News and Perspectives

**Autophagy: A Potential Mechanism for Resistance of Esophageal Squamous Cell Carcinoma to Therapy**

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Esophageal squamous cell carcinoma (ESCC) is one of the most prevalent malignant tumors in developing countries, especially in China. Although treatment strategies continue to improve, ESCC cells have been known to develop resistance to chemoradiotherapy, resulting in a dramatic decrease in the 5-year survival rate. Evasion of apoptosis is also recognized to result in resistance to anticancer therapies. However, some evidence has indicated that chemotherapeutic agents not only kill cells through induction of apoptosis, but also by non-apoptotic forms of cell death. Although the significance of non-apoptotic cell death in chemotherapy and the mechanisms by which it is induced remain unclear, there has been considerable progress in our thinking that autophagy might play an important role in resistance to therapy of ESCC cells.

Autophagy is an evolutionarily highly conserved process among all eukaryotes ranging from yeast to mammals. The functional relationship between autophagy and cellular death or survival is complicated in that, in several situations, autophagy promotes survival under conditions of stress and starvation, whereas in other cellular situations, autophagy constitutes an alternative pathway to cellular demise (autophagic cell death). Via performance of homeostatic functions, autophagy can work as a cellular housekeeper to respond to metabolic stress, including eliminating excessive or unnecessary proteins and injured or aged organelles. Therefore, autophagy may be viewed as a new potential survival mechanism in normal and tumor cells.

**Background and Evidence**

Many studies have indicated that autophagy plays a role as a survival mechanism and has a special housekeeping role in the turnover of cytoplasmic constituents, including mitochondria. Moreover, autophagy might prevent aggregate formation by degradation of proteins such as monomers and oligomers.

Although autophagy has been induced in many different cancer cell lines including esophageal cancer cells, the role of autophagy in regulating tumor cell death or survival remains unclear. Autophagy has several implications in human disorders and tumors, and can act as a cellular defense mechanism. Thus, it could play an important role in the mechanism by which tumor cells try to maintain survival.
In fact, many researchers have found that autophagy allows tumor cells to survive under chemoradiotherapy. In human colon cancer cells, inhibition of autophagy can augment 5-fluorouracil chemotherapy. Moreover, inhibition of autophagy induced by overexpression of melanoma differentiation-associated gene 7 (interleukin-24) can strongly augment antileukemia activity. Besides, many results have shown that inhibition of autophagy can enhance tumor cell death via apoptosis, which indicates that autophagy exerts a protective role on tumor cell survival.

Moreover, other studies have proven that tumor resistance to death can be enhanced through upregulation of autophagy in different tumor cell lines. Hypoxia-induced autophagy can decrease hepatoma cell sensitization to chemotherapeutic agents that affect their apoptotic potential. In breast cancer cells, autophagy activated by eukaryotic elongation factor-2 kinase also plays a protective role in cancer cells under metabolic stress. Thus, many experiments have suggested that induction of autophagy can help tumor cells to survive and resist to anticancer therapy.

Previous studies have shown that inhibition of autophagy can enhance the effects of apoptosis induced by chemotherapeutic agents in esophageal cancer cells. Therefore, we speculate that autophagy plays a role in ESCC as a survival pathway of treatment resistance.

Conclusion

In recent years, increasing attention has been focused on the role of autophagy in tumor cells. Although a consensus has not yet been reached regarding the role of autophagy in tumor cells, and more studies are needed to prove the impact of autophagy on ESCC, at least it provides us with a new direction to explore the mechanisms of treatment resistance of ESCC.

References