), an activator of AMPK and inhibitor of MTOR signaling.⁴³ In line with these observations is the requirement for autophagy in ILC development during homeostatic proliferation by promoting cell-intrinsic survival.⁴⁴ In this study, the authors treated ILCs with the AMPK activator metformin, which improved survival of autophagy-deficient lymphocytes; however, whether this is linked to a simultaneous metabolic switch has not been demonstrated. Lastly, FOXO1 (forkhead box O1)-induced autophagy is indispensable during NK cell development.⁴⁵

In summary, over the past decade, increasing evidence suggests links between autophagy and metabolic changes in innate immune cell differentiation. Except for macrophage differentiation, studies providing definite direct links between these processes are still rare. However, a bigger research effort has been undertaken to confirm causality between autophagy, metabolism and differentiation in lymphoid cells.

You become what you eat: Is autophagy feeding T cell metabolism and differentiation?

Early lymphoid lineage differentiation is already affected by loss of autophagy, as deletion of *Atg7* using the HSC-specific promoter *Vav* demonstrates a significant reduction in common lymphoid progenitor cells and lymphoid-primed multipotent progenitors as well as immature NK cells.²² While a

requirement for OXPHOS for the differentiation of HSCs has been fully established,⁴⁶ a recent study demonstrates that *Atg12*-deficient HSCs (like *Atg7*-deficient HSCs) fail to regenerate the hematopoietic system in transplant experiments, yet they display increased OXPHOS. Whereas this is not in line with other autophagy-deficient hematopoietic cells studied so far, in which loss of autophagy leads to decreased OXPHOS, and does not explain the block of differentiation metabolically, the authors suggest that the altered metabolism leads to epigenetic changes controlling differentiation.⁴⁷

T cell differentiation and lineage commitment involves frequent and rapid changes between metabolic states and relies on functional autophagy in some cases but not others.⁴⁸ Proliferating CD4⁺ Th1, Th2 and Th17 effector cells primarily use glycolysis, while the longer-lived, quiescent Tregs and Tmem use FAO and OXPHOS to support their catabolic lifestyle, until they are rechallenged with antigen for recall response.⁴⁸ Supporting a causative role of metabolism in the control of T cell differentiation, highly glycolytic effector Th17 cells can be reprogrammed to differentiate toward regulatory T cells (which preferentially use OXPHOS) simply by inhibiting glycolysis with 2-deoxyglucose,⁴⁹ whereas MTOR activation exacerbates glycolysis and negatively affects Treg differentiation and maintenance.^{11,50} Like Tregs, CD8⁺ Tmem have enhanced respiratory capacity, abundant electron transport chain proteins and high mitochondrial content.^{51,52} The mitochondria in CD8⁺ Tmem cells are present as an elongated and highly fused network mediated by the action of OPA1 (OPA1, mitochondrial dynamin like GTPase), and enforced fusion of mitochondria imposes a Tmem phenotype by augmenting OXPHOS.⁵¹ Conversely, inducing mitochondrial fission by knocking out OPA1 greatly reduces OXPHOS activity and is sufficient to impair CD8⁺ Tmem generation, while cytotoxic T lymphocytes are unaffected.⁵¹ To fuel this elongated, efficient mitochondrial network, free fatty acids must either be generated by lipolysis or taken up exogenously. Tissue-resident CD8⁺ Tmem are highly dependent on lipid uptake and transport molecules such as FABP4 (fatty acid binding protein 4) and FABP5, as deleting the corresponding genes results in impaired mitochondrial respiration and specific loss of this population *in vivo*.⁵³ In contrast, central CD8⁺ Tmem seem to adopt another strategy, using cell intrinsic lipolysis of lipid droplets to generate free fatty acids from triacylglycerol.⁵⁴ Deleting the gene encoding the lysosomal lipase LIPA accordingly results in decreased CD8⁺ Tmem but normal effector T cells in mice. Although no link was made to autophagy in this context, it is likely that lysosomal lipid droplet breakdown was mediated by the autophagic machinery. LC3-positive phagophore membranes can form around lipid droplets to deliver them to lysosomes for degradation.⁵⁵ This lipophagy pathway was recently described to provide free fatty acids for ATP generation in the context of neutrophil differentiation.³⁰

Lipophagy is a universal pathway in mammalian cells working in parallel with cytoplasmic lipases to provide free fatty acids for energy homeostasis and metabolic intermediates. While lipid-binding proteins usually shield the droplet from cytosolic lipase digestion, the autophagic machinery can robustly make a large amount of lipids available for degradation in times of metabolic demand to fuel mitochondrial respiration. In line with this idea, chaperone-mediated autophagy removes

the protective perilipins PLIN2 and PLIN3, which is followed by enhanced lipophagy and lipase activity.⁵⁶ Since lipophagy depends on the core autophagy machinery, knockout of *Atg7* will disrupt this pathway, and accordingly a strong phenotype of defective CD8⁺ Tmem formation and maintenance has been reported in this context.^{8,9} Since both of these studies also found elevated compensatory glycolysis in the absence of autophagy, we propose that autophagy may be the upstream pathway controlling the metabolic switch toward OXPHOS and FAO in CD8⁺ Tmem by enabling large-scale lysosomal lipolysis.

Treg formation mirrors many metabolic features of Tmem generation, such as decreased glycolysis and engagement of fatty acid metabolism and OXPHOS.^{57,58} Tregs also rely on autophagy for their formation and maintenance. Similar to other cell types, autophagy limits excessive glycolysis in Tregs.^{10,11} However, it remains to be established whether the autophagy machinery is the upstream pathway in both Tmem

and Tregs that enforces the switch toward mitochondrial respiration.

Although these studies used T cell-specific promoters to delete *Atg* genes, ensuring that the differentiation defect is cell-intrinsic, an additional cell-extrinsic influence on T cell differentiation has to be considered. Autophagy limits pro-inflammatory cytokine production and secretion by restricting innate immune sensing mechanisms such as inflammasomes in antigen-presenting cells.⁵⁹ Hence, autophagy-deficiency in antigen-presenting cells leads to an overall pro-inflammatory environment skewing T cell fate toward pro-inflammatory cell subsets such as Th17 and $\gamma\delta$ T cells.⁶⁰

Summary and outlook

While autophagy has gradually become well recognized as a central pathway for differentiation of immune cells (and other cells) over the last decade, its role in metabolic control of

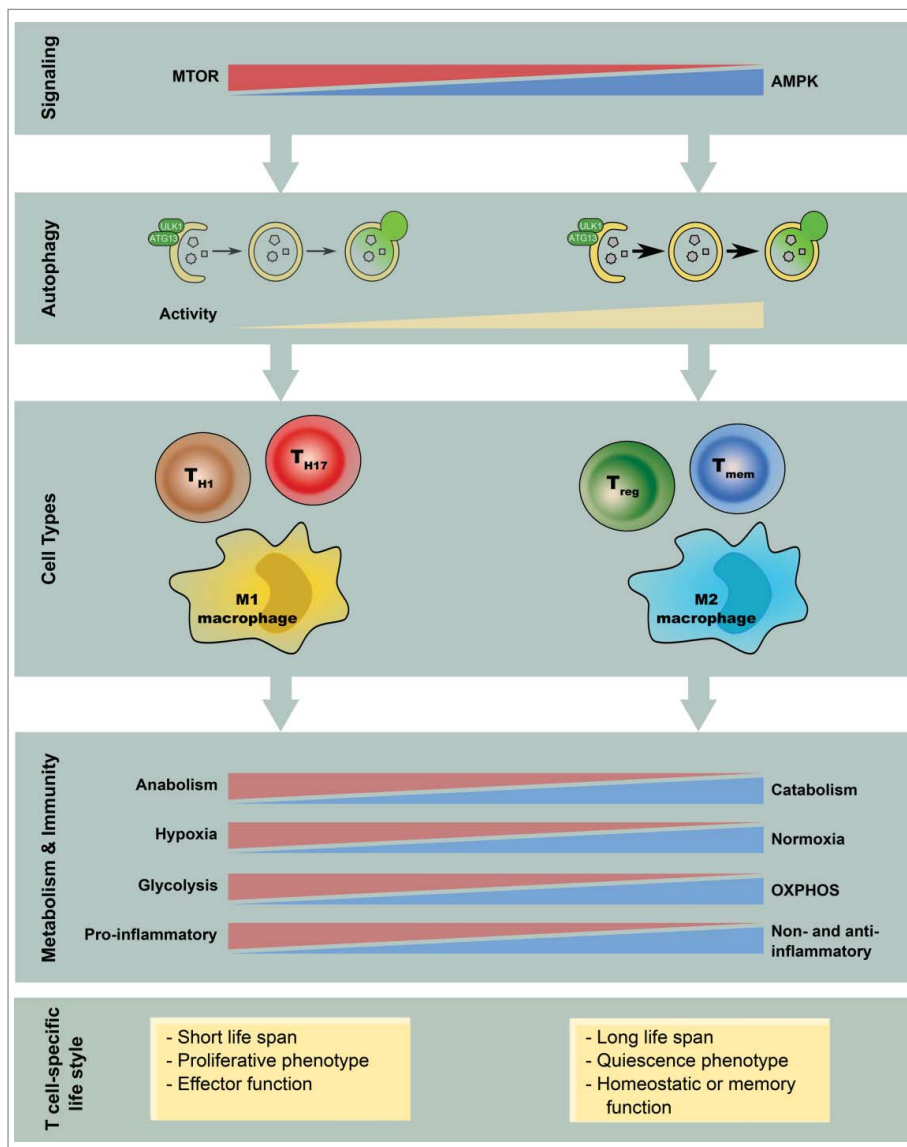


Figure 2. Autophagy drives cellular differentiation and changes in metabolic states. Differentiation of immune cells is dependent on the balance of MTOR and AMPK signal activation. Upon MTOR activation, autophagic flux decreases and gives rise to cells exhibiting activated, glycolytic and pro-inflammatory immune cell phenotypes. In contrast, shifting the balance toward AMPK signaling and increased autophagic activity results in differentiation into OXPHOS-dependent, non- or anti-inflammatory immune cells. This contrast between pro- and anti-inflammatory subsets is particularly apparent in T cell lineages.

hematopoietic differentiation is a more recent concept that has gained significant traction. We present and discuss here evidence that suggests that these 2 phenomena may be interconnected more than previously anticipated and may actually reflect parts of a common signaling axis that can determine lineage specification (Fig. 2). The cells that control inflammation, such as M2 macrophages, Tregs, and tolerogenic DCs tend to switch toward catabolic metabolism characterized by OXPHOS and FAO that suits their long-lived, quiescent lifestyle. This state may be enforced by autophagy, which supports mitochondrial metabolism and limits glycolysis. Accordingly, each of these typically anti-inflammatory cell types requires autophagy for its generation accompanied in many cases by active AMPK and MTOR repression.

Pro-inflammatory immune effector cells such as Th1, Th17 and M1 macrophages in contrast are characterized by anaerobic, glycolytic metabolism to support rapid, short-term proliferation and effector function in response to pathogenic stimulus. This shifts the balance of AMPK versus MTOR signaling toward MTOR activation and thus limited AMPK and autophagy activity in these cells. However, in particular, the complex regulation of MTOR signaling provides exceptions to these patterns.^{32,48} The importance of the metabolic balance as a common regulatory pathway mediating differentiation driven by AMPK, MTOR and autophagy in pro- or anti-inflammatory immune cells remains to be tested. Moreover, remaining challenges are to establish the mechanistic causality that connects these observations and how this fits in with other well-established routes to differentiation such as transcription and epigenetic regulation.

Abbreviations

AMPK	5' adenosine monophosphate-activated protein kinase
ATG	autophagy related
CD	cluster of differentiation
CSF3/G-CSF	colony stimulating factor 3
DC	dendritic cell
EIF4EBP1	eukaryotic translation initiation factor 4E binding protein 1
FABP	fatty acid binding protein
FAO	fatty acid oxidation
FNIP1	folliculin interacting protein 1
FOXO1	forkhead box O1
HIF1 A/HIF1 α	hypoxia inducible factor 1 α subunit
HSC	hematopoietic stem cell
IFN	interferon
ILC	innate lymphoid cell
IL	interleukin
KO	knockout
LAP	LC3-associated phagocytosis
LIPA/LAL	lipase A, lysosomal acid type
MAP1LC3/LC3	microtubule associated protein 1 light chain 3
MTOR	mechanistic target of rapamycin
NAMPT	nicotinamide phosphoribosyltransferase
NK-T	natural killer T cell
NK	natural killer cell

OPA1	OPA1, mitochondrial dynamin like GTPase
OXPHOS	oxidative phosphorylation
PIK3C3/VPS34	phosphatidylinositol 3-kinase catalytic subunit type 3
PLIN	perilipin
RPS6KB1/S6K1	ribosomal S6 protein kinase B1
SLE	systemic lupus erythematosus
SREBF/SREBP	sterol regulatory element binding transcription factor
Th1	T helper 1 cell
Th17	T helper 17 cell
Th2	T helper 2 cell
TFEB	transcription factor EB
TLR	toll like receptor
Treg	regulatory T cell
Tmem	memory T cell
ULK1	unc-51 like autophagy activating kinase 1

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