9 The Interplay of Autophagy and the Immune System in the Tumor Microenvironment

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Abstract

The tumor microenvironment (TME) is a very complicated ecosystem that consists of cancerous cells coexisting with various noncancerous and immune cells. TME shows exclusive cellular crosstalk between cancer and other cell types that have prominent consequences on tumor initiation, progression, and development. Of note, the immune system is an important determinant in the TME for tumor development, thus highlighting the importance of immunotherapy for better cancer treatment. Recently, the multifaceted role of autophagy in cancer immunity in the TME is extremely debated and exploited for the development of cutting-edge autophagy-based cancer immunotherapeutics. Interestingly, autophagy limits the immune responses by regulating the action of immune cells and the generation of cytokines. On the contrary, some immune cells and cytokines also manipulate the function of autophagy. A growing number of study spotlights the context-dependent role of autophagy in cancer immunity: it can activate the anti-tumor immunity by sustaining the integrity of the immune cells; however, it can also help the tumor cells to bypass the immune checkpoints by constraining the immune cell functions during hypoxia. In this chapter, we delineate the basic process of autophagy, the role autophagy in maintaining the crosstalk between cancer cells and stromal cells, and in particular, focusing more

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on the interaction of autophagy with cancer immunity. Finally, we highlight the role of autophagy as an ideal candidate for cancer immunotherapy.

Keywords

Cancer · Tumor microenvironment · Immune system · Autophagy · Tumor stroma · Immunotherapy

9.1 Introduction

The tumor mass is not a solitary structure, rather a diverse population of cancer cells, extracellular matrix proteins, secreted factors, resident, and infiltrating host cells, together known as the tumor microenvironment (TME). More specifically, the TME consists of tumor parenchymal cells, mesenchymal cells, fibroblasts, lymph vessels, blood, tumor-infiltrating immune cells, chemokines, and cytokines (Balkwill et al. 2012). TME has a vital role in tumor initiation, development, and regulation. The immune system is a critical player of the TME. In recent years, the significance of the interaction between the immune cells and cancer cells was constantly acknowledged and included in the rising hallmarks of cancer (Hanahan and Weinberg 2011). The cancer cells adopt several mechanisms that prompt them to evade immune surveillance and destruction. In the past decades, a large number of immunotherapy blueprints have been established based on the immune evasion mechanisms and their clinical significance has been validated. In contrast to the traditional approaches to cancer therapy, the immunotherapy acts through encountering the immune cells inside or outside the TME and attacks the cancer cells (Yost et al. 2019), thus making the immunotherapy strategy with higher specificity and with lower off-target effects. Recently, accumulating pieces of evidence support the function of autophagy in modulating the TME, including the immune system of the tumor cells (Deretic 2012), thus making it an ideal target for effective cancer therapy. Autophagy is essentially a eukaryotic homeostatic process that regulates cancer initiation and progression in many ways. It has a dual role in cancer as the fate of tumor cells regulated by autophagy is extremely ambience dependent which ranges among tumor types, stages, microenvironment, and genetic contents (White 2012). In the beginning, autophagy acts as a pro-death mechanism by removing the impaired organelles, proteins, lipids, and ROS, thus attenuating cancer by behaving as a cellular quality control process (Fulda and Kogel 2015). However, with the advancement of cancer and in therapy resistance, autophagy performs as a pro-survival mechanism to fulfill the substantial metabolic demands necessary for tumor survival (Das et al. 2018a, b, 2019a, b). So, more insight into the unraveling of the interplay of autophagy and the immune system will provide the major directions for future anticancer treatment strategies.

9.2 The Basic Process of Autophagy

Autophagy is an evolutionary conserved catabolic process that is often triggered by diverse cellular stress conditions. During this process, the damaged cellular components are degraded by the lysosomes and in turn, enrich the cellular nutrient pool (Das et al. 2018a). To date, autophagy is mainly classified into three types, like chaperone-mediated autophagy, microautophagy, and macroautophagy, depending on the mechanisms required for the selection and the delivery of cargos into the lysosomes (Yorimitsu and Klionsky 2005). In chaperone-mediated autophagy, the chaperone proteins are actively involved in the selection of the targeted substrates and their translocation into the lysosomes (Kaushik and Cuervo 2012). In microautophagy, the lysosomal membrane undergoes invagination to sequester the cytosolic components into intralysosomal vesicles (Mijaljica et al. 2011). Macroautophagy (herein referred to as autophagy) is the most commonly studied autophagy that sequesters the cytoplasmic damaged substances into the autophagosomes followed by their fusion into the lysosome to form endolysosome for hydrolytic degradation (Wong et al. 2011). The basic mechanism of autophagy is regulated by a group of ATG genes and it is preserved from yeast to mammals. The autophagy process is executed by the sequential development of the phagophore, autophagosome, and autolysosome regulated by the mammalian target of rapamycin (mTOR) (Bhol et al. 2019). Initially, upon stress various damaged cellular contents are entrapped by the initiation membrane or phagophore inside the cytosol; afterward, it gives rise to a complete double-membrane complex called the autophagosome. Further, the autophagosome merges with the lysosome to give rise to the autolysosome which helps in the hydrolytic deterioration of the damaged cellular entities, leading to enriching the nutrient pool (Mizushima et al. 2002) as shown in Fig. 9.1. However, the detailed molecular mechanisms of autophagy and its modulation in cancer cells were extensively depicted elsewhere in our recent review (Das et al. 2019a) and we refer the readers to this work for further details.

9.3 Autophagy in Maintaining the Crosstalk Between Cancer Cells and Tumor Stroma

Tumors occur from normal cells due to DNA mutations which lead to uninhibited cell growth. Initially, it has been thought that tumors are the collection of isolated diverse cell masses. But recent scientific results suggest that tumors are vastly heterogeneous and need to be considered as organs. It contains various types of special tumor cells and other tumor-related cell types such as immune cells, endothelial cells, and fibroblasts. These kinds of cellular components are called the tumor–stromal microenvironment (Maes et al. 2013; Denton et al. 2018). Tumor stroma comprises of various stress factors, like the absence of growth factors, intratumoral hypoxia, and tumor acidosis. Such kind of stress stimulates autophagy in tumor stroma to maintain energy homeostasis in cells by transporting intracellular damaged substances to lysosomes for degradation and recycling. Here, we are going

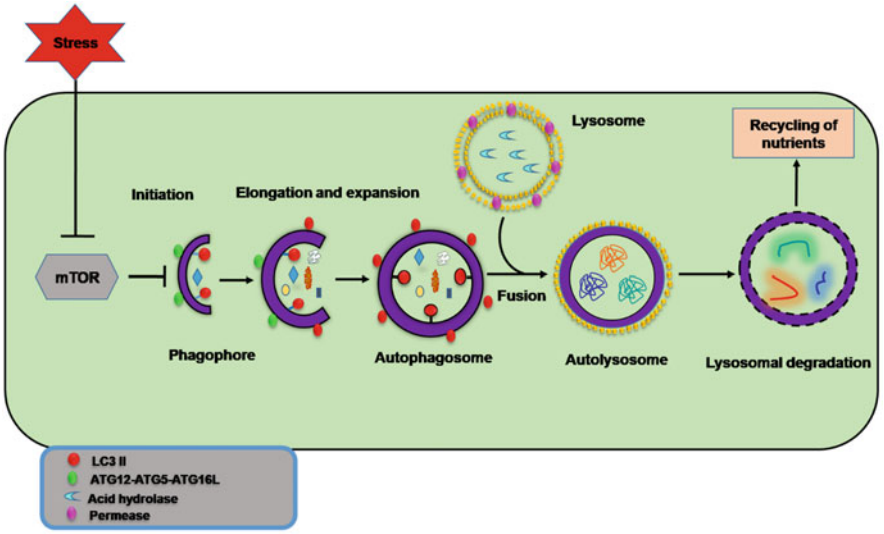

Fig. 9.1 The basic process of autophagy: Initially upon stress, the autophagy process begins with the inhibition of mTOR. Then the isolation membrane or phagophore is formed which further undergoes elongation and expansion by engulfing the damaged cargos and gives rise to a complete double-membrane structure called the autophagosome. Further, the autophagosome fuses with the lysosome to form the autolysosome. Finally, lysosomal degradation of damaged cargos takes place inside the autolysosome and the nutrients are recycled

to delineate the pivotal role of autophagy involved in the interactions between cancer cells and tumor stromal microenvironment.

9.3.1 Autophagy and Tumor-Associated Macrophages

Tumor-associated macrophages (TAMs) are classified as highly expressed innate immune cells in tumor stromal microenvironment (Lin et al. 2019). They are most important for cancer-related inflammation. Molecules secreted from tumor cells are accountable for the activation of macrophages. In the tumor stroma, TAMs perform a key role in the development of the tumor by generating cytokines, like IFN-γ, IL-6, IL-8, and IL-10 (Comito et al. 2014). Cytokines are important for the progression of chronic inflammation and the anti-tumor response, but they also initiate the advancement of cancer through inflammation. Chemokines, such as CCL2, engage monocytes from blood vessels in the tumor stromal microenvironment and later differentiate into TAMs (Chen and Bonaldo 2013). It has been illustrated that CCL2 plays a key role in apoptosis suppression in monocytes by stimulating antiapoptotic proteins (Roca et al. 2009). Besides that, CCL2 also hyper activates autophagy in monocytes to suppress apoptosis (Roca et al. 2009). This indicates that autophagy is very essential for the engagement of monocytes. CSF-1 is one of the important cytokines that differentiate macrophages from monocytes. As CSF-1 stimulates

monocytes, autophagy is triggered by the phosphorylation of ULK1 (Jacquel et al. 2012a, b). Another cytokine CSF-2 contributes an important role in the differentiation of monocytes to macrophages through the MAPK/JNK pathway through inhibiting Atg5 cleavage and the synergy between BECN1 and BCL-2, both are essential for autophagy activation (Zhang et al. 2012). Such autophagy induction helps a critical conversion from monocyte apoptosis to differentiation. Overall, these findings suggest that autophagy operates a very critical function in every step of TAMs production and which leads the cancer progression through supporting tumor cells during the transition to malignancy (Noy and Pollard 2014) (Fig. 9.2).

9.3.2 Autophagy and Cancer-Associated Fibroblasts

Cancer-associated fibroblasts (CAFs) are the special kind of cells present in tumor stromal microenvironment, which induces tumorigenicity by instigating the remodeling of the extracellular matrix or by producing cytokines (Xing et al. 2010). The function of autophagy in CAF biology is very complicated. In the early stages of tumor development, normal fibroblasts cells nearby to the tumor go through a critical adaptation due to the vice versa interaction with tumor cells and evolve into a more myofibroblastic phenotype. Such evolved fibroblasts are usually recognized as CAFs. It has been observed that increased autophagy acts an important role in CAFs to support energy metabolism and the growth of neighboring epithelial cancer cells (Fig. 9.2). Such kind of paracrine crosstalk is led by the secretion of hydrogen peroxide from the cancer cells, which leads to the generation of oxidative stress and induces senescence in neighboring CAFs (Martinez-Outschoorn et al. 2011). Senescent CAFs lost mitochondrial function due to the increased autophagy, and mitophagy (induced by oxidative stress) and shifted toward aerobic glycolysis, called "Warburg Effect," a hallmark of the cancer phenotype (Hanahan and Weinberg 2011). This generates metabolic byproducts such as glutamine, lactate, free fatty acids, and ketone bodies that nourish oxidative phosphorylation in the tumor cells and contribute to anabolic growth (Jaboin et al. 2009; Tittarelli et al. 2015). Besides that, autophagic elimination of a tumor suppressor protein, the caveolin-1 negatively regulates Ras signaling in tumor stroma (Martinez-Outschoorn et al. 2010) which is connected with early development from DCIS to invasive cancer (Witkiewicz et al. 2009), metastatic disease in prostate cancer, and lymph node metastasis in breast cancer (Di Vizio et al. 2009). Additionally, autophagy may also stimulate the release of MMPs and pro-migratory cytokines from CAFs (Lock et al. 2014), which leads to further metastasis of the tumor cells. It has been illustrated that the growth and the metastasis of tumor cells are promoted when they are co-injected with senescent fibroblasts and overexpressed with pro-autophagic molecules that are genetically modified in the nude mice (Jaboin et al. 2009). But on the other side, autophagy is upregulated in tumor cells and suppresses growth when they are transplanted alone. Such results demonstrate that CAFs generated metabolic byproducts through autophagy play a critical role in tumor–stromal cell growth by fulfilling the high energy demands of the tumor cells.

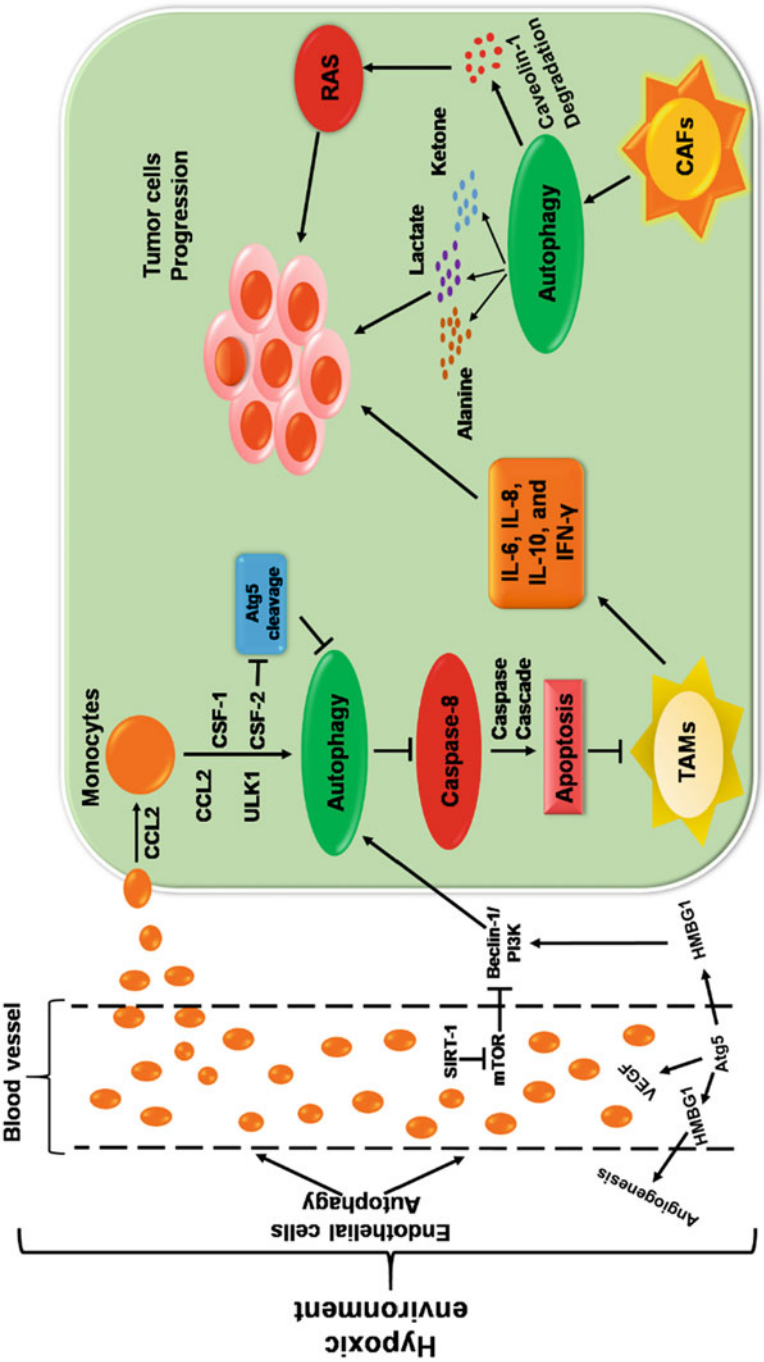

Fig. 9.2 Autophagy in the tumor stromal microenvironment. In the hypoxic and oxidative stress conditions in the tumor stroma, autophagy is stimulated by SIRT-1 and HMBG1 which helps endothelial and tumor cells to survive and grow. In the hypoxic tumor, monocytes from the endothelial cells are recruited into the cytosol by CCL2 chemokines. Monocytes are differentiated into TAMs via activated autophagy, which is stimulated by CCL2, CSF-1, CSF-2, and ULK1. Autophagy also suppresses apoptosis in monocytes. Later on, differentiated TAMs release cytokines, such as IL-6, IL-7, etc., which promote tumor progression. In oxidative stressed tumor stromal microenvironment, senescence CAFs go through autophagy and release metabolic byproducts, such as alanine, lactate, and ketone. Also, highly activated autophagy in such stressed condition degrades caveolin-1 which increases RAS activity and leads cancer development

9.3.3 Autophagy and Tumor-Associated Endothelial Cells

Emerging studies are indicating that autophagy is involved in the vital functions of the tumor-associated vasculature. In the high-stress tumor–stromal conditions, endothelial cells undergo nutrient deprivation and hypoxia due to low blood supply in solid tumors. Such conditions lead to vessel malfunction. For example, tumor vessels become more permeable and less stable as compared to normal vessels (Siemann 2011). Endothelial cells use autophagy as a survival mechanism to escape such stresses (Filippi et al. 2018). Study suggests that under the oxidative stress in the tumor stroma, autophagy is stimulated by SIRT-1, which helps endothelial cells to survive (Ou et al. 2014). SIRT-1, a NAD-dependent deacetylase, activates autophagy through PI3K/Beclin-1 and mTOR pathways. Under the metabolic stressors like hypoxia, such upregulation of autophagy in tumor-associated endothelial cells facilitates nutrients to them. Besides that, in the presence of high autophagic activity in tumor associate endothelial cells, Atg5 accelerates starvation–hypoxia evoked angiogenesis by alleviating α-subunit of hypoxia-inducible factor (HIF) complex and interfering with the VEGF signaling (Filippi et al. 2018; Du et al. 2012). Such interaction of Atg5 can also induce the secretion of a high mobility group box 1 (HMBG1) through an autophagy-modulated mechanism. HMBG1 is a leading chromatin-associated protein that is translocated into the cytoplasm and released to the outside of the cells due to increased metabolic stress in the endothelial cells (Sachdev et al. 2012). In the cytosol, HMBG1 binds to Beclin 1 and acts as a pro-autophagic factor (Kang et al. 2010). Besides that, it takes part in tissue remodeling and angiogenesis signaling (Sachdev et al. 2012). Thus it plays an important role in angiogenesis and also for the protection of tumor cells in the hypoxic microenvironment (Fig. 9.2). In another study, it has been found that Beclin $1^{+/-}$ knockout mice have shown elevated angiogenic activity in their endothelial cells only under hypoxic conditions (Lee et al. 2011). Such a result suggests that autophagy may also play an antiangiogenic role although the influence of Beclin 1 on HMGB1 secretion has not been evaluated in that study. These contradictory results could also indicate a distinct function of autophagy in tumor-associated endothelial cells.

9.3.4 Autophagy and the Immune System in the Tumor Microenvironment

The immune system of the human body, including innate immunity and adaptive immunity, operates a vital role in the immunosupervision of tumors. Autophagy works at the downstream of the pattern recognition receptors. In other words, these activated innate immune receptors upregulate autophagy. In the innate immune response, the crosstalk between the autophagy and the immune system begins with the innate immune receptors like toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors (NLRs), thereby facilitating several effector responses, including NKT cell activation, cytokine production, and phagocytosis.

However, in innate immune response, autophagy provides a substantial amount of the antigens which in a later stage are loaded onto the MHC class II molecules for presentation to the dendritic cell-mediated cross-priming to CD8+ T cells (Jiang et al. 2019). In the coming sections, we will discuss both of the mechanisms of the immune system in the tumor immune microenvironment and their crosstalk with autophagy (Fig. 9.3) that will decide the fate of tumorigenesis.

9.3.4.1 Innate Immunity and Autophagy in Cancer

Innate immunity-mediated autophagy is largely dependent on the innate immune receptors, such as TLRs and NLRs. TLRs and NLRs are highly upregulated upon sensing the pathogenic or tumor antigens that ultimately activate the innate immune response (Zhong et al. 2016).

TLRs

TLRs are the most thoroughly characterized pattern recognition molecules of the innate immune surveillance. The immune system recognizes the tumor antigens by TLRs and infiltrates the tumor stroma resulting in tumor destruction through direct lysis or the involvement of cytokine (Shi et al. 2016). However, increasing pieces of evidence show quite opposing outcomes in cancer development. In the recent years, several developments regarding the use of potential TLRs toward therapeutic possibilities have been elucidated, of which the detailed mechanisms of these must be explored for better understanding. The study suggests that toll-like receptors are the group of innate immune receptors expressed in a wide range of cancer cells that activate several immune responses by regulating autophagy. TLRs are believed to be the autophagy inductors that activate autophagy. TLR7 with the help of a downstream signaling adapter MYD88 or TRIF recruits TRAF6 and Beclin-1 that further stimulate and develop the autophagosomes (Shi and Kehrl 2010). TLR2 induces phagocytosis and autophagy by enhancing the host innate immune system through the induction of c-JNK and ERK signaling cascade (Anand et al. 2011; Fang et al. 2014). TLR4 generally expressed in the innate immune cells, particularly in the dendritic cells and the macrophages, is one of the important targets for immune-modulating drugs. TLR4 stimulates autophagy by triggering TRIF (toll-IL-1 receptor (TIR) domain-containing adapter inducing IFN)/RIP1 (receptor-interacting protein), and p38-MAPK signaling pathway (Xu et al. 2007). Lipopolysaccharides and alpha-GalCer are reported to activate TLR4 signaling induced macrophage activation through mitogen-activated protein kinases and cytokines such as iNOS, IL-, and TNF-a (Xu et al. 2007; Hung et al. 2007). Zhan et al. suggested that TLR-3 and TLR-4 facilitate lung cancer invasion and migration by promoting TRAF6 (TNF receptor-associated factor 6, E3 ubiquitin-protein ligase)-regulated induction of autophagy and cytokine production (Zhan et al. 2014). In the breast cancer patients, it has been observed that higher TLR4 expression is associated with the upregulated LC3 II expression in CAFs which is correlated with the more aggressive relapse and poor prognosis of the tumors (Zhao et al. 2017). Lin et al. exhibited that TLR2 signaling plays a crucial role in the genotoxic carcinogen diethylnitrosamine (DEN) induced liver tissue damage. TLR2 activated intracellular senescence and autophagy

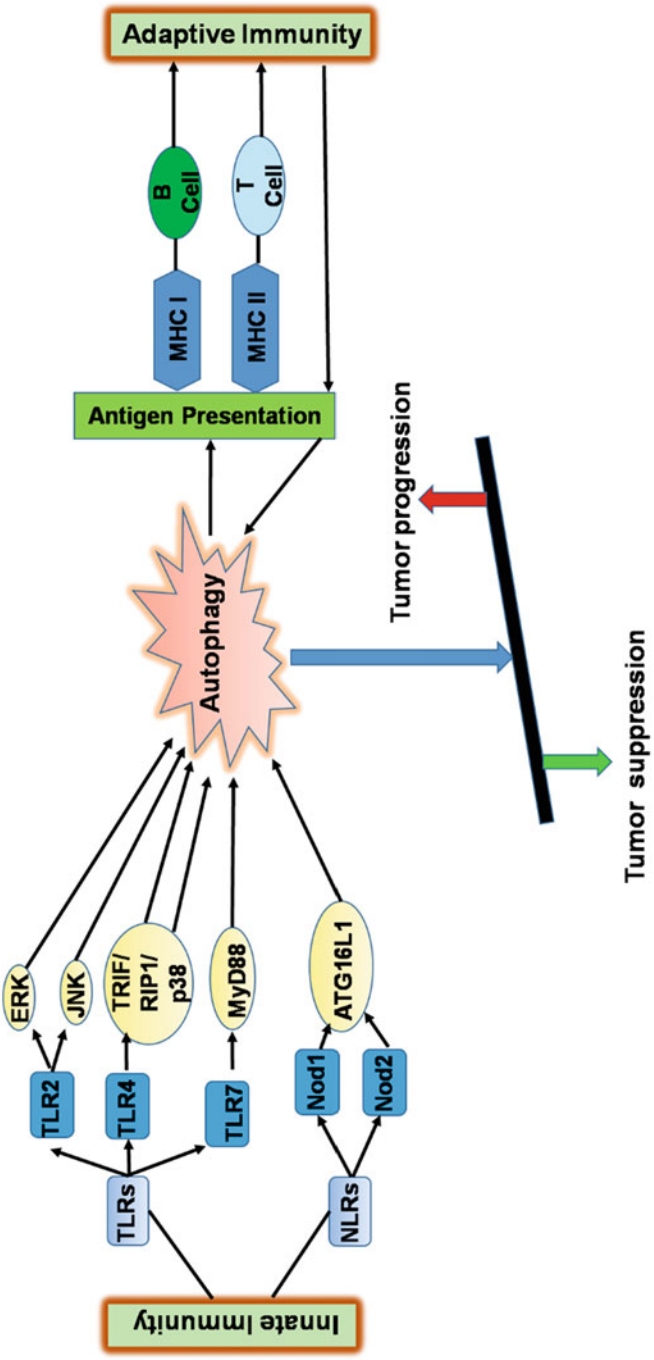

Fig. 9.3 Autophagy and the immune system in the tumor microenvironment. Activation of innate immune receptors like TLRs and NLRs induce autophagy. TLRs induce autophagy by JNK, ERK, MyD88, and TRIF/RIP1/P38 dependent pathway. NLRs up-regulate autophagy by engaging and interacting with ATG16L1. On the other hand, autophagy activates adaptive immunity by antigen presentation through MHCI and MHCII. Simultaneously, in adaptive immunity, antigen presentation also activates autophagy

eliminate the aggregation of ROS and DNA damage, thereby inhibiting the hepatocellular carcinoma development and progression (Lin et al. 2012, 2013). TLR3 in many instances acts as the possible therapeutic target for cancer immunotherapy. In human pharyngeal and oral squamous cell carcinoma cell lines, TLR3 induces apoptosis with the help of TLR3 ligand poly (I:C) (Estornes et al. 2012; Shatz et al. 2012). TLR3 ligand poly (I:C) not only destroys the tumors by apoptosis but rather they also destroys the TME by suppressing the angiogenesis in human hepatocellular carcinoma cells (Guo et al. 2012). Taking into account the dual effects of autophagy, the therapeutic options with TLRs agonists on autophagy cell death need an integrated consideration in clinical implications.

NLRs

NLRs are a group of cytoplasmic molecules that constitute a fundamental element of the innate immune response, generally recognize the bacterial cell wall components, and induce autophagy. Nod1 and Nod2 are the first and important NLRs recognized as the microbial associated molecular pattern (MAMP) detectors. ATG16L1, an important component of autophagosome formation, participates in the Nod1 and Nod2 directed autophagy by interacting with the plasma membrane (Travassos et al. 2010). Both of the Nod1 and Nod2 gene polymorphism is associated with an array of innate and adaptive immune response and autophagy in several cancer types (Kutikhin 2011). NOD1 is an intracellular receptor that induces autophagy and activates the NF–κB signaling in response to the Gram-negative bacterial peptidoglycan leading to the destruction of inflammation-based *Helicobacter pylori* which is believed as an imperative risk factor of gastric carcinogenesis (Suarez et al. 2015).

Others

Many stress-inducing factors activate interferon regulatory factor 8 (IRF8) which in turn activates the autophagy-related genes in dendritic cells. Autophagy-inducing stresses, such as IFNγ and TLR stimulation, macrophage colony-stimulating factor, and bacterial infection, activate IRF8 resulting in the activation of many genes involved in the formation of autophagosome and autophagy (Gupta et al. 2015). Furthermore, IFNγ contributes to the innate immune response and autophagy by the p38 MAPK signaling pathway (Matsuzawa et al. 2014). Inflammation-induced IFNγ attenuates gastric carcinogenesis by activating epithelial autophagy and T-cell apoptosis (Tu et al. 2011). Recent studies have shown that cytokines such as interleukins are also an important part of innate immunity that regulates autophagy. Furthermore, autophagy has a dominating role in the initiation and regulation of the inflammatory response by innate immune cells, mostly facilitated by IL-1 and its consequential effect on IL-23 secretion (Peral de Castro et al. 2012). Altogether, these studies have suggested the newer mechanisms that innate immune receptor-associated autophagy exhibits distinct regulation on carcinogenesis.

9.3.4.2 Adaptive Immunity and Autophagy in Cancer

In adaptive immunity, autophagy plays a pivotal role in anti-tumor effects through antigen presentation, cytokine release, thymus selection, lymphocyte development,

and homeostasis. Major histocompatibility complex (MHCI and MHCII) molecules are essential in carrying the intracellular and extracellular peptide epitopes which are consequently recognized by the CD4+ and CD8+ T cells respectively for adaptive immune destruction (Zhong et al. 2016).

Autophagy and Antigen Presentation in Cancer

Cross presentation is one of the critical aspects of the adaptive immune response. Any foreign antigens when entered into the cells are taken up and fixed, which are finally presented to the specific T-cells by antigen-presenting cells (APCs) for immunogenic destruction (Baker et al. 2013). Currently, it has been identified that autophagy has a pivotal role in antigen sequestration in cross-presenting the antigens to the MHC I molecules (Li et al. 2008). Interestingly, TNF-α induces mitophagy (a form of autophagy in the mitochondria) that enabled the delivery of the mitochondrial antigens by the MHC-I molecules at the cell surface (Bell et al. 2013). There have been instances of the interrelationship between MHC-I-regulated autophagy and cancer immune response. Autophagy-induced lysosomal proteolysis and proteasomal degradation regulate the MHC-I molecules mediated cross-presentation of tumor antigens (Li et al. 2009). Apart from endogenous MHC-I peptides, the endogenous system also helps in the processing of MHC-II presentation. During the MHC-II presentation of the exogenous antigens, the lysosomal proteases degrade them and process them for the fusion with the MHC-II loading compartment for the immune surveillance (Gannage and Munz 2010). More specifically, autophagy also helps in the transport of the nuclear and cytosolic antigens for presentation to the CD4+ T cells by the MHC-II molecules (Crotzer and Blum 2009).

Role of Autophagy in the Regulation of T Cells Development and Function in Cancer

T cells depend on the basal autophagy to maintain their homeostasis and activation. Defects in autophagy by deletion of autophagic molecules such as Atg7, Atg3, Atg5, PI3K, and BECN1 can lead to improper T cell activation and differentiation (Pan et al. 2016). The survival of the naive T cells depends upon increased autophagy along with the stromal cells' interaction with the TCR and IL-7 signaling (Sena et al. 2013). After TCR stimulation, it has been noticed that autophagy is enhanced in the T cells along with increased calcium levels that further activate the AMPK via ULK1 complex phosphorylation (Kim et al. 2011; Botbol et al. 2015). There has been mounting evidence on the connection between the autophagy and the regulatory T cell manipulating antitumor immunity. Autophagy acts as a key regulatory mechanism for CD4+ T cell homeostasis. It is observed that autophagy is augmented in the murine CD+ T cells upon activation via JNK and Vps34 and importantly causes the growth factor-withdrawal cell death (Li et al. 2006). It has been also noticed that c-Met expressed on the tumors could act as a potential epitope against the helper T lymphocytes which is partly regulated by autophagy (Kumai et al. 2015). Many studies have delineated the effect of impaired autophagy on the development of T cells. Defective autophagy more frequently affects the CD8+ T cells than the CD4+ T cells. Inhibition of mTOR in the effector CD8+ T cells induces

memory CD8+ T cell production in lymphoid rather than the mucosal tissue. Therefore, it can be predicted that CD8+ T cells are more reliant on autophagy (Kovacs et al. 2012; Sowell et al. 2014).

Role of Autophagy in the Regulation of B Cells Development and Function in Cancer

Autophagy acts a significant role in the development and the survival of the B cells. Autophagy is very much essential for the pro and pre-B cell transition and activation of the B cell in response to the stimulation of BCR. Autophagy is also very much necessary to sustain a normal number of peripheral B cells and their survival (Arnold et al. 2016). The development and the maturation of B cells require the pro-autophagy genes (Pan et al. 2016). Further, the knockdown of Atg5 prevents the transition between pro- and pre-B-cell stages in the bone marrow (Chanut et al. 2014). B cell activation is induced by the tumor-derived autophagosomes (termed "DRibbles") resulting in the production and secretion of cytokine. Moreover, DRibbles upregulates the CD40L expression on the macrophages with simultaneously enhances the expression of CD40 on the B cells. Macrophages play a significant role in the presentation of the antigens on the B cells for specific T cell activation (Zhou et al. 2015). Taken together, the current set of data indicates that autophagy serves a pivotal role in the advancement of the certain subgroups of B cells and memory B cells (Chen et al. 2014).

9.4 Autophagy as a Candidate for Cancer Immunotherapy

Among the diversified options available for cancer treatment, immunotherapy-based treatment options are gaining much attention nowadays. The basic mechanism involved in the cytotoxic effect of immunotherapy is based on the regulation of the response of the immune cells thereby preventing the binding with the immune suppressor or cancer cells (Chen and Mellman 2017; Galon and Bruni 2019). Several approaches have been implemented to enhance the immune system for better clinical outcomes. Nevertheless, partly due to tolerogenic effects, most of the strategies have been unsuccessful (Green et al. 2009). Recently, autophagy emerged as a potential mechanism connected to cancer immunotherapy. Targeting autophagy-mediated cross-presentation and immune responses may be considered as a potential therapeutic strategy for cancer treatment. In the subsequent sections, we will discuss the dual role of autophagy not only as a pro-death but also as a pro-survival inductor in the cancer immunotherapy.

9.4.1 Autophagy as a Pro-death Mechanism in Cancer Immunotherapy

In the TME, autophagy may act as a pro-death signal that retards the tumor progression and enhances the antitumor immunity in response to therapy. Several nanoparticle-based therapeutic options that trigger autophagy in cancer have been

developed. These nanoparticles act as adjuvants that ultimately deliver the tumor antigens for the autophagosome formation and tumor destruction. In alpha-alumina (α-Al(2)O(3)) nanoparticle-based tumor regression, the former acts as the carrier of the tumor antigens that delivers the antigens to the autophagosomes in the tumor dendritic cells that further present the antigen to T cells by autophagy (Li et al. 2011). Similarly, monobenzone triggers melanosome autophagy by inhibiting the processing and the shedding of melanocyte differentiation antigens, leading to tyrosinase ubiquitination. The whole process activates the dendritic cells and cytotoxic T-cells which efficiently eliminate the melanoma in vivo (van den Boorn et al. 2011). Likewise, targeting folate receptors alpha (FRα) which is highly expressed on the human ovarian cancer cells suppressed cancer cell proliferation. MORAB-003 (farletuzumab) is a humanized mAB interferes with the folate metabolism by targeting the FRα, as a consequence of which, MORAB-003 induces autophagy and hinders cancer cell proliferation (Wen et al. 2015). Conventional chemotherapeutics administrations are more efficient when they elicit the immunogenic cell death (ICD) followed by a series of molecular events, like pre-apoptotic cell surface display of calreticulin, the release of high mobility group box 1 (HMGB1), and ATP secretion during the blebbing phase of apoptosis from the dying cells during the post-apoptotic stage (Pol et al. 2015). Autophagy is more effective in immunotherapy rather than conventional chemotherapy. Autophagy caused immunogenic cell death via T cell activation and mannose-6-phosphate receptor upregulation on the surface of the tumor cells (Ramakrishnan et al. 2012). Autophagy may act as the energy provider to the immune cells like DCs and T lymphocytes by the immunogenic release of ATP from the dying cells in the tumor bed whereas autophagy deficit hinders the ability of cancer cells to elicit an immune response (Michaud et al. 2011). BCG, a potential vaccine against TB, has shown its efficiency as an antitumor immunotherapy agent and it has been seen that a combinatorial approach of BCG and ionizing radiation effectively resulted in autophagic cell death in the colon cancer cells by the generation of ROS (Yuk et al. 2010). Moreover, cytokines also function as mediators of autophagy activation and cancer cell death. For instance, IFN-γ hinders gastric cancer progression by promoting epithelial cell autophagy (Tu et al. 2011). However, the role of IFN1 in anticancer treatment of chronic myeloid leukemia is not fully understood. Zhu et al. demonstrate that the active involvement of autophagy in IFN1-mediated cell death is through the upregulation of JAK1-STAT1 and the ReLA signaling pathway (Zhu et al. 2013).

9.4.2 Autophagy as a Pro-survival Mechanism in Cancer Immunotherapy

Besides the cancer regression, autophagy also plays an important role in tumor promotion, ignoring the immunotherapeutic administration. Autophagy impairs the anticancer immune response and avails tumor cells to evade immune surveillance, thereby promoting tumor growth and progression. In the inner tumoral region, hypoxic condition rises due to an inadequate supply of oxygen. Hypoxia in the

tumor microenvironment has been proved as a mechanism of cancer cell survival by attenuating the therapeutic intervention by interfering with various signaling cascades. It has been reported that hypoxia-induced autophagy plays a major role in diminishing the effect of immunotherapy in cancer cells (Qiu et al. 2015). For example, hypoxia-stimulated autophagy can suppress T-cell-mediated cytotoxicity in lung cancer cells (Jaboin et al. 2009; Pan et al. 2016). Hypoxia-induced autophagy impairs CTLs-mediated tumor cell lysis that is associated with the hypoxia-dependent phosphorylation of STAT3 (pSTAT3), which in turn activates tumor cell survival, proliferation, and immune escape (Teng et al. 2014; Noman et al. 2012). Hypoxia-induced autophagy also interrupts the NK-mediated killing of the cancer cells by degrading the NK-derived Granzyme B (Baginska et al. 2013). During hypoxia, HIF-2α is localized to the nucleus and triggers the expression of autophagy sensor ITPR1 (inositol 1,4,5-trisphosphate receptor, type 1), ultimately deactivates the NK-mediated cell lysis and decreases immunotherapeutic effect (Hasmim et al. 2015; Messai et al. 2014). In the hypoxic melanoma cells, autophagy degrades the channel protein connexin 43, resulting in the destabilization of immune synapse that interferes with the NK-cell mediated lysis of the cell (Tittarelli et al. 2015). In some preclinical models, it has also been proved that inhibition of autophagy in combination with the other therapeutic approaches augments the cytotoxicity of cancer cells and inhibits the cancer progression. Recent studies have found that attenuating autophagy with chloroquine increases the efficacy of high-dose interleukin-2 (HDIL-2) in inhibiting cancer therapy by immunotherapeutic approach (Liang et al. 2012). Similarly, chloroquine enhances the HDIL-2-mediated antitumor immunity, triggering the NK cells, T-cells, and DCs in renal cell carcinoma. Administration of chloroquine blocks the autophagy and limits ATP production by inhibiting the Oxidative phosphorylation (Lotze et al. 2012). Moreover, chloroquine blocks the radiation-induced autophagy in breast cancer cells and promotes cell death via DCs mediated immunogenic cell death (Ratikan et al. 2013). Intrinsically, autophagy provides resistance to the immunological anticancer therapy by diminishing the immune effector mechanisms. Therefore, protective autophagy is activated against sepsis-induced T lymphocyte apoptosis and immunosuppression. Overall, the downregulation of autophagy in T lymphocytes may lead to an increased rate of apoptosis and decreased cell survival (Lin et al. 2014). Interleukin 24, an exclusive member of the IL-10 family, shows universal cancer-specific toxicity. A combination of autophagy inhibitors and IL-24 may be an encouraging strategy for tumor immunotherapy. In oral squamous cell carcinoma, 3-MA, a PI3K inhibitor enhances the IL-24 induced apoptosis by acting upon Vps34 and PI3Kγ (Li et al. 2015).

9.5 Conclusions

Despite significant advances in the detection techniques and the development of promising therapeutic approaches, like surgery, radiotherapy, and chemotherapy, cancer is still one of the major causes of death worldwide due to the adverse effects

of these approaches and their inefficacy against all the tumors. However, prompt evolution of immunology, molecular biology, cell biology, and other relevant fields is believed to expedite the advancement of immunotherapy which successfully reduces tumor growth with minimal off-target effects on the host cells. In the complex tumor microenvironment, the fate of the tumor cells depends on the interactions among tumor cells with the immune cells. In line with this, autophagy has a significant role in the regulation of cancer development in the TME that makes it an ideal target for cancer therapy. Of note, autophagy has a multifaceted role in the TME. It can contribute to the survival as well as the destruction of the cancer cells depending upon the stages of cancer. Collectively, the study suggests that autophagy can stimulate antitumor immune responses through promoting differentiation, maturation, and also maintaining internal homeostasis in the immune cells. However, hypoxia-induced autophagy suppresses immune cell functions and facilitates tumor cell evasion from the immune surveillance. Thus, a better understanding of the in-depth molecular mechanisms associated with the crosstalk between the context-dependent roles of autophagy and the immune system in the TME will further magnify the therapeutic strategies against cancer.

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