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Role of autophagy in suppression of inflammation and cancer

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Abstract

Autophagy is a crucial component of the cellular stress adaptation response that maintains mammalian homeostasis. Autophagy protects against neurodegenerative and inflammatory conditions, aging, and cancer. This is accomplished by the degradation and intracellular recycling of cellular components to maintain energy metabolism and by damage mitigation through the elimination of damaged proteins and organelles. How autophagy modulates oncogenesis is gradually emerging. Tumor cells induce autophagy in response to metabolic stress to promote survival, suggesting deployment of therapeutic strategies to block autophagy for cancer therapy. By contrast, defects in autophagy lead to cell death, chronic inflammation, and genetic instability. Thus, stimulating autophagy may be a powerful approach for chemoprevention. Analogous to infection or toxins that create persistent tissue damage and chronic inflammation that increases the incidence of cancer, defective autophagy represents a cell-intrinsic mechanism to create the damaging, inflammatory environment that predisposes to cancer. Thus, cellular damage mitigation through autophagy is a novel mechanism of tumor suppression.

Introduction

Macroautophagy (referred to as autophagy hereafter) is a mechanism for the capture of cellular components (cytoplasm, proteins, lipids, and organelles) in double membrane vesicles (autophagosomes) that traffic to and fuse with lysosomes where the cargo is degraded [1]. In normal and tumor cells, autophagy functions to maintain cellular homeostasis. Basal autophagy degrades long-lived proteins and is responsible for regulation of organelle turnover. Autophagy is dramatically induced in response to starvation or damaging stress. In starvation, autophagy allows the recycling of intracellular components to provide an internal source of macromolecular building blocks to maintain cellular metabolic function. In response to cellular stress, autophagy is crucial in preventing the accumulation of damaged proteins and organelles that are toxic. Failure to remove this intracellular debris leads to cell death, tissue damage, and chronic inflammation that is tumor promoting. Thus, autophagy promotes survival and mitigates damage, and in the setting of cancer this represents a double-edged sword [2]. On the one hand, blocking autophagy-mediated stress survival by inhibiting autophagy in tumor cells is probably advantageous in the setting of cancer therapy. On the other hand, promoting autophagy and preventing persistent tissue damage and chronic inflammation that is a breeding ground for genesis of genome mutations

that create tumors and drive their progression, may be useful in the setting of cancer prevention. Restoration of autophagy may be especially important where activation of oncogenic pathways, such as the PI-3 kinase/mTOR pathway, suppresses autophagy. Thus, autophagy modulation is a promising new approach to cancer treatment and prevention, but the application is clearly context-dependent. Determining when and how to modulate autophagy in cancer is an exciting challenge that will provide new insight into cancer biology and approaches to enable cancer eradication.

Mammalian homologs of many yeast autophagy genes (*atg*) have been identified [1] and analysis of inactivating mutations in these genes in mice and cells has begun to elucidate their function. The picture that has emerged is that autophagy sustains cellular and mammalian viability and is thereby an important pro-survival mechanism. It is also clear that autophagy deficiency in mice creates a broad spectrum of phenotypes of impaired development and disease. These findings are consistent with the requirement for autophagy in supporting metabolism and in damage prevention by elimination of cellular garbage, analogous to what is known from yeast. This review will focus on the role of autophagy in regulation of oncogenesis.

Autophagy-mediated cellular degradation sustains survival

Mice deficient for the essential autophagy genes *atg5*, *atg7*, or *atg3* fail to survive the neonatal starvation period and their cells display reduced amino acid and ATP levels suggesting bioenergetic impairment [3,4•,5]. *atg5* is also required for pre-implantation development in mice [6] and for B-cell development and for sustaining viability of B-1a cells in the periphery [7]. *atg7* is required for adipose differentiation and for controlling the balance between white and brown fat [8,9]. These findings support a role for autophagy in specific aspects of mammalian growth and development, particularly in stress, by supporting cellular and organismal metabolism.

Autophagy prevents tissue damage and disease

Mice with central nervous system-targeted deficiency for either *atg5* or *atg7* accumulate poly-ubiquitinated protein aggregates and abnormal mitochondria and undergo neuronal degeneration with age [10,11••]. Moreover, autophagy defects exacerbate neurodegeneration associated with proteinopathies, such as Huntington's and Parkinson's diseases, owing to the failure to suppress mutant protein accumulation [12]. Evidence suggests that mutant protein accumulation impairs both autophagy and proteasome-mediated protein degradation, suggesting that defective autophagy not only prevents the degradation of long-lived and mutant proteins, but also that of short-lived proteins destined for proteasome-mediated degradation [13,14]. This may amplify the consequences of defective autophagy on the cellular proteome. Thus autophagy is required for turnover of normal but particularly mutant proteins targeted for degradation with poly-ubiquitin, and the failure of this protein garbage disposal mechanism may contribute to cell death and tissue degeneration.

Autophagy-defective cells and tissues, particularly liver, accumulate excessive triglycerides in lipid droplets [15•]. Cells normally store triglycerides, but during starvation, lipophagy (autophagy of lipid droplets), is required to access this fat storage to supply fatty acids to support metabolism [15•]. Thus, the metabolic impairment caused by defective autophagy includes limited access to both amino acid and lipid stores that provide the building blocks for protein, nucleic acid and membrane synthesis and ATP generation.

Organelle removal through autophagy is important for normal development and is partly tissue-dependent. Loss of the *atg1* homolog *ULK1* [16] or *atg7* [17] impairs autophagy and clearance of mitochondria during differentiation of reticulocytes leading to anemia.

Similarly, deficiency in the facilitators of mitophagy (autophagy of mitochondria), *nix* or *bnip3*, impairs mitochondrial clearance, causing anemia [18,19]. Although reticulocyte differentiation may be an extreme case of development that is dependent on organelle removal through a specialized form of autophagy, the persistence of mitochondria and other organelles, particularly those that are damaged, can potentially promote disease in many tissues.

There is a spectrum of tissue-specific phenotypes that are observed in autophagy deficient mouse models, consistent with the fact that not all mouse tissues are equally affected by loss of autophagy. One explanation for this variation is that long-lived or stressed cells may be particularly reliant on autophagy for maintenance of metabolism and protein quality control, while other tissues may depend on autophagy to prevent abnormal lipid and organelle accumulation. Thus, the tissue of origin probably influences the manifestation of tissue damage and the disease spectrum caused by defective autophagy.

Deficiency in *atg7* targeted to the liver causes accumulation of p62 and poly-ubiquitinated protein aggregates and induction of p62-dependent liver damage [20••]. p62 is an adaptor protein that regulates various signal transduction pathways [21]. p62 also binds poly-ubiquitinated proteins, aggregates, and binds the autophagosome component LC3 (ATG8), serving to deliver protein cargo to autophagosomes for degradation [22•]. Thus p62 contributes to the autophagic degradation of poly-ubiquitinated proteins and is itself an autophagy substrate and a possible biomarker for defective autophagy.

Allelic loss of the essential autophagy gene *beclin1* (*atg6*) in mice causes accumulation of p62, p62-containing protein aggregates, and endoplasmic reticulum chaperones in liver and lung tissues, symptomatic of protein quality control failure [23••]. Comparative proteomic analysis of wild type and *beclin1* deficient tumor cells under normal and stress conditions similarly revealed p62 and chaperone upregulation in mutant cells, which also displayed accumulation of metabolic enzymes, abnormal mitochondria, reactive oxygen species (ROS), activation of the DNA damage response and cell death [23••]. Liver tissue from *beclin1* mutant mice shows increased apoptosis, tissue damage, and inflammation that progresses to steatohepatitis, and hepatocellular carcinoma (HCC) [23••]. Allelic loss of *beclin1* also renders mice prone to spontaneous lung adenocarcinomas and lymphomas [23••,24,25•]. Interestingly, deficiency in *atg16L1* and *atg5* in intestinal Paneth cells produces a tissue injury response resembling Crohn's disease (CD), consistent with the identification of *atg16L1* as a risk factor for CD in humans [26]. In humans, CD, like other chronic inflammatory conditions, is associated with a higher incidence of colorectal cancer. Although the entire scope of the elements of the autophagy-defective phenotype that promote cancer is not known, a role for aberrant p62 accumulation and inflammation is indicated.

Collectively, these studies provide strong evidence for a pro-survival role for autophagy in mammals, through the maintenance of energy homeostasis and protein and organelle elimination and quality control. Failure of autophagy has pleiotropic phenotypes leading to cell death, impaired differentiation, oxidative stress, toxic protein and organelle accumulation and persistence, tissue damage, inflammation, and mortality in mammals. This can lead to tissue dysfunction, inflammatory conditions, and cancer.

Autophagy promotes tumor cell survival

In normal and in tumor cells, common responses to stress are autophagy and apoptosis induction. Although autophagy can delay apoptosis, cell death eventually limits autophagy [27]. Apoptosis is commonly inactivated in tumor cells where it permits sustained survival,

progression, and resistance to therapy. The role of autophagy in cancer therapy is discussed in detail elsewhere [2].

The prolonged stress survival afforded by defective apoptosis, conferred to tumor cells by either a gain-of-function of anti-apoptotic Bcl-2 or Bcl-x_L or by deficiency in the core proapoptotic machinery, Bax and Bak is truly remarkable [28••,29••]. So much so, the absence of cell death is insufficient to account for sustained stress survival of apoptosis-defective tumor cells. It became apparent that stress caused by growth factor withdrawal or oxygen and glucose deprivation potentially activates autophagy, which supports long-term survival of apoptosis-defective cells [28••,29••]. Apoptosis-defective tumor cells use autophagy to survive stress for weeks where they enter a state of dormancy [27]. Tumor cells can exit dormancy to resume cellular proliferation when the stress is eliminated and normal growth conditions are restored [27]. Genetic or pharmacologic suppression of autophagy promotes cell death by necrosis *in vitro* and *in vivo* [28••], suggesting that both tumor and normal cells utilize autophagy to maintain survival in stressful conditions [2,30–32].

Stress is a common feature of tumors, which have hypoxic regions lacking oxygen and probably also growth factors and nutrients due to abnormal or insufficient vasculature [33]. Autophagy localizes to these hypoxic regions where it supports tumor cell survival [28,34,35••]. The oxygen-sensing hypoxia-inducible transcription factors activate autophagy along with other metabolic and pro-angiogenic pathways that are critical of cellular adaptation to metabolic stress [36]. The induction of autophagy in hypoxic regions may also hamper therapy, as it is the tumor cells that reside in these hypoxic regions that are notoriously refractory to treatment. This ability of tumor cells to activate autophagy and survive stress by a process that leads to dormancy and later re-growth represents a fundamental obstacle to the successful eradication of cancer [2,27,30]. In the long-term it will be important to determine the mechanism of tumor cell dormancy and recovery, the role that autophagy plays, and how to disable this pathway to increase the efficiency of cancer therapy by preventing tumor cell persistence and re-growth [2]. In the short-term, lysosomotropic agents such as chloroquine that block flux through the autophagy pathway and prevent autophagic cargo degradation can be used as autophagy inhibitors in cancer cells [2,37–40,41•]. This may enhance cell death, particularly of stressed tumor cells or in combination with therapeutic mTOR inhibition where autophagy may have been utilized to promote survival, potentially undermining treatment.

Autophagy prevents cell and tissue damage

Mice with genetic defects in autophagy have tissues with signs of metabolic impairment, and that accumulate abnormal organelles, lipid droplets, p62-containing and poly-ubiquitin-containing protein aggregates that are apparently toxic. In non-dividing, terminally differentiated neuronal cells, this toxicity is manifested as cell death and neurodegeneration. In tissues with regenerative capacity (liver, for example), this toxicity and cell death results in inflammatory and growth stimulating cytokine production, cell cycle reentry, proliferation, and cancer. The mechanism by which autophagy defects cause tissue damage, how this damage promotes cancer, and identification of therapeutic opportunities to prevent this damage and suppress cancer development are clinically important to determine.

Toxicity and tissue damage resulting from defective autophagy is partly due to the aberrant accumulation of p62, since p62 deficiency can delay mortality of mice with liver-specific *atg7* deficiency [20••]. Furthermore, autophagy-defective kidney tumor cells accumulate p62, which is sufficient for production of high levels of ROS, activation of the DNA damage response, and cell death [23••]. Conversely, knockdown of p62 or the presence of ROS

scavengers, suppresses ROS and DNA damage response activation in autophagy-defective tumor cells, suggesting that aberrant p62 accumulation leads to oxidative stress and tissue damage (Figure 1) [23••]. Persistent p62 accumulation in autophagy-defective tumor cells is sufficient to enhance tumorigenesis, suggesting that a gain-of-function of p62 is oncogenic [23••]. This suggests that limiting p62 accumulation through autophagy is one contributing factor to tumor suppression (Figure 1). p62 deficiency also suppresses lung adenocarcinoma by activated K-ras, supporting a general role for p62 in regulating cancer [42••]. The mechanism by which deregulated p62 is oncogenic is not yet clear, but may be related to (i) elevated oxidative stress, genome damage, and mutation accumulation; (ii) toxicity, chronic cell death, and inflammation; and (iii) deregulation of signal transduction and gene expression as p62 is an adaptor protein in various cancer-related signaling pathways (Figure 1). The potential contribution of damaged mitochondria accumulation or metabolic alterations caused by deficient autophagy remain to be examined.

Chronic tissue damage resulting from defective autophagy leads to inflammation and cancer

Inflammatory conditions promote cancer partly by elevating oxidative stress and cancer-causing mutations. In turn, oncogenic events promote inflammation that can enable tumor progression by altering the tumor microenvironment [43]. In many cases the root cause of chronic inflammation is known: persistent infection with a pathogen (for example, hepatitis B and C virus-associated HCC; *H. pylori*-associated gastric cancer) or toxin exposure (for example, alcohol-associated HCC; smoking-associated lung cancer). Defective autophagy recreates this inflammatory state without the need for a tissue extrinsic source of damage, but rather through a cell-intrinsic mechanism. As such, the failure to remove cellular garbage in autophagy-defective cells and tissues and the resulting cellular dysfunction and death, is an inflammatory stimulus that creates a cancer-prone environment. The concept that an autophagy-mediated cellular garbage disposal mechanism functions to limit tissue damage and inflammation and is ultimately the mechanism of tumor suppression is novel. Interestingly, autophagy suppresses disease resulting from alpha-1-antitrypsin (AT) mutations, which produce an aggregation-prone protein, chronic lung and liver disease, inflammation, and cancer [44,45]. This supports the possible role for autophagy-mediated protein quality control in tumor suppression [23••].

How inflammation is stimulated in autophagy-defective tissues may be related to the occurrence of chronic cell death in the case of the liver. Loss of canonical NF- κ B survival signaling in hepatocytes increases hepatocyte cell death by apoptosis. Cell death, in turn, activates liver resident macrophages (Kupffer cells) to produce cytokines (TNF- α , IL-6, and HGF) to promote NF- κ B activation and compensatory proliferation of remaining hepatocytes [46]. This chronic inflammatory environment that promotes HCC requires NF- κ B-dependent production of inflammatory mediators by Kupffer cells. Targeted *atg7* deficiency in the liver elevates stress-responsive NRF-2 and its downstream targets, indicating that defective autophagy creates high levels of stress [20••]. Indeed, livers from *beclin1* mutant mice have elevated apoptosis, NF- κ B activation, and TNF- α production, consistent with defective autophagy promoting stress, cell death, tissue damage, compensatory inflammation and HCC [23••]. It will be of great interest to test if suppression of Kupffer cells and inflammation rescues HCC associated with allelic loss of *beclin1*, and if this mechanism is also responsible for spontaneous tumor development in other tissues such as lung. Autophagy also facilitates senescence, the deficiency in which may enhance oncogene-activation induced cancer to progress in an inflammatory microenvironment [47•].

Conclusions

Autophagy is an important survival pathway in tumor cells as well as normal cells that is especially crucial in situations of metabolic or damaging stress, and perhaps also the stress of oncogene activation or tumor suppressor gene inactivation. The ability of autophagy to keep tumor cells alive in stress, suggests that inhibiting autophagy or the downstream uncharacterized dormancy and recovery pathways is potentially useful to improve cancer therapy. Alternatively, autophagy defects in mouse models impair protein, lipid, and organelle degradation, which is crucial to mitigate oxidative cellular damage, particularly during metabolic stress. Cell and tissue damage resulting from defective autophagy manifests as ROS production, accumulation of p62, ER chaperones, and DNA damage response, NF- κ B and NRF-2 activation, genome damage, chromosome instability, cytokine production, cell death, and inflammation. This condition of chronic tissue damage and inflammation is associated with HCC, lung adenocarcinomas, and other cancers. As in the case of chronic infection and toxin exposure, defective autophagy-mediated cellular garbage disposal creates a damaging tissue inflammatory state that is a tumor-promoting environment. This mechanism of autophagy-mediated tumor suppression by cellular garbage disposal suggests that stimulation of autophagy in this setting may constitute an important approach to cancer prevention. Going forward, it will of interest to identify which aspects besides p62 accumulation promote oncogenesis when autophagy is impaired, and how to use this information to reduce cancer risk and improve cancer treatment outcome. It is also crucially important to establish how autophagy interfaces with other oncogenic pathways to influence tumorigenesis, such as controlled by p53, Ras, Myc, and so on, as well as the PI-3 kinase pathway.

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Figure 1.

Mechanism by which autophagy defects promote cancer. Metabolic stress triggers oxidative damage, and p62 accumulation. Autophagy induction is responsible for the degradation of damaged cellular material, proteins, lipids, and organelles [23••]. In autophagy-defective cells, the degradation and recycling of cellular components is prevented, leading to persistence of p62, p62-containing protein aggregates and damaged mitochondria, and coordinate ROS production and activation of the DNA damage response. This alters the cellular proteome and gene expression, and leads to genome damage and chromosome instability, or cell death and inflammation. Evidence suggests that increased p62 accumulation, genome damage and inflammation may contribute to increased tumorigenesis in autophagy-defective cells and tissues.