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Autophagy and T cell metabolism

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Abstract

Autophagy, a highly conserved catabolic process that involves the degradation and recycling of intracellular components in the lysosome, has emerged as a key process in the maintenance of T cell homeostasis and the regulation of T cell differentiation and function. In this review, we provide an overview of the mechanisms that mediate the regulation of autophagy in T cells and discuss different cellular processes that are under the control of autophagy in CD4⁺ and CD8⁺ T cells. A special emphasis is placed on the role that autophagy plays in the modulation of T cell metabolism and the consequences of this regulation on functional states and programs of differentiation in specific T cell populations.

1. Introduction

Autophagy is a highly conserved, ubiquitous catabolic process defined by the degradation of intracellular components in the lysosome. There are at least three major forms of autophagy: microautophagy, chaperone-mediated autophagy, and macroautophagy. Macroautophagy, the form of autophagy that is the focus of this review, has emerged as a critical process in T cell biology [1, 2]. It is characterized by the sequestration of cytosolic components in double-membrane organelles (“autophagosomes”) and subsequent degradation of cargo following fusion with lysosomes. In addition to having basal levels of macroautophagy activity, T cells induce macroautophagy in response to T cell receptor (TCR) and common- γ chain cytokine receptor signaling [3–6]. Despite traditionally being viewed as an in-bulk degradation system, many subsequent studies have supported the ability of this catabolic process to selectively target substrates for degradation [reviewed in [7]]. The ability of macroautophagy to degrade cellular components in bulk as well as selectively is a key feature of its role in the regulation of T cell fate and function.

Beyond classical TCR/costimulation signaling paradigms, we now appreciate that T cells integrate a complex set of inputs that determine their fate and function [8]. An important role for cellular metabolism in the regulation of T cells has been established [8, 9]. The metabolic programs engaged by T cells during specific contexts are not solely hallmarks of cellular states and bioenergetic needs but instead are active drivers of T cell fate and

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function. Macroautophagy is an important process in the regulation of cell metabolism, which has gained increasing attention due to its ability to modulate T cell fate and function, at least in part through the regulation of T cell metabolism. Moreover, as an outcome of TCR and IL-2 signaling, macroautophagy represents an important mechanistic link between T cell signaling and metabolic programs [3, 4, 10, 11].

2. Metabolism drives T cell fate and function

Upon antigen recognition, T cells rapidly upregulate aerobic glycolysis—a metabolic hallmark of T cell activation whereby cells employ glycolysis despite high levels of oxygen [9]. Perhaps paradoxically, the rate of aerobic glycolysis, which produces less ATP per molecule of glucose than mitochondrial oxidative phosphorylation, is increased at a time when expectedly T cells would require more efficient metabolism to meet a large energetic and biosynthetic demands to sustain cell proliferation and cytokine production. The purpose of increased glycolytic activity remains to be fully elucidated, but likely extends beyond that of merely providing ATP or even carbon for biosynthesis, as glucose does not contribute to most of carbon in proliferating T cells [12]. It has been proposed that glycolysis may be necessary to replenish NAD^+ , which is reduced to NADH for use as a cofactor by many enzymes [13], and it also may provide some metabolic intermediates for macromolecule synthesis, including nucleotides, amino acids, and fatty acids [14]. In addition, metabolites also may directly act as signaling molecules [15]. There is also evidence that glycolysis not only supports metabolic processes that are necessary for T cell activation but also may directly control effector responses. For instance, increased glycolytic activity engages available glyceraldehyde 3-phosphate dehydrogenase (GAPDH), thereby relieving GAPDH-mediated post-transcriptional inhibition of $\text{IFN}\gamma$ translation [16].

Regardless of the precise roles of glycolysis in T cells, the fact that glucose uptake by T cells is a limiting factor to proliferation and effector cytokine production [17] underscores the ability of metabolism to drive T cell responses. This intimate link between T cell metabolism and function has been expanded by studying the role of metabolism in another antigenic outcome: anergy—a mechanism of peripheral T cell tolerance that classically is thought to arise from suboptimal stimulation [18, 19]. Metabolic inhibition during T cell activation induces anergy even in the presence of costimulation, while anergic cells fail to upregulate their metabolism in response to re-stimulation [20].

In addition to the regulation of T cell activation and tolerance, T cell metabolism has also been shown to direct T helper subset fates. Th1, Th2, and Th17 cells (effector T cells, Teffs) express high levels of the glucose transporter Glut1 and have increased glycolytic activity compared to regulatory T cells (Tregs), which have increased rates of lipid oxidation [21]. These characteristics do not merely represent metabolic profiles of Teffs versus Tregs, but they actively determine differentiation and polarization. For example, Th17-polarizing conditions have been shown to induce expression of glycolytic enzymes and to increase glycolytic activity, while inhibition of glycolysis reciprocally reduces generation of Th17 cells and promotes Treg differentiation [22]. Mechanistically, glycolysis, and likewise glutaminolysis, may drive Th17 differentiation at least in part by limiting the availability of fructose-6-phosphate to the hexosamine/N-glycan branching pathways, which leads to

upregulation of the expression of IL-2 receptor- α (CD25) and drive Treg differentiation [23].

In addition to increased glycolytic activity, glutaminolysis is also upregulated upon TCR stimulation through enhanced glutamine uptake and increased glutaminase activity [24, 25]. Activation-induced changes in glycolysis and glutaminolysis must be carefully modulated to drive appropriate immune responses. The uptake of glucose and glutamine is regulated by tightly controlled expression and trafficking of transporters of these key nutrients [25–30]. Globally, metabolic regulators, including c-Myc, estrogen-related receptor alpha (ERR α), hypoxia-inducible factor (HIF)-1 α , AMP-activation protein kinase (AMPK), and mammalian Target of Rapamycin (mTOR), modulate nutrient uptake as well as expression and activity of metabolic enzymes [8, 31–36]. Notably, these regulators have dual roles in the regulation of both T cell metabolism and function [8]. Moreover, some of them, such as mTOR and APMK, have well-defined roles in the regulation of macroautophagy [33, 37–39], which supports a common link among the regulation of T cell function, metabolism, and macroautophagy.

mTOR has been established as a key regulator of metabolism, macroautophagy and T cell fate and function. The mTOR complex 1 (mTORC1), formed by mTOR, regulatory-associated protein of mTOR (Raptor), DEP domain-containing mTOR-interacting protein (Deptor), 40kDa proline-rich Akt substrate (PRAS40), and mammalian lethal with SEC13 protein 8 (mLST8), has been shown to modulate glycolysis, the pentose phosphate pathway, and lipid biosynthesis by inhibiting 4E-BP1 and activating S6K1, which in turn increase expression of HIF1 α and the processed active form of sterol regulatory element-binding protein (SREBP1), respectively. Downstream, HIF1 α was shown to mediate glycolytic responses, while SREBP1 was shown to mediate changes in the activity of the pentose phosphate pathway and lipid biosynthesis in mouse embryonic fibroblasts [31]. Using a variety of mTORC1- and mTORC2-deficient T cell systems, several groups have previously shown that mTOR regulates Th1, Th2, Th17, and Treg differentiation [40–44]. Furthermore, mTOR also has been shown to regulate CD8⁺ memory formation [45].

AMPK is another regulator of T cell metabolism and function that also has well-defined roles in the regulation of macroautophagy [37]. In T cells, AMPK is activated by TCR signaling events that lead to increases in intracellular calcium levels and activation of the calmodulin-dependent protein kinase kinase (CaMKK) pathway; it has been proposed that activation of AMPK following TCR engagement occurs in anticipation of depletion of energy stores during T cell activation rather than in response to the classical stimulus of energy stress [34]. AMPK phosphorylates a variety of downstream targets to activate catabolic pathways and inhibit anabolic pathways—including glucose, fatty acid, and protein metabolism [46, 47]. Moreover, when glucose levels are low, AMPK can further support the necessary metabolic requirements of T cells by increasing glutamine uptake and glutaminolysis, [48]. In addition to promoting energy production, AMPK inhibits processes that consume energy. For example, AMPK phosphorylates acetyl-CoA carboxylase 1 (ACC1) to inhibit fatty acid biosynthesis [49]. AMPK also inhibits mTOR activity to limit protein synthesis via phosphorylation of tuberous sclerosis complex 2 (TSC2) [50] and Raptor [51]. At least in part due to its ability to regulate metabolic switches in response to

glucose deprivation, especially the upregulation of fatty acid oxidation and restraint of mTORC1 activity, AMPK also plays an essential role in CD8⁺ T cell memory formation [52, 53].

Altogether, studies on mTOR and AMPK and other metabolic regulators over the past decade highlight the notion that T cell metabolism is not merely a downstream effect of T cell activation and differentiation, but rather it can actively participate in the instruction of these processes. Identifying key regulators and cellular processes that coordinately modulate T cell metabolism, function, and fate currently is an area of intense research. In this review, we will discuss a metabolic process, macroautophagy, which has been identified as a critical regulator of T cell biology and exists alongside the hitherto described metabolic regulators and signaling axes.

3. Autophagy maintains both basal and induced T cell functions

Autophagy has gained increasing attention due to the different roles it plays in human physiology and the pathogenesis of many diseases, including cancer, neurodegeneration, inflammatory diseases, autoimmunity, heart disease, and liver disease [reviewed in [54]]. Autophagy constitutes one of two main cellular pathways for protein degradation (the other being the ubiquitin-proteasome pathway). Three main forms of autophagy have been described in mammalian cells that represent different mechanisms through which substrates can reach the lysosome. Microautophagy is characterized by invaginations of lysosomal membranes that capture cargo and then pinch off and are degraded by lysosomal hydrolases [55]. Chaperone-mediated autophagy is defined by the heat shock-cognate protein of 70 kDa (Hsc70)-mediated recognition of KFERQ-motif-containing soluble proteins, which are then transported to the lysosomal membrane to interact with the lysosome-associated protein type 2A (LAMP-2A). Once substrates bind LAMP-2A, multimers of this protein assemble to form a translocation complex that translocates protein substrates across the lysosomal membrane to be degraded [56]. Macroautophagy is characterized by the generation of *de novo* formed double-membrane vesicles (“autophagosomes”) that enclose cytosolic content and eventually fuse with the lysosome. Although CMA is also implicated in the regulation of T cell fate and function at least in part by degrading negative regulators of T cell activation [57], we will focus this review on macroautophagy (from here on referred to as “autophagy”), due to more extensively established links between this form of autophagy and cellular metabolism in T cells.

Briefly, the process of autophagy is initiated by the action of two complexes, the Unc-51-like kinase (ULK) complex and the Beclin-1/Vacuolar protein sorting protein 34 (Vps34) PI3K-III complex, which regulate the formation of an initial limiting membrane [58, 59] (Fig. 1). Subsequent elongation of that initial limiting membrane and autophagosome maturation to enclose cytosolic content (“cargo”) is regulated by the cascade of two ubiquitin-like conjugation systems of autophagy-related (Atg) proteins: Atg12-Atg5-Atg16(L) and Atg8/microtubule-associated protein 1 light chain 3 (LC3)-phosphatidylethanolamine, which associate with the autophagosome membrane [60–62]. Autophagosomes eventually fuse with lysosomes in a process mediated by Soluble NSF (N-

ethylmaleimide-sensitive factor) Attachment Protein Receptor (SNARE) proteins to form autolysosomes, where cargo will be degraded and recycled back into the cytosol [62–64].

Although in the past autophagy was described as a non-selective, in-bulk degradation process, evidence in recent years demonstrates that autophagy can selectively sequester and degrade specific organelles (*e.g.* mitophagy, ERphagy...), pathogens (xenophagy), lipid droplets (lipophagy), ribosomes (ribophagy), protein aggregates (aggresophagy), macromolecules, and even specific proteins [reviewed in [65]]. This specificity can be achieved through adaptor proteins that recognize the cargo and interact with LC3 through specific motifs (WXXI/L)—termed “LC3-interacting regions” (LIR) [66]. Autophagic cargo receptors include, among others, p62/sequestosome-1 (SQSTM1), neighbor of BRCA1 gene 1 (NBR1), nuclear dot protein 52 kDa (NDP52), Tax1-binding protein 1 (TAX1BP1), and optineurin (OPTN). Importantly, these adaptors contain a ubiquitin-binding domain, which can recognize ubiquitinated substrates, LIRs, and dimerization/multimerization domains [66].

In addition to its catabolic capacity to turnover macromolecules and organelles in basal conditions, autophagy is also induced under stress conditions, such as nutrient deprivation, oxidative stress, hypoxia, or ER stress [67]. The capacity of autophagy to degrade cellular content in basal and stress-induced conditions mediates important functions in cellular metabolism. These include generating energy substrates, recycling essential molecular building blocks from proteins, lipids, and glycogen and controlling the activity of metabolic regulators [68]. These functions may be especially important as T cells encounter different environmental stresses as they travel throughout the immune compartment and peripheral tissues with varying nutrient and oxygen levels. Moreover, T cells may also experience cell-intrinsic stressors, such as antigen-recognition-mediated activation, that can also induce autophagy [3–5].

We discuss the roles of autophagy in T cells in the next section with special focus on the role of autophagy in T cell metabolism. However, it also is important to acknowledge the role that autophagy has in the regulation of differentiation and function of other lymphocyte populations, including B and NKT cells [69–73], and also in many other cells and processes that participate in an immune response, including pathogen clearance, anti-viral type-I interferon responses, or antigen presentation [reviewed in [74, 75]]. Furthermore, Atg proteins can also engage in autophagy-independent processes, some of which (*e.g.* LC3-associated phagocytosis) have been shown to participate in the generation of efficient immune responses [76, 77].

Autophagy is an essential catabolic process in T cells

Although the activity of autophagy is maintained at lower levels in resting T cells, it is markedly upregulated upon activation [3–6]. The potential purposes of this upregulation are summarized in Figure 2. Using a variety of autophagy-deficient T cell models, several groups have demonstrated a key homeostatic role of autophagy in T cell proliferation and survival [6, 78–81]. Based on observations that T-cell-specific Atg3-, Atg5-, and Atg7-deficient mice had reduced numbers of CD4⁺ and CD8⁺ T cells in the spleen and lymph nodes, it was also determined that autophagy-deficient T cells showed increased rates of

apoptosis, marked by greater caspase-9 expression [6, 78, 80]. In addition, in a Beclin-1-deficient T cell model, decreased numbers of CD4⁺ and CD8⁺ T cells correlated with increased rates of apoptotic cell death [79]. Beclin1-deficient cells also had increased levels of pro-caspase 3 and 8, Bim and Bcl-2 [79]. Autophagy (more specifically, mitophagy) has a key role in regulating the homeostasis of mitochondria by controlling their turnover as a quality control mechanism [78, 80]. Consequently, increased apoptotic cell death in autophagy-deficient cells has been linked to inefficient clearance and accumulation of mitochondrial content in peripheral T cells, which results in increased ROS production [78, 80]. Owing to autophagy-related perturbations in turnover of mitochondria and pro-apoptotic factors, these data support that decreased survival, at least in part, may explain decreased CD4⁺ and CD8⁺ T cell numbers in autophagy-deficient models. In addition to defects in survival, reduced CD4⁺ and CD8⁺ T cell number may also be explained by defects in proliferation in autophagy-deficient cells. The cyclin-dependent kinase inhibitor CDKN1B/p27/Kip1 was found to be elevated in autophagy-deficient naïve T cells and its accumulation after TCR stimulation resulted in reduced proliferation [82]. Collectively, these studies support that autophagy is necessary for the targeted degradation and turnover of organelles, apoptotic and cell cycle proteins, which need to be carefully modulated to sustain proliferation and survival of T cells.

Upon stimulation, several signaling events downstream of the TCR must occur to initiate and maintain activation. Autophagy has been shown to modulate at least one major TCR signaling event. Bcl10, which mediates TCR-to-NFκB signaling, is recognized by the autophagic cargo receptor, p62, and degraded following activation in effector T cells. Consequently, inhibition of autophagy by 3-methyladenine led to the accumulation of Bcl10, supporting an important role of autophagy to prevent unchecked TCR signaling that would otherwise lead to inappropriate T cell responses [83].

In addition to participating in the regulation of T cell proliferation, survival, and TCR signaling, autophagy has recently been shown to control CD8⁺ T cell memory generation [10, 84]. Mice bearing Atg7-deficient CD8⁺ T cells showed impaired memory formation using influenza or murine cytomegalovirus models, as well as diminished recall responses to secondary influenza infection [84]. Similarly, in a granzyme-Cre Atg7^{fl/fl} mouse model, CD8⁺ T cells had cell-intrinsic defects in memory formation in response to lymphocytic choriomeningitis virus infection [10]. Autophagy activity may increase at the peak of CD8⁺ Teff responses, suggesting that autophagy could play an important role during the transition from Teff to T memory (Tmem) CD8⁺ cells [10]. Both studies also linked defects in CD8⁺ T cell memory formation to failure to induce metabolic switches, namely the upregulation of fatty acid oxidation, which is key to CD8⁺ T cell memory formation [10, 52, 84].

3. Regulation of autophagy is cell type and context dependent

Given the array of functions of autophagy in T cells, the regulation of autophagy activity is essential to properly control T cell function. Studies on the ability of nutrient stress to induce autophagy have revealed mTOR as a negative regulator of autophagy and AMPK as a positive regulator of autophagy. As previously discussed, these are also well-characterized metabolic regulators. This overlap among regulators of T cell function, metabolism, and

autophagy highlights not only their intimate link but also suggests a central role for autophagy in the control of T cell metabolism and its downstream effects on T cell function.

mTOR and AMPK coordinately regulate autophagy, especially in response to changes in the availability of nutrients. AMPK has been shown to activate autophagy activity through phosphorylation of ULK [37], an important driver of early autophagosomes formation, as well as by inhibition of mTOR activity through phosphorylation of TSC2 [50] and Raptor [51]. mTOR is able to negatively regulate autophagy by inhibiting ULK-AMPK interactions [37] as well as preventing the formation of the ULK-Atg13-FIP200 complex [85]. Nevertheless, there is growing evidence that other mechanisms also contribute to the regulation of autophagy in addition to mTOR- and AMPK-mediated mechanisms as compounds such as the disaccharide trehalose, spermidine or resveratrol can induce autophagy without affecting mTOR kinase activity [86–89].

Our understanding of T-cell specific mechanisms of regulation of the induction of autophagy is still limited. Over the past decade, evidence from several groups has shown that autophagy is induced in activated T cells [3–6]. Given the role of mTOR as a canonical negative regulator of autophagy, at least in other cell types [37, 85, 90–92], it is intriguing that mTOR activation is not merely required for T cell activation but also acts as a tolerance avoidance mechanism [93] and yet the induction of autophagy, which mTOR negatively regulates, is also necessary for efficient activation-induced proliferation [4]. These observations suggest that TCR stimulation activates both mTOR and autophagy, which supports the existence of mTOR-independent mechanisms of autophagy induction in T cells.

We have recently characterized the cytokine-mediated regulation of autophagy in effector CD4⁺ T cells [3]. Cytokines that signal through the common γ -chain receptor, including IL-2, IL-4, IL-7, and IL-15, activate autophagy in a JAK-mediated manner in naïve and effector CD4⁺ T cells [3]. Given the important role of IL-2 signaling in the regulation of T cell function [94], it is possible that some of the IL-2-mediated effects might be achieved in part through the induction of autophagy.

Overall, greater characterization of the regulation of autophagy in T cells is still needed to further our understanding of the mechanisms that control the activity of this essential process in T cells, as well as to provide further insight into its physiological roles.

4. Autophagy is a novel regulatory mechanism of T cell metabolism

Over the past couple decades several studies have revealed that cellular metabolism is not only a passive hallmark of T cell function but rather an active driver of T cell fate and function [8, 9, 95, 96]. At the same time, autophagy has emerged as an essential catabolic process in T cell biology. We are beginning to appreciate that autophagy may be a mechanism by which T cells regulate metabolism and thereby modulate differentiation and function. Indeed, defects in cytokine secretion and cell proliferation upon activation of autophagy-deficient effector T cells is associated with a decreased ability to upregulate ATP production [4]. It is likely that the ability of autophagy to degrade proteins, lipids and glycogen to provide energy substrates [68] may support activation, while inhibition of this

catabolism would prevent efficient activation. A new mechanism has been recently proposed to support the ability of autophagy to regulate T cell metabolism through the activation of mTORC1. In process regulated by TAX1BP1, autophagy-mediated degradation of cytosolic proteins provides L-cysteine that activates mTORC1 to drive metabolic changes necessary for cell proliferation [97]. Consequently, CD4⁺ T cells deficient in TAX1BP1 fail to initiate glycolytic anabolic changes to meet the energetic demands of activation and show reduced Hexokinase 2 and Glut1 expression [97].

As mentioned above, in addition to an important role in meeting the metabolic demands of T cell activation, autophagy has also been implicated in the regulation of T cell metabolism during the transition from CD8⁺ Teff to Tmem. Autophagy-deficient CD8⁺ T cells showed defects in memory formation that were associated with metabolic perturbations, especially of mitochondrial fatty acid oxidation [10]. In those cells Glut1 expression was not properly downregulated during the transition from Teff to Tmem [84]. It is also possible that the metabolic switch from glycolysis to fatty acid oxidation that is required to drive efficient CD8⁺ memory formation might also depend on the ability of autophagy to degrade lipid droplets [98], which has been recently shown to be essential to support neutrophil differentiation [99]. Furthermore, metabolic defects in mitochondrial oxidative phosphorylation may be further compounded by failure to turnover mitochondria in autophagy-deficient T cells [4, 78, 80].

Autophagy activity is also increased in Tregs compared to other CD4⁺ T cells, which restrains glycolytic activity, at least in part through inhibition of PI3K-PDK1-mediated mTORC1 activity and c-Myc expression [11]. Consequently, mice with a T cell specific deletion of Vps34 showed defective homeostasis and function of Tregs, whereas Tregs from Foxp3-Cre *Atg7^{fl/fl}* mice had impaired Treg lineage stability with greater loss of *Foxp3* expression and acquisition of inflammatory cytokine expression [11, 70]. Similar results were observed in mice with a deletion of *Atg16L1* in T cells, where Treg but not Th2 homeostasis was markedly affected [100]. Interestingly, supporting a key role of autophagy in the regulation of Treg metabolism, deletion of *Atg16L1* in Tregs resulted in increased expression of glycolytic enzymes while the expression of enzymes involved in fatty acid oxidation was reduced [100]; furthermore, decreasing glycolytic activity by targeting pyruvate dehydrogenase kinase or by inhibiting c-Myc expression and function rescued *Foxp3* stability defects in autophagy-deficient Tregs [11].

5. Concluding remarks

Although the mechanisms by which autophagy regulates T cell differentiation and function are still not fully characterized, it has become evident that autophagy may coordinate the metabolic programming of T cells to determine fate and function. The ability of autophagy to act upstream of canonical metabolic regulators suggests a central regulatory role in these processes.

Dysregulated autophagy activity is also fundamental to many diseases in which T cells either play a role in pathogenesis or can be manipulated pharmacologically to improve outcome [54]. In response, a growing number of pre-clinical and clinical trials are underway to test

both novel autophagy modulators and re-purposed therapies that are now understood to target autophagy [101, 102]. An emerging theme in T cell metabolism and autophagy is the differential requirement in specific T cell subsets [10, 11, 21, 40, 52, 84]; therefore, it is intriguing to envision therapeutic strategies that could target T cells and further gain specificity on effector or regulatory subsets based on their intrinsic needs for autophagy.

Although autophagy has been well studied in other cell types, additional studies in T cells are needed to understand the fundamental mechanisms that regulate its activity. Furthermore, it is also important to define interactions and possible feedback mechanisms between autophagy and metabolic regulators, as has been shown for mTOR [11, 97]. How other metabolic regulators may be modulated by autophagy in T cells is currently unknown. Despite unifying themes of protein motifs on substrates or adaptor proteins that mediate autophagy selectivity, further characterization of the wide array of potential substrates of autophagy in T cells and better tools to predict when these targets may be degraded are also required, as selection of autophagosome cargo appears to be intimately linked to the functional state of T cells. The identification of specific substrates would further inform the metabolic requirements of T cells and would enhance our understanding of the role of autophagy in different immune contexts.

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Highlights

- Autophagy, a key catabolic process in T cells, regulates cell homeostasis and survival.
- Autophagy is induced in CD4⁺ T cells in response to TCR engagement and common- γ chain cytokine receptor-mediated signaling.
- Context-dependent induction of autophagy regulates T cell differentiation and function.
- Autophagy modulates T cell metabolism by regulating glycolysis and oxidative phosphorylation.

Figure 1. Mechanism of autophagy in T cells

TCR-induced expression of IL-2 leads to activation of the IL-2 receptor (IL-2r), which leads to the activation of autophagy in T helper cells in a JAK1.3-dependent manner. The initiation of autophagy and formation of the limiting membrane and then phagophore are driven by two complexes: the ULK-complex—ULK/FIP200/Atg101/Atg13; and the Beclin-1/Vps34 complex (class III phosphatidylinositol-3-kinase complex (PI3KC3) containing Beclin-1, Vps34, Vps15, Atg14 and Ambra1). Two cascades of ubiquitin-like conjugation systems regulate the elongation and maturation of the *de novo* formed double-membrane vesicle to form the autophagosome, which eventually fuses with the lysosome to degrade cargo. The lipidation of LC3 to PE allows association with the membranes of the autophagosome. This allows specific substrates to be targeted to the autophagosome by interaction with LC3 via LC3-interacting motifs as well as autophagic cargo receptors with LC3-interacting regions. The specific sequestration and degradation of substrates complements in-bulk mechanisms of degradation of organelles, macromolecules (*i.e.* proteins, lipids, glycogen), and other cellular components.

Figure 2. Roles of autophagy in T cells

Engagement of the TCR and CD28 signaling pathways is required for full activation of T cells, which can be further augmented by signaling through the IL-2r. Autophagy is maintained at basal levels in naïve and resting T cells and the cargo of autophagosomes largely consists of organelles, such as mitochondria (1), which is an important quality control mechanism. TCR- and IL-2r-signaling induce autophagy. Upon activation the cargo nature switches to mostly cytosolic components, and activation-induced degradation of specific proteins (p27, caspases, Bim or Bcl10) has been described to control proliferation, survival and activation. Important roles of Autophagy have been reported in the regulation of cell homeostasis (2); TCR signaling transduction (3); the breakdown of macromolecules to recycle cellular building blocks and generate signaling metabolites (4); and the regulation of T cell metabolism (5). In addition, macroautophagy has been shown to be necessary for CD4⁺ T cell activation, cell survival, and proliferation (6), differentiation of specific CD4⁺ T helper subsets, (7), enforcing Treg lineage stability (8), and for generation of CD8⁺ memory T cells (9).