

The Hypothesis of an Effective Strategy for Resistance of Hepatocellular Carcinoma to Therapy-autophagy

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours and its five-year survival rate remains low. Autophagy is a catabolic process conserved among all eukaryotes ranging from yeast to mammals. Recently, many studies show that tumour cells can utilize autophagy as a cellular defence mechanism when facing metabolic stress. Thus, we hypothesize that autophagy may play an important role in the resistance of hepatocellular carcinomas to therapy. Although the exact role of autophagy on tumour cells is still complex and further studies are needed to prove the impact of autophagy on HCC, it suggests that autophagy may be a new therapeutic target for the resistance to therapy of HCC.

Keywords: Autophagy, hepatocellular carcinoma, chemo-resistance

La Hipótesis de una Estrategia Efectiva para la Resistencia del Carcinoma Hepatocelular a la Terapia Autofágica

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RESUMEN

El carcinoma hepatocelular (CHC) es uno de los tumores malignos más comunes, y su tasa de supervivencia a los cinco años sigue siendo baja. La autofagia es un proceso catabólico conservado en todos los eucariotas, que abarca desde las levaduras hasta los mamíferos. Recientemente, numerosos estudios han demostrado que las células tumorales pueden utilizar la autofagia como un mecanismo celular de defensa frente al estrés metabólico. De este modo, sostenemos la hipótesis de que la autofagia puede desempeñar un papel importante en la resistencia de los carcinomas hepatocelulares a la terapia. Aunque el papel exacto de la autofagia en las celulares tumorales sigue siendo complejo, y se requieren más estudios a fin de probar el impacto de la autofagia en el CHC, hay indicios de que la autofagia puede ser un nuevo objetivo terapéutico para la resistencia a la terapia del CHC.

Palabras claves: Autofagia, hepatocelular carcinoma, quimio-resistencia

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignant tumours and the third leading cause of cancer-related deaths worldwide (1). At present, many therapeutic strategies including surgery and chemotherapy have been widely used, but the prognosis of HCC patients remains very

poor and their five-year relative survival rate is only 3 – 5% in most countries (2). However, the treatment effect is still not satisfactory because of the chemo-resistance of HCC cells, which is partially attributed to insensitivity to cell death from cytotoxic agents (3). It is well-known that the avoidance of apoptosis is one of the hallmarks of cancer cells (4) and that failure to induce apoptosis by anticancer treatments contributes to chemotherapeutic failure and tumour progression. Despite the role of autophagy and its underlying molecular mechanism, it is still controversial in cancer, especially in tumour progression. There have been important advances in the thinking that autophagy may be one of the important strategies involved in resistance of HCC cells to therapy.

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Autophagy is an evolutionarily self-catabolic degradation pathway where cellular components are digested and recycled to sustain cellular metabolism and prevent the accumulation of damaged proteins and organelles (5, 6). It is still unclear whether autophagy represents a survival mechanism under conditions of stress or contributes to cell death after cytotoxic therapy, which is different from apoptosis and is often termed autophagic cell death [Type II programmed cell death] (7). Autophagy may occur when cells need to generate intracellular nutrients and energy, for example, during multiple stresses like starvation for amino acids or glucose, hypoxia and unfolded protein. Basal autophagy can serve as an important housekeeper mediating the removal of dysfunctional proteins and damaged organelles (8), thus autophagy can be regarded as a new potential survival mechanism in normal and cancer cells.

HYPOTHESIS

Both animal and human studies have indicated that autophagy has a role in allowing cancer cells to overcome metabolic stress such as hypoxia and lack of nutrients (9), and has a special homeostatic role as a complement to the ubiquitin-proteasome system (10). Moreover, autophagy can also contribute to intracellular quality control, especially in turnover of aggregate-prone proteins (11).

Although autophagy has been induced in many different cancer cell lines including hepatocellular carcinoma cells using different agents such as chemo-therapeutics (12, 13), the role of autophagy on death or survival of tumour cells is still complex. Autophagy has several adaptive roles in human diverse pathologies including cancer and other diseases, and can act as a cytoprotective survival pathway. Thus, once cancer occurs, many cancer cells up-regulate basal autophagy and utilize autophagy to enhance fitness and survival in the hostile tumour micro-environment (14).

In fact, more and more experimental researchers suggest that autophagy can allow cancer cells to survive under chemo-radiotherapy. In human colon cancer cells, inhibition of autophagy can potentiate anti-angiogenic effects of sulforaphane by inducing apoptosis (15). Moreover, inhibition of autophagy can enhance the cell-killing effect of radiotherapy in human oesophageal squamous carcinoma cells (16). In addition, inhibition of autophagy can augment cancer cell death through apoptosis, which indicates that autophagy may act as a protector of tumour cells, allowing their survival.

Other studies have proven that induction of autophagy can enhance tumour resistance in different tumour cell lines. HMGB1-induced autophagy promotes chemotherapeutic resistance in leukaemia cells (17). In breast cancer cells, autophagy protects breast cancer cells from epirubicin-induced apoptosis and facilitates epirubicin-resistance development (18). Thus, many results suggest that induction of

autophagy can protect tumour cells against cancer treatment.

Previous studies have shown that inhibition of autophagy can potentiate the cell death induced by anticancer drugs in HCC cells (19, 20). Therefore, we present a hypothesis that inhibition of autophagy may be a novel approach for HCC therapy.

CONCLUSION

In recent years, the relationship between autophagy and cancer cells has attracted extensive attention worldwide. Although the exact role of autophagy on tumour cells is still complex and further studies are needed to prove the impact of autophagy on HCC, it is suggested that autophagy may be a new therapeutic target for the resistance of HCC to treatment.

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