Biochimica et Biophysica Acta 1868 (2017) 40–50

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Autophagy as a potential target for sarcoma treatment

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ARTICLE INFO

Article history:
Received 25 November 2016
Received in revised form 23 February 2017
Accepted 23 February 2017
Available online 24 February 2017

Keywords:
Autophagy
Sarcoma
Targeted cancer therapy

ABSTRACT

Autophagy is a constitutively active, evolutionary conserved, catabolic process for maintaining homeostasis in cellular stress responses and cell survival. Although its mechanism has not been fully illustrated, recent work on autophagy in various types of sarcomas has demonstrated that autophagy exerts an important role in sarcoma cell growth and proliferation, in pro-survival response to therapies and stresses, and in therapeutic resistance of sarcoma. Thus, the autophagic process is being seen as a possibly novel therapeutic target of sarcoma. Additionally, some co-regulators of autophagy have also been investigated as promising biomarkers for the diagnosis and prognosis of sarcoma. In this review, we summarize contemporary advances in the role of autophagy in sarcoma and discuss the potential of autophagy as a new target for sarcoma treatment.

Contents

1. Introduction

Sarcomas are a large and heterogeneous group of more than 50 malignant primary neoplasms of mesenchymal origin [1]. Although the frequency of patients with sarcoma is restricted to approximately 1% of all adults with cancer, some types, such as osteosarcoma and Ewing sarcoma, disproportionally affect children and adolescents. Since the 1980's, the use of chemotherapy significantly increased the survival rate of patients with certain types of sarcoma, including osteosarcoma, Ewing sarcoma, and rhabdomyosarcoma [2,3]. Currently, surgery,chemotherapy and radiation therapy is standard treatment for sarcoma. However, progress has slowed in recent years, and efforts to improve outcomes with intensifying regimens or adding new agents

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http://dx.doi.org/10.1016/j.bbcan.2017.02.004
0304-419X/

have not improved clinical results [4]. Therefore, development of new therapeutic strategies is critical for these patients.

Cytotoxic chemotherapy or radiotherapy promotes apoptotic cell death or type I programmed cell death, but cancer cells can develop the capability to block those pathways, leading to therapeutic resistance and more aggressive tumors [5]. Therefore, further exploration of new therapies to efficiently induce cell death and overcome chemotherapy resistance can be helpful to overcome this problem. Recently, research of autophagy in sarcoma has shed new light on how we might be able to treat these malignancies.

Autophagy is a constitutively active, evolutionary conserved, physiologic self-degradative process which assures cellular homeostasis and arouses survival mechanisms under various stresses, such as radiation and chemotherapy [6]. Recent data has illustrated that mutations in genes involved in autophagyhold an important role in the pathogenesis of diverse diseases, including cancer [7–10]. Recently, the 2016 Nobel Prize for Physiology or Medicine has been awarded to Dr. Yoshinori Ohsumi, for his discoveries of mechanisms for autophagy. Specifically, autophagy has been shown to be involved in cancer metastasis through modulating tumor cell motility and invasion, cancer stem cell differentiation, resistance to chemotherapy, epithelial-to-mesenchymal transition (EMT), tumor cell dormancy and escape from immune surveillance [8]. Among the multiple responses occurring in tumor cells undergoing anti-cancer therapy, the functional importance of autophagy in cancer treatment remains unclear. Based on past discoveries and the majority of current preclinical or clinical trial studies, autophagy could play an important role [10–20]. Increased autophagy allows tumor cells to survive under the conditions of hypoxia, acidosis, or chemotherapy [21–23]. Several clinical studies have demonstrated that inhibition of autophagy enhances the anti-cancer activity of chemotherapeutic agents [13–16,18–20]. These data have led to a variety of clinical trials to assess autophagy inhibition in combination with conventional chemotherapy. In this context, autophagy inhibition is likely emerging as a promising therapeutic strategy against cancer, including sarcoma.

In this review, we summarize the current state of knowledge regarding the relevance of autophagy in sarcoma and the therapeutic implications of autophagy regulation in the treatment of sarcoma.

2. Mechanism and regulation of autophagy in sarcoma

In most cells, autophagy is constitutively active at a low baseline level to maintain cellular homeostasis by clearing up abnormal organelles and proteins. When facing stress conditions, such as nutrient starvation, hypoxia, growth factor insufficiency, acidosis or drug exposure, the level of autophagy can be upregulated rapidly to provide more nutrients and energy for cells [24]. This stress-induced autophagy is mostly non-specific [24]. But the baseline autophagy can be selective depending on their targets, such as mitochondrial autophagy or mitophagy (targeting mitochondria), reticulophagy (targeting endoplasmic reticulum), ribophagy (targeting ribosome) and others [25].

There are three primary types of autophagy identified in eukaryotic cells, including macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (Table 1) [26]. Macroautophagy (hereafter referred to as autophagy) is the best characterized pathway and includes several main steps: induction, vesicle nucleation and elongation, autophagosome formation and autolysosome formation (Fig. 1) [27]. The autolysosomes then digest the harmful proteins, organelles, toxins and even themselves, consequently providing nutrients and better survival condition for cells. Sarcoma tumor cells can utilize this pathway to escape from death caused by chemotherapy treatment and prolong their survival under the conditions of metabolic stress induced by different chemotherapies.

The process of autophagy in sarcoma can be regulated by AuTophaGy-related genes (ATGs) through different autophagic signaling pathways. During the initiation of phagophore membrane, various organelles have already been reported as primary membrane sources, such as endoplasmic reticulum, mitochondria, endoplasmic reticulum mitochondria, plasma membrane, Golgi-derived small vesicles and recycling endosomes, however, the origin of autophagosomes is still unclear [32–37].

Following autophagy induction, the nucleation complex and the ATG1 (Unc-51-like kinase 1/2, ULK1/2) complex plays an important role in the early stages of autophagy. The nucleation complex mainly comprises class III phosphatidylinositol 3 kinase (PI3KC3) and Beclin-1 (ATG6). This complex is the best-known pathway for regulation of autophagy in sarcoma [38,39]. After Beclin-1 release from the Bcl-2 and Bcl-XL apoptotic associated complex, Beclin-1 will combine with PI3KC3, and autophagy is activated. Overexpression of Bcl-2 and Bcl-XL are frequently observed in several types of sarcomas. The Bcl-2 and Bcl-XL protein could be ideal therapeutic targets due to their dual role of inhibiting apoptosis and autophagy-associated tumor cell survival. On the other hand, the ULK1/2 complex is recruited to the pre-autophagosomal structure after autophagy induction. The activated ULK1/2 complex can enhance the activity of the autophagy nucleation complex by phosphorylation. Finally, the activated PI3KC3-Beclin-1 complex can join with the ULK1/2 complex to trigger the elongation of the phagophore. Moreover, ATG9 and ATG12 complexes can join in the process of phagophore expansion [40]. (Table 2)

Then, the next essential step of phagophore elongation is the lipidation of the ubiquitin-like protein ATG8 (microtubule-associated protein 1 light chain 3, LC3). In the LC3 conjugation system, LC3 can convert into LC3-I through the joining of ATG4, afterwards LC3-I can convert into LC3-II via the joining of ATG7, ATG3 and PE

Table 1
Comparisons of the characteristics of three primary types of autophagy.

Types of autophagy	Characteristics	Associated research on sarcoma	Refs.
Macroautophagy	❖ The most universal type of autophagy ❖ Can be selective or non-selective ❖ Dynamic membrane rearrangement for engulfing portions of the cytoplasm ❖ Can sequestrate large structures ❖ Engulfment of portions of cytoplasm into a double-membrane autophagosome which will fuse with lysosome	Yes	[26,28]
Microautophagy	❖ Can be selective or non-selective ❖ Dynamic membrane rearrangement for engulfing portions of the cytoplasm ❖ Can sequestrate large structures ❖ Direct engulfment of portions of cytoplasm at the lysosome surface by invagination, protrusion, and septation of the lysosome membrane	None	[26,29]
CMA	❖ Selective ❖ No membrane rearrangement ❖ Translocate only proteins that have a pentapeptide motif KFERQ in its amino acid sequence directly across the membrane of the lysosome through mediating by chaperone	None	[26,30,31]

Abbreviations: CMA chaperone-mediated autophagy; Refs references.