MINI-REVIEW

Autophagy in Cervical Cancer: An Emerging Therapeutic Target

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Abstract

Cervical cancer is a leading cause of morbidity and mortality in women worldwide. Although the human papillomavirus (HPV) is considered the major causative agent of cervical cancer, yet the viral infection alone is not sufficient for cancer progression. The etiopathogenesis of cervical cancer is indeed complex; a precise understanding of the complex cellular/molecular mechanisms underlying the initiation, progression and/or prevention of the uterine cervix is therefore essential. Autophagy is emerging as an important biological mechanism in targeting human cancers, including cervical cancer. Furthermore, autophagy, a process of cytoplasm and cellular organelle degradation in lysosomes, has been implicated in homeostasis. Autophagic flux may vary depending on the cell/tissue type, thereby altering cell fate under stress conditions leading to cell survival and/or cell death. Autophagy may in turn govern tumor metastasis and subsequent carcinogenesis. Inflammation is a known hallmark of cancer. Vascular insufficiency in tumors, including cervical tissue, leads to depletion of glucose and/or oxygen perturbing the osmotic mileu causing extracellular acidosis in the tumor microenvironment that may eventually result in autophagy. Thus, targeted manipulation of complex autophagic signaling may prove to be an innovative strategy in identification of clinically relevant biomarkers in cervical cancer in the near future.

Keywords: Autophagy - cervical cancer - microtubule associated protein light chain 3 - therapeutics

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Introduction

Cervical cancer has emerged as a leading cause of morbidity and mortality in women worldwide (Walboomers et al., 1999; Pandey et al., 2012). Although Human Papillomavirus (HPV) is the major etiological agent of cervical cancer, yet the viral infection alone is not sufficient for cancer progression (Zur, 2002; Pandey et al., 2010). Deciphering the underlying cellular and molecular mechanisms in cervical carcinogenesis is one of the major study goals of researchers worldwide in the vaccine era. Autophagy is emerging as an attractive therapeutic target in human cancers, including cervical cancer. Autophagy, a process of cytoplasm and cellular organelle degradation in lysosomes, has been implicated in homeostasis and under altered biological/metabolic conditions such as cellular stress, the cell may undergo survival and/or cell death; autophagy may in turn govern tumor metastasis and subsequent carcinogenesis (Janku et al., 2011; Kung et al., 2011; Mathew and White, 2011; Wu, 2012). Autophagy, one of the nonapoptotic cell death mechanisms, is characterized by engulfment of cytoplasm and organelles into double-membrane bound structures, autophagosomes, and delivery to and subsequent degradation in lysosomes; it may be triggered under physiological conditions, such as nutrient starvation or in response to various stress stimuli, such as radiations or cytotoxic compounds (Yang and Klionsky, 2003; Liu et al., 2011). Furthermore, microtubule-associated protein light chain 3 (LC3) protein is an established hallmark of autophagy in diverse cell types (Wang et al., 2011; Zhang et al., 2011). Research in the past decade has substantially increased our understanding of non-apoptotic programmed cell death events, such as lysosomal-mediated cell death, necroptosis and autophagy (Kreuzaler and Watson, 2012) cross-talk between various components of each of these cell death pathways further governs subsequent cancer progression under stressful conditions.

Overview of Autophagy

A precise understanding of the complex autophagy machinery is essential to understand the underlying cellular and molecular mechanisms in carcinogenesis, including carcinoma of the uterine cervix. Autophagy ("self-eating") was first described by Christian de Duve in 1963 as a lysosome-mediated degradation process for non-essential or damaged cellular constituents (de Duve; 1963; de Duve and Wattiaux, 1966). There are various components involved in the autophagy pathway; cross-

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talk between these components governs the fate of the cell under altered physiological conditions in biological systems (He and Klionsky, 2009; Chen and Klionsky, 2011). Microtubule-associated protein light chain 3 (LC3) protein, a mammalian homologue of yeast Atg8, is localized in autophagosomes and autolysosomes after processing; the amount of LC3-II cleaved product is correlated with the extent of autophagosome formation, providing the first molecular marker for the detection of autophagic activity (Kabeya et al., 2000; Tanida et al., 2004). Class III PI3K is the homologue of Beclin-1 (mammalian homologue of yeast atg6), and their bond through common helix domain directly results in the occurrence of autophagy; in this regulatory frame, Beclin-1 undertakes a central place because of its necessary function in the formation of autophagic vacuoles (Chen and Klionsky, 2011); several mammalian homologues of yeast autophagy-related genes (Atgs) have been identified, and the mechanisms of yeast autophagy are largely conserved in mammals. They participate in the Atg12-binding system and LC3-modifing system during autophagosome formation. In the first ubiquitin-like system, Atg12 is conjugated to Atg5 immediately after its synthesis and this process is regulated primarily by the E1 ligase-like protein Atg7 (Lee et al., 2012). The Atg12/Atg5 complex subsequently leads to the formation of larger protein complexes that are further transported onto the membrane, which is necessary for the formation of autophagic vesicles (Kabeya et al., 2000; Tanida et al., 2004). Phosphatidylethanolamine (PE), a lipid molecule that is considered to anchor Atg8/LC3-II to membranes, is a crucial element of LC3-modifing system; Atg8/LC3-I (mammalian MAP/LC3 proteins) is ligated to PE in a series of biochemical reactions assisted by Atg7, transforming into Atg8/LC3-II and thus leading to the formation of autophagic vacuoles (Behrends et al., 2010). A complex interplay between cell death and/or survival including necrosis, apoptosis and autophagy may in turn govern tumor metastasis, and subsequent carcinogenesis (Figure 1a). Further, vascular insufficiency in tumors may lead to depletion of glucose/oxygen and contribute to increased reactive oxygen species production, extracellular acidosis in tumor microenvironment that may eventually result in autophagy, thereby implicating glucose depletion and or deprivation (GD) as an important trigger for autophagy (Dengjel et al., 2008; Bensaad et al., 2009). Identifying potential therapeutic intervention points in the complex autophagic machinery that activate and/or inhibit autophagy by targeting regulatory molecules of the complex autophagic pathway may enhance our understanding of the complex etiology of cervical carcinogenesis.

Moreover, autophagy flux/activity in the cell under GD-conditions may be determined by western blot, wherein the conversion of the two known isoforms of LC-3A/B, I and II, may be monitored on SDS-PAGE; a representative data showing the LC3 isoforms (LC3 Antibody was purchased/procured from Cell Signaling Technology Inc., USA) during a time-course (0-48 h.) experiment carried out in colorectal carcinoma cell line SW-480 (GAPDH was used an an internal reference) has been depicted in **Figure 1b (it may be noted that the major part of this autophagy

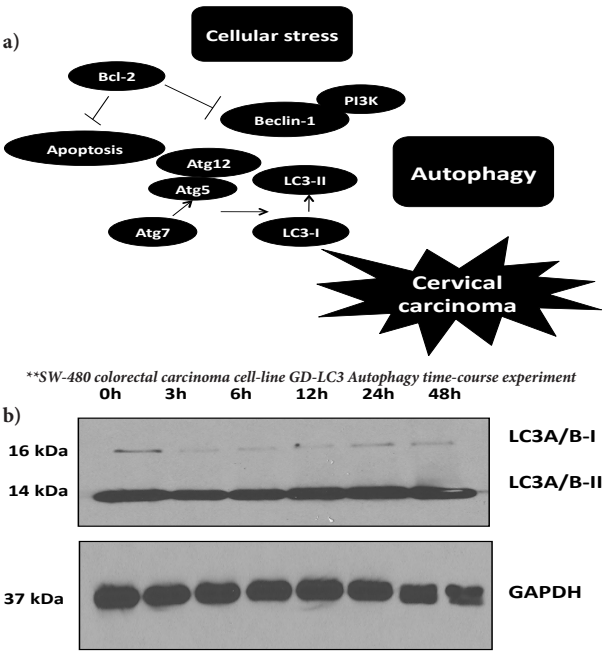

Figure 1. a) The Complex Autophagic Machinery, b) Autophagic Marker LC3 Detection by Western Blot Technique. For glucose depletion (GD) as Autophagy trigger, SW480 colorectal cancer cells were rinsed with glucose-free RPMI-1640, followed by incubation in GD medium (glucose-free RPMI-1640 medium with 10% heat-inactivated FBS and 1% PS) for 0-48 h. Western blot analysis was performed to investigate the expression of LC3, a known hallmark of autophagy; GAPDH was used as an internal reference. **This data was part of S.P.'s postdoctoral fellowship research at UTMB, TX, USA

cancer research data was earlier part of the lead author's postdoctoral research project at UTMB, TX, USA)**. Further research design(s)/experiment(s) on similar lines may be beneficial in fully dissecting the role of LC-3 I and II in other cancers, including cervical cancer.

Autophagy in Cervical Cancer

Autophagy is emerging as an attractive therapeutic target in understanding the etiopathogenesis of cervical cancer. We extracted a total of 25 articles after performing a comprehensive literature search using Pubmed and have included the most relevant papers on autophagy in cervical carcinoma in the present review that may be beneficial in understanding the biochemical/molecular mechanisms associated with cervical cancer.

An elegant study by Zhu et al has aimed to identify the expression of autophagy-related proteins LC3 and Beclin-1 in cervical normal epithelial cells as well as squamous cancer cells, and to assess the prognostic significance of Beclin 1 and LC3 expression in FIGO stages I and II cervical squamous cell carcinoma. The immunohistochemical expression of Beclin 1 and LC3 were evaluated in 26 formalin-fixed paraffin-embedded cervical normal tissue samples and 50 tumor samples of FIGO stage I-II cervical squamous cell carcinoma, respectively (Zhu, 2012). Cervical normal squamous epithelial cells and carcinoma cells expressed high Beclin 1 immunoreactivity in 96.2% (25/26) and 28.0% (14/50)

of patients, and expressed high LC3 immunoreactivity in 76.9% (20/26) and 26.0% (13/50) of cervical cancer patients, respectively. Expression levels of both Beclin 1 and LC3 were not associated with age, FIGO stage, pathologic differentiation, and lymph node metastasis; overall, the study concluded that expression levels of both Beclin-1 and LC3 were significantly lower in cervical squamous cancer cells than normal squamous epithelial cells, and expression of Beclin 1 and LC3 may have prognostic significance in early stage cervical squamous cell carcinoma. The central regulator in the complex autophagic machinery is Beclin-1, the expression and/or activity levels of which may in turn tilt the malignant/cancerous cell's fate towards apoptotic cell death or autophagy, a form of non-programmed cell death. Altered Beclin-1 expression levels have been investigated in cervical cancer, cervical intraepithelial neoplasia (CIN) and normal cervical tissues (Cheng et al., 2012); a total of 122 cervical cancer cases, 35 cases with cervical intraepithelial neoplasia (CIN) and 31 cases with uterine fibroids were collected by the authors. They observed Beclin 1 positive rate in normal cervical tissues, CIN tissues and cervical cancers as 83.9%, 74.3% and 53.3%, respectively, and it was significantly different between the three groups ($p<0.01$); Beclin 1 expression was negatively correlated with cervical cancer differentiation, lymph node metastasis, recurrence and death ($p<0.05$). Metformin, a potential drug for the treatment of cervical cancers, induced both apoptosis and autophagy in cervical cancer cells when Liver Kinase B1 was expressed in C33A, Me180, CaSki, HeLa, HT-3 and MS751 cells (Xiao et al., 2012). Autophagy gene Beclin 1 overexpression has been shown to inhibit the proliferation and growth of HeLa cells in vitro and vivo, while promoting autophagy and apoptosis of HeLa cells (Wang et al., 2011). Autophagy plays an important role in preventing cisplatin-induced apoptosis in HeLa cervical cancer cells suggesting that inhibition of autophagy may improve cisplatin chemotherapy (Xu et al., 2012).

Oxidative stress is one of the known hallmarks of inflammation and cancer; a recent study demonstrates that ROS plays a critical role in oridonin-induced apoptosis and autophagy (Zhang et al., 2011). The association of HPV infection with the expression of ATPase family AAA domain containing 3A (ATAD3A), an anti-autophagy factor, in cervical cancer has been investigated; HPV infection correlated with increased ATAD3A expression and drug resistance in cervical cancer and persistent HPV infection may stabilize ATAD3A expression to inhibit autophagy as well as apoptosis and to increase drug resistance (Chen et al., 2011). Another study by Wang et al examined Beclin 1 protein expression in 81 cervical squamous carcinoma tissue specimens by immunohistochemistry and E6/E7 genes of HPV type 16 by polymerase chain reaction (Wang et al., 2011). The expression of Beclin 1 was associated with pelvic lymph node metastasis and histological grade, but did not correlate with age, FIGO stage, cervical infiltration, size of tumor, and type of cervical lesion. Overall, the study concluded that decreased Beclin 1 expression levels may be related to tumorigenesis and cervical cancer development, but is not significantly associated with HPV 16 infection. To investigate the effect(s) of Beclin 1, an autophagy gene, on the expression of angiopoietin (Ang) protein and Tie-2 receptor in CaSki human cervical cancer cells, Sun et al. (2011) have reported that overexpression of Beclin 1 can inhibit the proliferation of CaSki cells by altering the balance among the expression levels of Ang-1, Ang-2 and Tie-2. A major difference between cancer and normal tissues is the preferential utilization of glycolysis by cancerous cells; an interesting study by Stein et al assessed p62 as an autophagic resistance marker. The authors conducted a phase I study of 2-deoxyglucose (2DG), and assessed 2DG uptake with fluorodeoxyglucose (FDG) positron emission tomography (PET); five out of eight patients assessed with FDG-PET scanning demonstrated decreased FDG uptake by day 2 of therapy, thereby suggesting competition of 2DG with FDG, and five of six patients assessed for p62 showed a decrease in p62 at 24 h (Stein et al., 2010).

A recent study observed the effect of autophagy on paclitaxel-induced CaSki cell death through the regulation of Beclin1 gene expression and explored the interaction between autophagy and apoptosis; it was concluded that Beclin1 plays an important role in the regulation of anti-tumor activity and overexpression of Beclin1 in CaSki cells may enhance the apoptotic cell death induced by paclitaxel (Sun et al., 2010). Autophagy and apoptosis may have differential contribution(s) to carboplatin-induced death of cervical cancer SiHa cells; overexpression of Beclin1 in SiHa cells may enhance apoptosis signaling induced by carboplatin (Sun et al., 2009).

Resveratrol-induced autophagy and apoptotic cell death mediated by Cathepsin L has been reported in cervical cancer cells (Hsu et al., 2009). Hypoxia and vascular insufficiency in the necrotic core of malignant/cancerous cells of the tumor microenvironment contributes to drug resistance and cancer progression (Fels et al., 2008). This study suggested that the mode of cell death was cell type-dependent as DLD1 colorectal carcinoma cells showed enhanced apoptosis while HeLa cervical carcinoma cells activated autophagy, blocked apoptosis, and eventually led to necrosis; pharmacologic or genetic ablation of autophagy was associated with increased levels of apoptosis.

Overall, the results suggested that hypoxic tumor cells which are comparatively more resistant to genotoxic agents are hypersensitive to proteasome inhibitors; therefore, combining clinically used proteasome inhibitor bortezomib with therapies that target the normoxic fraction of human tumors can lead to more effective tumor control. Etoposide, a cytotoxic agent, may cause cell death in cervical carcinoma by both apoptosis and autophagy; electron microscopy studies demonstrated that autophagosomes/autolysosomes exhibited an autophagic appearance in the presence of etoposide (Lee et al., 2007). Blocking autophagy by inhibitors, including 3-methyladenine, suppressed both the expression of Beclin 1 protein and the antitumor effect of etoposide. Beclin1, a central player in the autophagy signal transduction pathway, may be a critical molecular switch in fine tuning autophagy and apoptosis through caspase-9, thereby

regulating tumorigenesis (Wang et al., 2007). Thus, targeting components of the autophagy signaling pathway may help in identifying potential therapeutic targets for cervical cancer treatment and patient prognosis in the near future.

Therapeutic implications

Targeting autophagy is an attractive therapeutic strategy in understanding the complexities involved in diverse cancers ranging from cervical cancer to colorectal carcinoma. Inhibition of the autophagy signal transduction pathway has recently revealed promising results in increasing pro-death activity of multiple cancer therapeutics. Autophagy is an evolutionarily conserved pathway with several roles in carcinogenesis and cancer therapy (Liu and Ryan, 2012); autophagy may inhibit the initiation of tumorigenesis by limiting cytoplasmic damage, genomic instability and subsequent inflammation, and functional loss of certain autophagy genes may in turn predispose the cell/biological system towards cancer.

On the contrary, autophagy may also be protective by promoting cell survival under stressful metabolic conditions, such as glucose-depletion; however, depending on the duration of the stressful physiological mileu and the cancer cell type, autophagy flux/activity may be altered thereby tilting the cell's fate from survival to death. This altered metabolic flux under stress conditions, such as glucose deprivation, may be observed in terms of expression levels of the autophagy marker LC-3 isoforms by western blot; an elegant example of this phenomenon has been depicted in Figure 1b. Further autophagy assays/experimental techniques such as electron microscopy, acridine orange staining, etc. for detection of autophagosomes and confirmatory experiments may be beneficial in fully understanding the autophagic flux activity in malignant and/or cancer cell types.

Novel agents, such as mTOR inhibitors that induce autophagy, have been promising in treating renal cell carcinoma; a recent study has reported the potential use of the small molecule STF-62247, an autophagic cell death inducer, to modulate radiation by radiosensitization of renal cell carcinoma in vitro through the induction of autophagy, thereby improving patient prognosis (Anbalagan et al., 2012). FTY720, a synthetic sphingosine analog, has been implicated as a promising autophagy-blocking and anti-neoplastic agent in mantle cell lymphoma (Alinari et al., 2012). MicroRNAs have recently been demonstrated as significant modulators of the autophagic pathway in many pathological processes, most notably cancer (Fu et al., 2012). Autophagy is an emerging cell death mechanism in pancreatic cancer and esophageal cancer (Mujumdar and Saluja, 2010; O'Donovan, et al., 2012). Preclinical models and early phase clinical trials in autophagy are in progress to study the inhibition of autophagy in restoring chemosensitivity and enhanced tumor cell (Yang et al., 2011). Autophagy has also been shown to induce cell senescence, which may in turn stop cancer progression (Lee et al., 2012). Targeted manipulation of autophagy in cancer will indeed provide novel therapeutic avenues for drug development and designing optimal therapeutic strategies for cancer therapy in patients. To conclude, the complex autophagic signaling may prove to be an innovative strategy in identification of clinically relevant biomarkers in cervical cancer in the near future, thereby leading to a better understanding of the etiopathogenesis of human cancers, including cervical cancer.

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