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 milieu 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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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 fully dissecting the role of LC-3 I and II in other cancers, including 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) 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)
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Autophagy is a key cellular process that involves the degradation of cellular components and organelles through the autophagy-lysosome pathway. In cancer cells, autophagy can play a dual role, either as a protective mechanism against stress or as a contributor to cell death. In cervical cancer, autophagy has been shown to be upregulated, suggesting its involvement in the disease progression and resistance to chemotherapy.

The expression of Beclin 1, a key protein in the autophagy pathway, has been studied in cervical cancer. Beclin 1 is involved in the initiation of autophagy and its overexpression has been correlated with a poor prognosis in cervical cancer patients. Beclin 1 expression is associated with advanced FIGO stage, lymph node metastasis, and histological grade, indicating its potential as a prognostic marker.

Beclin 1 expression levels are also associated with other clinicopathological factors. For instance, Beclin 1 expression is decreased in normal cervical tissues compared to cervical neoplasia and cancerous tissues. This suggests that Beclin 1 may play a role in the early stages of cervical cancer development.

In cervical cancer cells, Beclin 1 expression is associated with drug resistance and apoptosis. The overexpression of Beclin 1 can enhance the apoptotic cell death induced by chemotherapeutic agents such as etoposide and paclitaxel. Beclin 1 plays a critical role in the regulation of anti-apoptotic factors and the autophagic machinery.

Overall, Beclin 1 expression in cervical cancer cells can be a potential therapeutic target for the treatment of cervical cancer. Further studies are needed to understand the mechanisms of Beclin 1 expression and its role in cervical cancer development.

The use of autophagy inhibitors, such as bortezomib, may be a promising approach for the treatment of cervical cancer. However, the combination of autophagy inhibitors with other therapeutic agents may be necessary to overcome drug resistance and improve treatment outcomes.

In conclusion, autophagy and Beclin 1 are important targets in cervical cancer, and further research is needed to develop effective therapeutic strategies to target autophagy in cervical cancer.
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 milieu 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 isofoms 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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**References**


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