Pathology – Research and Practice 211 (2015) 101–108

Contents lists available at ScienceDirect

Pathology – Research and Practice

journal homepage: www.elsevier.com/locate/prp

Review

Autophagic responses to hypoxia and anticancer therapy in head and neck cancer

Haiwei Wu, Shengyun Huang, Dongsheng Zhang*

Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Road, Jinan 250021, China

ARTICLE INFO

Article history:
Received 8 June 2014
Received in revised form 21 October 2014
Accepted 11 November 2014

Keywords:
Head and neck squamous cell carcinoma
Autophagy
Hypoxia
Anticancer therapy

ABSTRACT

Autophagy is a major intracellular pathway involving in the degradation and recycling of cytosolic material, including organelles, proteins, and ribosomes. Autophagy is commonly active in tumor cells and could be induced by stress conditions such as hypoxia, nutrient depletion and anticancer therapy. Increasing evidence supports the role of autophagy in modulating cancer behavior in head and neck squamous cell carcinoma (HNSCC). Despite recent advances in surgery combined with chemotherapy and radiotherapy, the survival rate of patients with HNSCC has not been improved substantially. To adapt to the hostile microenvironment induced by stress condition including hypoxia and anticancer therapy, more biological changes such as autophagy are induced in tumor cells contributing to their malignant and aggressive behavior. In the present review, we summarized recent findings on the molecules involved in the autophagy induced by hypoxia and anticancer therapy and basic mechanisms of autophagy, and focused on elucidating the role of autophagy in tumor progression of HNSCC. Some novel studies on the relationships between mircoRNA and autophagy were also discussed in this review. A better understanding of this knowledge may provide new ideas and targets for effective prevention and treatment in HNSCC.

Contents

* Corresponding author at: Department of Oral and Maxillofacial Surgery, Shandong Provincial Hospital Affiliated to Shandong University, 324 Jingwu Road, Jinan 250021, China. Tel.: +86 531 68773236; fax: +86 531 87035697.
E-mail address: ds63zhang@yeah.net (D. Zhang).

http://dx.doi.org/10.1016/j.prp.2014.11.010
0344-0338/

Introduction

According to epidemiological data, approximately 650,000 new cases of head and neck cancers are diagnosed annually worldwide, and account for 12% of all malignancies [1,2]. HNSCC mainly derives from the epithelium mucosa cell of oral cavity, oropharynx, laryngopharynx and larynx. As for its unique anatomical locations, the main risk conditions for HNSCC are alcohol and tobacco exposure. Recently, the human papillomavirus (HPV) has been proved another potential cause of HNSCC [3]. Surgery, radiation and chemotherapy are the most common treatment for HNSCC. Though great improvement has been achieved in therapeutic modalities, survival of patients with HNSCC has not improved significantly over the last 30 years, with the overall 5-year survival not exceeding 50% [4]. Increasing evidence support the opinion that autophagy plays an important role in tumor cell death or survival mechanisms under metabolic stress condition including hypoxia and anticancer treatment [5].

It is widely accepted that tumor-associated microenvironment facilitates tumor cell with a protective shell that impedes drug or radiation access and encourages tumor cell to overcome treatment-induced stress [6]. Hypoxia, as the fundamental biological phenomenon of solid tumors, plays an important role in seeding and maintenance of the tumor microenvironment [7]. In the clinical reports, the presence and a greater extent of tumor hypoxia has been shown to be a negative prognostic indicator associated with treatment resistance and tumor malignance in HNSCC [8]. Recently, hypoxia-induced autophagy has been demonstrated to exert great effect in the tumor cell survival by removing of potentially toxic damaged proteins and organelles [9].

The molecules involved in the autophagy induced by hypoxia and anticancer therapy and basic mechanisms of autophagy would be discussed in the following, and the role of autophagy in tumor progression would be explored, which may do favor to future directions in the treatment for HNSCC.

Autophagy and HNSCC

An introduction of autophagy

Autophagy is a genetically programmed, evolutionarily conserved process for the degradation and recycling of cellular proteins and organelles. Autophagy has gained much attention among oncologists because of increasing evidence indicating that autophagy is closely associated with both tumorigenesis and resistance to anticancer therapy. Autophagy requires the formation of a double-membrane autophagosome which initiates from the engulfment of the phagophore by endoplasmic reticulum to enclose and degrade cytoplasmic proteins and organelles [10]. Autophagy is elaborately regulated by a limited number of highly conserved genes called ATGs (for AuTophaGy gene), with two protein conjugation necessary for autophasome formation, the Atg12-Atg15 and Atg8-phosphatidyl ethanolamine conjugation systems [11]. Recent studies show that autophagosomes can sequester cytosolic material in a selective or nonselective way. Selective autophagy is associated with BNIP3-mediated mitophagy and degradation of p62 that binds ubiquitinated protein aggregates to target them for degradation [12,13], while nonselective autophagy involves microtubule-associated protein light chain 3 (LC3), a protein which is usually considered as an indicator of autophagy, after conversion from its cytosolic form LC3-I to its autophagosome membrane-associated form LC3-II [10,14,15].

Whether autophagy is beneficial for tumor cell survival or death has been a controversial topic. Because oncogenic cells with high proliferation rate usually have a great demand for oxygen and nutrients, cells often encounter metabolic stress and hypoxia even in the presence of ample external nutrients [16]. To adapt to the hostile mircoenvironment, autophagy prolongs cell survival by recycling amino acid and energy and removing the damaged organelles. It is widely accepted that autophagy contributes to the survival of tumor cells under various stress condition and up-regulation of autophagy is intricately associated with tumor aggressiveness. For instance, the induction of autophagy in hypoxic areas promoted tumor cell survival and conferred aggressive phenotype in immunocompetent murine HNSCC models [17]. By exploring LC3B expression and its relationship with clinicopathological factors, autophagy proved to be a pro-survival factor in human colorectal cancer and enhances the aggressiveness of colorectal cancer cells [18]. The up-regulation of autophagy in response to metabolic and genotoxic stress contributes to tumor aggressiveness and resistance to radiation and chemotherapy, and it provides a new target for cancer treatment [10,16,19].

However, recent studies discovered that autophagy was also involved in a type of programmed cell death-autophagic cell death. Programmed cell death (PCD) is a physiological process regulated by an intracellular program which plays key role in ultimate decisions of cancer cell fate, including apoptosis (the type I PCD), autophagy (the type II PCD) and a type III PCD termed programmed necrosis [20]. Compared with apoptosis and necrosis as critical mechanisms for cell death, autophagy may play a dual role in cell viability [11,21]. As discussed above, beside autophagy's role in cytoprotection, studies do show that autophagic cell death has great effect on killing of tumor cells in certain circumstances [22]. For example, Atg5-dependent autophagic cell death was found in cervical cancer cells treated with ursolic acid (UA) and inhibition of Atg5 increasing the survival of cancer cells treated with UA [23]. Zhang et al. [24] found that resveratrol could induce autophagic cell death by regulating the AMPK/mTOR pathway. Similarly, increased autophagy contributes to pancreatic beta cell death in Pdx1 deficiency and following nutrient deprivation [25]. Increasing researches report the effect of autophagic cell death in suppressing the tumor development. There is an opinion that autophagic cell death likely reflects an attempt by cancer cells to survive the stress stimuli that initiated their death process and it impedes rather than accelerates the efficiency of apoptotic/necrotic execution [19]. Recently, oncogene-induced senescence (OIS), a cellular progress that drives tumor cells to cell cycle arrest limiting the proliferation of tumor cells, is linked to autophagy. Autophagy may promote rapid protein turnover and facilitate the translation of proteins highly necessary for OIS establishment [26]. This may contribute to understanding of auphagic cell death in suppressing tumorigenesis.

Autophagy-related gene expression in HNSCC

Initially, studies of the functions of Beclin 1 helped oncologists to realize the connection of impaired autophagy and cancer development [11,22]. The Beclin 1(BECN1, also called ATG6) gene encodes a 60-kDa coiled-coil protein that interacts with the prototypic apoptosis inhibitor Bcl-2 [27] and plays critical role in the regulation of autophagy. Beclin 1 binds to several proteins, such as Vps34, Atg14L, Ambra1, UVRAG, Bif-1, p150 and Rubicon, to regulate the maturation of the autophagosome [16]. The Beclin 1 autophagy gene is widely detected in cases of human breast, ovarian, prostate, and lung cancer [28–30]. Decreased Beclin 1 expression is often associated with poor prognosis, whereas ectopic Beclin 1 expression contributes to the limitation of tumor proliferation, indicating Beclin 1 as a tumor suppressor gene. However, in nasopharyngeal carcinoma, elevated Beclin 1 expression is shown to be correlated with poor prognosis, suggesting varied prognostic values of Beclin 1 depend on intrinsic properties of the tumor type [31].