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Review Article

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# The Impact of Autophagy on The Differentiation of Immune Cells

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**Abstract**

*Autophagy, as a conservative lysosomal degradation pathway, has been well studied for its multiple functions in the immune system. Autophagy has been gradually explored for the regulation of immune cell differentiation. In order to explore the specific mechanism, it is necessary to summarize the role of autophagy in the proliferation and differentiation of immune cells. It is summarized the effects of autophagy in some researches on the function and differentiation of immune cells by introducing the function of autophagy selective degradation. In this review, we discuss the effect of autophagy in the differentiation of immune cells.*

**Keywords:** Autophagy, Immunocytes, Differentiation

## Introduction

People rely on the immune system to cope with the invasion of foreign pathogens. Our immune system is composed of a series of immune cells, including innate immune cells and adaptive immune cells. Innate immune cells mainly play a non-specific anti-infection effect. They are defense cells formed in the long-term evolution of the body. They can quickly produce immune response to the invading pathogens, and can also remove the damaged, aging or distorted cells in the body. Adaptive immune cells can produce specific response to a certain antigen and generate immune memory, therefore protect the body from being infected by pathogens carrying the same antigen for a long time.

Autophagy is a highly conservative intracellular degradation process, which can promote the degradation of cytoplasmic protein and damaged organelles. The degradation products can be reused in cell synthesis and metabolism process [1]. Both innate and adaptive immunity are affected by autophagy. Autophagy has been widely concerned in promoting phagocytic function of innate immune cells and improving antigen presenting ability of antigen presenting cells, and has an important role in virus immunity [2, 3]. Adaptive immune system needs a lot of nutrients to reserve, so as to complete the process from lymphocyte proliferation and differentiation to antibody production and memory cell formation. Autophagy is an important way to regulate metabolism. It can regulate the energy sources in cells by selectively degrading key metabolic organelles or substances, such as mitochondria, peroxisome and lipid drop [4-6]. Autophagy can help to quickly redirect the metabolism and logistics of cells [7].

Here, we reviewed the effects of autophagy on the proliferation, differentiation and function acquisition of various immune cells.

Autophagy Participates in Cell Preparation Before Differentiation

Immunocytes originated from bone marrow derived hematopoietic stem cells (HSCs). HSCs are hematopoietic precursor cells with high self-renewal ability and multiple differentiation potential. Lymphoid cells, including T and B cells, are usually derived from lymphoid stem cells differentiated by HSCs, while monocytes and macrophages are derived from myeloid stem cells. HSCs are located in the low oxygen environment in vivo. In order to generate the two kinds of precursor stem cells continuously, HSCs produce energy by low mitochondrial activity and high glycolysis, and maintain low level of reactive oxygen species (ROS) to obtain high antioxidant capacity [8].

Autophagy can ensure the self-renewal and reconstruction ability of HSCs in quiescent state by degrading mitochondria and maintaining low ROS level. Experiments show that the absolute number of HSCs in mice with deletion of autophagy related gene 5 (ATG5) is significantly reduced, and the survival ability and reconstruction ability of HSCs are decreased. Researchers believe that this is caused by the damage of mitochondrial clearance function mediated by autophagy [9]. It is shown in further observation that the immunocytes' population in spleen and lymph nodes of mice are also changed. The number of lymphocytes and red blood cells decreases significantly, which reflects that the defect of autophagy also affects the further differentiation of HSCs. An important sign for the end of quiescent state and the beginning of differentiation of HSCs is the transition of intracellular energy metabolism pathway from glycolysis to oxidative phosphorylation, followed by the gradual increase of ROS level generated by mitochondria [10].

Notch signal is a highly conserved pathway regulating cell proliferation and differentiation, which can inhibit the multi lineage differentiation of hematopoietic stem cells. Some experiments have found that ROS can down-regulate intracellular Notch signal by triggering autophagy, thus promoting the differentiation of hematopoietic stem cells [11]. These findings indicate that autophagy plays an important role in the maintenance of resting state and differentiation of HSCs. Some researchers found that low dose cytarabine can induce autophagy and promote differentiation of acute myeloid leukemia cells, which becomes a potential mechanism for the treatment of acute myeloid leukemia [12]. Therefore, autophagy may play a key role in the treatment of leukemia associated with HSCs differentiation and maturation disorder.

## The Selective Function of Thymus

Thymus is the place for differentiation, proliferation and selection of T lymphocytes. Thymocytes are transformed into T lymphocytes by thymus selection, and autoimmune tolerance is established. Thymus epithelial cells (TECs) are the key cells in the thymus selection process [13]. The TECs can be divided into two types, the cortical TECs (cTECs) are responsible for the positive selection, and the medullary TECs (mTECs) for the negative selection. The cTECs can obtain MHC restriction by expressing self-peptide-associated major histocompatibility complex (pMHC) and T cell receptors (TCRs). Autophagy plays a certain role in the process of presenting autoantigen by cTECs. Autophagosome formed by cytoplasm content can be fused with lysosome, and the presented protein can be processed into MHC-II related peptide, therefore affect the expression of MHC-II related peptide in cells [14]. The presence of autophagy can be detected in more than 60% cTECs and the deletion of ATG5 affects the positive selection of some CD4+ T cells [15]. However, autophagy plays a controversial role in the process of mTECs negative selection. Some experiments have found that the absence of mTOR pathway can seriously affect or even interrupt the differentiation of mTECs. Considering the inhibition of mTOR pathway on autophagy, the researchers detected the flux of autophagy and found that the level of autophagy increased, and confirmed that the increase of autophagy can reduce the production of mTECs, but Aichinger et al. proved that autophagy can also promote the expression of endogenous autoantigen of MTCs, it supports the selection of CD4+ T cells' tolerance [16, 17]. In the process of MTEC differentiation, autophagy plays different roles in various stages and even plays a role of inhibition according to the needs of cell function. This means that there is still a great exploration space for the study of autophagy regulation in the differentiation of TECs.

## Autophagy Participates in The Differentiation of Immune Cells

### Macrophages

Macrophages can phagocytize cell fragments and pathogens, which is an important defense line of the human immune system. In vitro, colony stimulating factor-1 (CSF-1) can induce the differentiation of monocytes into macrophages, which requires the participation of autophagy [18]. On this basis, obba et al. began to investigate the potential mechanism of autophagy affecting the differentiation of monocytes into macrophages [19]. It is found that CSF-1 receptor can activate CAMKK2-PRKAA1-ULK1 pathway, which is essential for the induction of autophagy. This pathway can restore part of normal monocyte differentiation in patients with chronic myelomonocytic leukemia (CMML). The two terminal types of macrophages include M1 and M2. The former secretes pro-inflammatory factors to participate in the immune process, while the latter secretes anti-inflammatory factors to regulate the immune response. Liu et al. studied ATG5 knockout mice and found that autophagy deficiency could induce pro-inflammatory macrophage phenotype by promoting M1 and inhibiting M2 macrophage polarization [20]. Similarly, the differentiation potential of M2 macrophages in Atg7 knockout mice was also inhibited [21]. Further observation showed that the above two kinds of mice had weight gain, and ATG5 knockout mice manifested obvious fatty liver. The catabolism of lipid droplets in liver is completed by lysosomes. Some studies have shown that autophagy participates in the catabolism of liver lipid droplets, while the polarization of M2 macrophages depends on fatty acid oxidation (FAO) [22, 23]. When autophagy is deficient, the cell activities will be hindered. It is speculated that autophagy may affect the polarization of M2 macrophages by participating in the lipolysis of lysosomes.

### Neutrophils

Granulocytes are the largest proportion of inflammatory cells in the blood, especially neutrophils. Neutrophils contain a large number of lysosomal enzymes, which can phagocytize pathogens and prevent the spread of pathogenic microorganisms in the body. However, after cell lysis, lysosomal enzymes will be released to dissolve surrounding tissues and form abscesses. Some researchers believe that the production of bone marrow neutrophils is regulated by autophagy. In ATG5 deficient mice, the proliferation of bone marrow neutrophil precursor cells and the accelerated differentiation of neutrophils were observed. Mature neutrophils accumulated in bone marrow, blood, spleen and lymph nodes, but the activity of these mature cells was not affected [24]. It is speculated that autophagy may negatively regulate the differentiation of neutrophils. However, the research of Leveque-El Moutti et al. showed that neutrophils could be stimulated by granulocyte colony-stimulating factor (G-CSF) while the stimulation was impaired in the absence of autophagy [25]. These results suggest that autophagy is involved in cytokine induced neutrophil differentiation, but may inhibit the production of precursor cells. Recently, some scholars have found that autophagy mediated lipid degradation can provide free fatty acids to support mitochondrial respiratory pathway, which is very important for neutrophil differentiation. Inhibition of autophagy mediated lipid degradation can lead to differentiation defects, which also corresponds to the fact that M2 type macrophage differentiation depends on FAO to a certain extent, it is speculated that autophagy mediated lipid degradation is involved in the differentiation of these two types of cells [26].

### Dendritic Cells (DCs)

Up to now, it is believed that autophagy can improve the antigen presenting ability of DCs, but the evidence of autophagy affecting DCs' early differentiation has not been found. However, autophagy plays an anti-apoptotic role in the transition from monocytes to DCs, and can indirectly promote the differentiation of DCs. The transition from monocytes to DCs is based on the anti-apoptotic process mediated by Bcl-2, while IL-10 can induce apoptosis of newborn DCs and inhibit autophagy. Previous studies have shown that IL-10 induced apoptosis was related to the decrease of Bcl-2 level and the extensive destruction of autophagy flux. Furthermore, this study found that the autophagy inhibitor, 3-MA, could inhibit

the differentiation of DCs by promoting apoptosis. It is speculated that autophagy plays a protective role in the process of monocyte differentiation into DCs [27].

MTOR signaling pathway contains two complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Tuberous sclerosis complex 1 (Tsc1) is an upstream negative regulator of mTOR pathway. Wang et al. knocked out Tsc1 in DCs, and the mTORC1 activity of DCs was enhanced, accompanied with the increase of glycolysis, mitochondrial respiration and lipid synthesis [28]. These metabolic processes are conducive to the differentiation of DCs, but not conducive to their continuous proliferation. It is believed that excessive activation of mTOR will cause abnormal cell growth and substance production, which will lead to metabolic stress. Once metabolites accumulated, it will cause cell cycle arrest and induce apoptosis. Autophagy plays an important role in scavenging intracellular metabolic by-products, especially ROS produced by mitochondrial respiration. It is speculated that the excessive activation of mTOR signal inhibits the activity of autophagy, thus hinders the clearance of metabolic by-products and the proliferation of DCs.

DCs are the only professional antigen presenting immune cells in human body. Therefore, they can easily affect the differentiation and function of T-lymphocytes, whereas they are affected by autophagy. If treated with yeast-derived whole β-glucan particles (WGPs), the intracellular autophagy activity of DCs would be enhanced, and the expression of MHC-II complex and costimulator CD86 would be increased on the surface of DCs. When autophagy was inhibited, the DCs' proliferation and IFN- γ secretion were decreased. These changes of DCs affect the proliferation of CD4+ T cells, and can induce helper T (Th) cells' differentiation towards Th1 type [29]. However, some scholars have found that in the experiment of allogeneic hematopoietic stem cell transplantation, the DCs of mice with Atg16L1 deficiency is often over-activated. It is confirmed that the number of DCs and the costimulatory molecule expression are increased, which leads to the proliferation and overreaction of T cells. It is suggested that autophagy has a certain effect in preventing over immunity [30]. However, this opinion is contradictory to the research that autophagy can promote the expression of DCs surface markers. Therefore, the mechanism of autophagy on the maturation of DCs promotes the maturation of immune phenotype needs further investigation. To summarize, it can be seen that the autophagy activity of DCs affects the differentiation process of T lymphocytes, which is undoubtedly a new vision for the treatment and prevention of human infectious diseases.

## Lymphocytes

### T lymphocytes

After selected in thymus, T lymphocytes can be divided into two categories according to their expression markers: CD4 + T cells and CD8 + T cells. The former helps the immune cells to exert their function and regulate immunity, while the latter mediates cytotoxicity and composes cellular immunity.

Autophagy is very important for maintaining the T-lymphocyte homeostasis [31]. In addition, autophagy participates in the energy metabolism pathway, which also plays a key role in regulating the proliferation and differentiation of T cells. IL-21 can stimulate mTORC1 and mTORC2, activate mTOR signal pathway, inhibit the autophagy of regulatory T cell (Treg), and affect the differentiation and function of Treg cells [32]. MTOR signaling pathway can also affect the differentiation balance of Th1 / Th2. Experiments showed that mTORC1 specific knockout T cells could not develop into Th1 cells, while Th2 differentiation was not affected [33]. It has also been found that arctiin can reduce Th1 cell differentiation by inhibiting mTORC1 activity [34]. Autophagy also has a negative effect on Th cells' differentiation, that is, autophagy can induce the degradation of transcription factor PU.1 of Th9, which negatively regulates the homeostasis and differentiation of Th9 [35]. Although autophagy has not been proved to affect the differentiation of CD8+ T cells, autophagy is essential for the formation of memory CD8+ T cells. Some scholars have observed that autophagy is not necessary for the cloning and amplification of normal CD8 + T cells, but it has a significant effect on the formation of memory T cells. Defective autophagy pathway damages the formation of memory CD8 + T cell [36]. Metabolism also plays an important role in the formation of CD8+ memory T cells [37]. Some studies show that memory T cells rely on FAO in mitochondria [38]. Considering the regulatory function of autophagy on lipid degradation, the importance of autophagy can be seen in maintaining the survival of memory T cells.

### Invariant Natural Killer T Cells (iNKT Cells)

As a congenital T cell, the iNKT cells can recognize glycolipid antigen presented by CD1d and can induce DCs' maturation to start and maintain adaptive immune response. Many researchers have found that autophagy is essential for the proliferation and differentiation of the iNKT cells. In the absence of autophagy, the apoptosis of the iNKT cells increases in thymus [39]. The absence of Vps34, an important protein regulating autophagy initiation, will directly cause its development suppression in the stage 0 [40]. Autophagy defects can lead to the accumulation of mitochondrial superoxide and the death of apoptosis cells, which is unfavorable for the production of iNKT memory cells [41]. MTORC1 is important for the maturation of the iNKT cells. The development suppression of iNKT cells can be observed in mice with mTOR pathway defects. The number of iNKT cells in the early stage of mTOR knockout group is 60% lower than that of wild control group [42]. However, other studies have shown that mTORC1 can affect the development of iNKT cells whether it is low or over activated [43]. According to the inhibition of mTOR signaling pathway on autophagy, the exact mechanism of autophagy on the development and differentiation of iNKT cells needs further investigation.

### B lymphocytes

B lymphocytes are the important component of humoral immunity. Under the assistance of CD4 + T cells, B cells receive signals from B cell receptor (BCR) and costimulatory molecule CD40 for activation and proliferation after antigen stimulation, then differentiate into plasma cells (PCs), germinal center (GC) B cells and memory B cells [44].

The important function of GC is to export mature PCs and memory B cells. Compared with other resting B cells, B cells in GC show higher autophagy rate, which is related to the need for adequate nutrients for rapid proliferation. Martinez Martin et al. believed that the transition from typical autophagy to atypical autophagy played an important role in controlling the differentiation of B cells [45]. When the phosphoinoside interacting protein 2 (WIPI2), a

component of autophagy mechanism, is knocked out, the level of typical autophagy in B cells decreases, while the level of atypical LC3-II increases. Although the production of B cells in GC can be affected, the differentiation into antibody secreting cells (ASCs) is easier to be induced. The ability of ATG5 specific knockout B cells to differentiate into PCs is impaired, thus the effective antibody response cannot be produced [46]. In addition, autophagy can limit the expression of transcription inhibitor Blimp-1 and immunoglobulin through selective inhibition of endoplasmic reticulum and its stress signal response, so as to optimize the survival ability and ensure the survival of memory B cells [47]. MTOR signaling pathway can play an important role in the early and late stage of plasma cell differentiation through mTORC1. The inhibition of mTOR in mature plasma cells will lead to the low expression of key immunoglobulin binding protein (BIP) and interfere with the synthesis of plasma cell antibody, while the absence of mTOR will not affect the maintenance of long-lived memory plasma cells [48]. Furthormore, metformin can also change the AMPK-mTOR-STAT3 signaling pathway, that is, up-regulate the expression of AMPK and inhibit the activity of mTOR-STAT3, and limit the differentiation of B cells into PCs and GCs [49]. It is not difficult to see that autophagy not only plays a crucial role in the terminal differentiation of different types of B cells, but also exert an essential effort in maintaining the immune function of B cells.

## Summary

We can find that most of the cell activities are catabolism in regulatory and memory immune cells. Autophagy can support these cells to maintain a low metabolic state and ensure that the metabolic by-products can be removed in time, which plays a key role in maintaining the long-term effect of memory cells. However, effector immune cells tend to proliferate rapidly to cope with the challenge of infection. Active mTOR signal can promote the synthesis of intracellular substances, which is conducive to cell proliferation. Autophagy is inhibited correspondingly, but autophagy still plays an important role in the normal immune function of effector immune cells. There are still many gaps in the direct evidence that autophagy affects the differentiation of these immune cells. Autophagy indirectly participates in metabolism as the downstream of mTOR or AMPK pathway, or affects the immune function by changing the autophagy activity of key cells in the immune process, thus affecting the differentiation of related immune cells. Therefore, with more and more attention paid to the treatment and prevention of diseases today, autophagy has become a new research hotspot in the fight against infectious diseases by regulating the differentiation of immune cells and guiding the immune function to a favorable direction. The specific mechanism of autophagy and whether it can be applied in clinic still requires plenty experiments to explore.


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