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Autophagy as a novel strategy for treatment of gastric cancer: A hypothesis

Authors' Contribution:

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Gastric cancer is the second most frequent cause of cancer-related death in the world and also causes much morbidity. The acquired resistance of cancer cells to drug reagents is becoming a major obstacle for successful cancer therapy. Recently, many studies have revealed that macroautophagy (here referred to as autophagy) may be a prosurvival factor and protect the cancer cell from the development of drug-induced death. Thus, we propose that autophagy may play an important role in the resistance of gastric cancer to therapy. Although the exact role of autophagy in tumor cells is still unclear and further studies are needed to prove the role of autophagy in gastric cancer, recent research findings suggest a new direction in investigating the mechanism underlying resistance of gastric cancer to therapy.

Key words: autophagy • gastric cancer • chemotherapy

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708 — — 21

Background

Gastric cancer is the second most frequent cause of cancer-related death in the world and almost two-thirds of the cases occur in Asian countries, especially China and Japan [1]. Although current major therapies, including surgery and chemotherapy, have been widely used, the prognosis of gastric cancer is generally rather poor, with 5-year relative survival below 30% in most countries [2]. However, the main cause of treatment failure in gastric cancer is the development of multidrug resistance to cytotoxic chemotherapies, which is at least in part related to the anti-apoptosis effect [3]. It is well known that the resistance of cell death is one of the hallmarks of cancer cells [4]. Although the relationship between autophagy and cancer is still unclear, especially in the regulation of cancer development and progression, there has been much important progress in our understanding that autophagy may have important roles in the treatment of gastric cancer cells.

Autophagy is an evolutionarily conserved catabolic process by which damaged or long-lived cellular proteins and organelles are degraded [5]. In the cancer cells it is still unclear if autophagy represents a survival mechanism or is involved in type II programmed cell death (PCD), which is termed autophagic cell death [6]. Autophagy is up-regulated when cells need to generate intracellular nutrients and energy, for example, during starvation, growth factor withdrawal, or high bioenergetic demands [7]. Moreover, basal autophagy can serve as an important homeostatic cellular recycling mechanism responsible for degrading unnecessary or dysfunctional cellular organelles and proteins in all living cells [8]; thus, autophagy can be viewed as a potent cytoprotective survival pathway in normal and cancer cells.

Hypothesis

Recently, accumulating evidence has indicated that autophagy is particularly activated during metabolic stress such as nutrient depletion and hypoxia, and has a special homeostatic role mediating removal of old or dysfunctional proteins and organelles, and is particularly important for cell survival during conditions of metabolic stress [9]. Moreover, autophagy is the only mechanism for degrading large structures such as protein aggregates and damaged organelles [10].

Although autophagy has been induced in many different cancer cell lines, including gastric cancer cells using different agents such as chemotherapeutics [11,12], the role of autophagy in tumor cell death or survival is still unclear. Autophagy has

several adaptive roles in diverse human pathologies, including cancer and other diseases, and can act as a cytoprotective survival pathway. Thus, under many conditions, autophagy is induced in response to many different forms of stress, including nutrient and growth factor deprivation and chemotherapeutics, and is utilized as a protective mechanism against cell death in the hostile environment [13].

In fact, more and more results have suggested that autophagy can provide a survival advantage to tumors treated with chemotherapeutic agents. In human hepatocellular carcinoma and colorectal carcinoma cells, inhibition of autophagy enhances anticancer effects of atorvastatin in digestive malignancies [14]. Moreover, inhibition of autophagy by 3-Methyladenine (3-MA) can potentiate cisplatin-induced apoptosis in esophageal squamous cell carcinoma cells [15]. In addition, many studies have revealed that inhibition of autophagy can augment cancer cell death through apoptosis, which indicates that autophagy may act as a protector in tumor cell survival.

Furthermore, other studies have proved that induction of autophagy can enhance tumor resistance in different tumor cell lines [16]. Hypoxia-induced autophagy can decrease hepatoma cell sensitization to chemotherapeutic agents that affect their apoptotic potential [17]. In gastric cancer cells, oxaliplatin-induced protective autophagy partially prevents apoptosis in gastric cancer MGC803 cells [18]. Thus, results of many studies suggest that induction of autophagy can protect tumor cells against cancer treatment.

Previous studies have shown that inhibition of autophagy can potentiate the cell death induced by anticancer drugs in gastric cancer cells [19–21]. Therefore, we speculate that inhibition of autophagy may be a strategy for overcoming gastric cancer resistance to therapy.

Conclusions

In recent years, the role of autophagy in cancer cells has been investigated extensively. Although the impact of autophagy on tumor cells is still unclear and more studies are needed to prove the effects of autophagy in gastric cancer, recent research results suggest that autophagy may be a new target for combatting resistance of gastric cancer to therapy.

Conflict of interest statement

The authors declare that they have no conflict of interest in any matter related to this work.

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