**ABSTRACT**

Liver cancer is the second most frequent cause of cancer death in men and the sixth leading cause of cancer death in women. Hepatocellular carcinoma (HCC) represents the major subtype in liver cancer and its five-year survival rate remains very poor. Sorafenib, a molecular targeted therapeutic agent, was the first drug approved for the treatment of patients with HCC. However, the clinical response of sorafenib was seriously limited by drug resistance. Autophagy is an evolutionarily conserved mechanism among all eukaryotes. Recently, many studies have indicated that autophagy can be activated as a cellular protective mechanism in many tumour cells. Thus, we hypothesized that autophagy may play an important role in resistance to sorafenib in hepatocellular carcinoma. Although the exact role of autophagy in the sorafenib resistance of HCC is still complex and further studies are needed to be proven, at least it suggests that autophagy may be a new therapeutic target for the sorafenib resistance of HCC.

**Keywords:** Autophagy, chemo-resistance, hepatocellular carcinoma

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**INTRODUCTION**

Liver cancer is the second most frequent cause of cancer death in men and the sixth leading cause of cancer death in women (1). Among the primary liver cancers, hepatocellular carcinoma (HCC) represents the major subtype (2). Presently, although many different treatments including surgery...
and chemotherapy have been widely used, the therapeutic effect on the patients with HCC is still limited (3). Therefore, it is very important and critical to find new agents with better efficacy and safety in the treatment of patients with HCC.

Recently, molecular targeted therapies have created an encouraging trend in the management of HCC (4). Sorafenib, a molecular targeted therapeutic agent, was the first drug approved for the treatment of patients with unresectable HCC by the Food and Drug Administration of the United States of America [USA] (5). Sorafenib, acting as a multikinase inhibitor, combines two anticancer activities: blocks tumour cell proliferation by targeting Raf/MAPK-ERK kinase (MEK)/extracellular signalling-regulated kinase (ERK) signalling and inhibits tumour angiogenesis by targeting VEGFRs and PDGFR tyrosine kinases, since kinases play key roles in tumour cell proliferation, apoptosis and tumour angiogenesis (6−8).

However, development of resistance and limited efficacy of sorafenib in patients with advanced HCC are deficiencies of the therapy (9). Thus, it is very important to explore the detailed mechanisms underlying the resistance to this compound to help improve the therapeutic effect of HCC.

Macroautophagy (hereafter referred to as autophagy) is an evolutionarily conserved mechanism by which cytoplasm and organelles are digested via autophagosomes and autolysosomes and cellular components are recycled for energy utilization (10). In addition to its homeostatic role, the autophagic process allows cells to survive nutrient stress, by providing amino acids and fatty acids to maintain metabolic levels. So autophagy may be regarded as a probable mechanism for drug resistance. For example, inhibition of autophagy can enhance the effects of apoptosis induced by cisplatin in oesophageal cancer cells (11).

The Raf-MAK-ERK pathway, as one of the targets of sorafenib, is one of the molecular regulation mechanisms of autophagy (12), which indicates an underlying association between sorafenib and the regulation of autophagy. Moreover, a previous study has proven that inhibition of autophagy can potentiate the antitumour effect of the multikinase inhibitor sorafenib in HCC (13). Thus, we speculate that autophagy inhibition may be a novel way of increasing the efficiency of sorafenib in the treatment of HCC.

**Background and evidence**

Although autophagy can be activated by different anticancer drugs in many different cancer cell lines including HCC cells (14), the exact role of autophagy in tumour cell death or survival is still unclear. Autophagy can be up-regulated to promote cell survival through the degradation of cellular proteins and organelles when facing cellular stress, and can be regarded as a mechanism which can promote the growth of established tumours (15). Thus, it could serve as a potent oncogenic mechanism to promote tumour cell survival.

In fact, many studies have indicated that induction of autophagy can enhance tumour resistance to different anticancer therapies in different tumour cell lines (16). In breast cancer cells, Aurora kinase A inhibition-induced autophagy can trigger drug resistance, which may represent a novel mechanism of drug resistance in apoptosis-aimed therapy for breast cancer (17). In oesophageal cancer cell, autophagy can promote these drug-resistant cancer cell survival and recovery following treatment with chemotherapeutics (18).

In addition, autophagy may function importantly in HepG2 cell resistance to oxaliplatin and the resistance could be recovered apparently by inhibition of autophagy (19). Therefore, these results have indicated that autophagy may play an important role in the mechanism of the tumour cells resistant to anti-cancer drugs.

Other studies have proven that autophagy can protect tumour cells against the effect of sorafenib. In the HCC cells, autophagy can be activated by sorafenib and inhibition of autophagy by chloroquine and siRNA can augment the growth inhibitory effect of sorafenib, which suggests that the combination of autophagy modulation and molecular targeted therapy is a promising therapeutic strategy in treatment of HCC (20). Moreover, other reports have also noted that sorafenib can stimulate autophagy through inhibition of class III RTKs, and that in a dose-dependent effect this response can either be a protective form of autophagy or a toxic form of autophagy (21, 22). These findings suggest that inhibition of autophagy induced by sorafenib can improve treatment efficacy. Thus, in combination with therapeutic strategies that aim to inhibit autophagy in patients treated with conventional chemotherapy, novel targeted therapy with sorafenib represents a promising approach with higher efficacy for patients with HCC.

Previous studies have suggested that inhibition of autophagy can enhance the efficacy of sorafenib in HCC cells (20−22). Therefore, we present that autophagy may facilitate the sorafenib resistance of HCC cells, which might be one of the mechanisms of tumour recurrence and metastasis.

**CONCLUSION**

In recent years, the role of autophagy in the chemoradiotherapy resistance of cancer cells has been investigated extensively. Although the function of autophagy in sorafenib resistance is still uncertain and more studies are needed to explore the possible resistance mechanism, at least it offers a new potential strategy for overcoming resistance to sorafenib.

**REFERENCES**