Editorial

Autophagy elicits a novel and prospect strategy to starve arginine-dependent tumors

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With the development of the social economy and the improvement of people's living standards, chronic non-communicable diseases have become the main cause of death, and malignant tumors are one of the leading causes of death worldwide. In recent years, the incidence of malignant tumors has shown an upward trend. It was reported that there were 17 million new cases of cancer (all cancers combined excluding non-melanoma skin cancer) and 9.6 million deaths from cancer worldwide in 2018 (1) with, lung, liver, stomach, and bowel cancers being the four most common causes of cancer death.

Exploring effective treatment methods to fight cancer has always been a priority in medicine for modern human societies, and this is reflected in the level of worldwide research attention in this area. The most significant marker of cancer cells is their unrestricted growth and movement capabilities (1,2). Therefore, the key molecules of major pathways regarding the growth and metabolism of cancer cells have become important targets of anti-cancer drug research (2). Disruption of these signaling pathways in cancer cells usually leads to growth inhibition or death of tumor. In recent times, the research direction of anti-cancer drugs has mainly focused on interfering with DNA synthesis, unwinding and replication; interfering with hormone, protein, and folic acid balance; inhibiting angiogenesis and signal pathways necessary for tumor growth; and immunotherapy (3).

Because some tumors are often associated with intrinsic chemoresistance, the nutritional deprivation of tumors has become an important means to deal with them based on their auxotrophy. Autophagy should also be mentioned in the treatment of tumors with nutritional deficiencies. Autophagy is a mechanism by which some damaged, degenerated, or senile proteins and organelle components in cells are transported to lysosomes for degradation. This is a self-rescue method to maintain cell component renewal or homeostasis physiologically and provide energy under stress conditions. Autophagy plays a complex role in tumorigenesis, progression, and treatment, and can be considered a controversial subject, demonstrating sometimes inhibitory and sometimes beneficial tumor effects. Some tumors improve the micro-environment of tumors by autophagy, providing nutritional components for tumors to promote their growth. On the other hand, autophagy sometimes may cause the damage or even death of tumors cells (4,5), with the effect of autophagy varying from stage to stage in cancer.

Recently, Poillet-Perez *et al.* reported that the autophagy of host cells controls the fate of cancer cells (6), a notion which opens new theoretical space for the treatment of those cancers associated with autophagy and nutritional deficiency, and broadens the research horizons for therapeutic drugs. Owing to the decreased expression of argininosuccinate synthetase (ASS) and /or ornithine transcarbamylase (OTC), several types of tumor are arginine auxotrophic. For example, liver cancer cells lack ASS1, OTC, ASL (Argininosuccinate lyase), while kidney cancer cells lack ASS1 and ASL. These cancer cells are arginine-deficient types; that is to say, they cannot synthesize arginine by themselves, and can only obtain it from the extracellular environment (7,8). Poillet-

Perez *et al.* demonstrated that the autophagy of host cells is crucial to releasing arginine into the extracellular microenvironment, leading to an increase in the host's serum arginine level. In the study, it was observed that the growth of tumor cells was significantly inhibited when ATG7 or ATG5 was knocked out in mice. Further studies confirmed that the level of ARG1 increased significantly in host cells without autophagy. ARG1 was mainly expressed in the liver and could be released from hepatocytes into circulation, which promoted the transformation of arginine into ornithine, resulting in a significant reduction of arginine in the host serum, thus inhibiting the growth of arginine-dependent tumors. Meanwhile, when mice with inhibited autophagy were supplemented with arginine, the tumor inhibition disappeared. All evidence strongly supports the theory that cancer cells benefit from host autophagy to utilize arginine to grow (6).

As it has been known for many years that the majority of melanoma cells have a significant vulnerability to arginine deprivation, exploiting a potential enzyme-mediated arginine depletion strategy for the selective destruction of tumor cells, and arginine deprivation enzymes, such as arginase, arginine deiminase, and arginine decarboxylase, has been found to be an effective therapy to control the growth of tumors (8,9). Poillet-Perez *et al.* elicited a unique way to decrease the concentration of arginine indirectly through controlling the autophagy of the host, and successfully reduced the growth of arginine-dependent tumors. This discovery has not only uncovered a new method to control the concentration of arginine in the tumor microenvironment of the host itself, but also has significantly increased the number of potential target molecules in drug research work by regulating and controlling the key process of autophagy, thus successfully multiplying the potential avenues of anti-tumor drug investigation. This means that arginine-hunger treatment of melanoma cells will have a wider range of implementation method.

Combination of anti-tumor therapy might be more convenient and advantageous in further study. This coupling clearly provides us with an extremely useful and novel strategy in binding autophagy and auxotrophy therapy. In fact, the treatment of arginine depletion is not effective for all cancers; in particular, it has been found that when the supply of arginine is cut off, some cancer cells can activate alternative feeding pathways to continue to grow, for instance, shifting from a glucose-dependent state to a glutamine-dependent state. Thus, combining multiple approaches to treat cancer is both a necessary and promising measure (10). In ASS1-deficient sarcoma, arginine deprivation therapy with pegylated arginine deiminase (ADI-PEG20) was not enough to starve cells to death in a prolonged state. However, when arginine starvation was used in combination with the clinically available drug, chloroquine, this inhibited autophagy, and sarcoma cells died (7). Combining ARG1 treatment with PD-L1/PD1 pathway blockade was also more effective than when either of these treatments were used alone (11). Blocking autophagy enhanced the cytotoxicity of the recombinant human arginase in triple-negative breast cancer cells (12). Therefore, the complex regulatory pathway of autophagy can provide a richer and more promising base for novel combination therapy research due to the multitude of potential targeting molecules it makes available.

Although the control of host autophagy can cut off the nutrition of tumor cells and provide a new way to control the growth of tumors, there are still several problems to be considered in the future. The autophagy of host cells is a normal physiological phenomenon: it is necessary for life. Thus, it is necessary to determine how much autophagy-inhibition intensity and time will begin to affect the host's base physiology. Autophagy itself has dual effects on cancer cells, as both stimulation and inhibition of autophagy are cancer treatment strategies (13). The mechanism of cancer processing is exceptionally complex, so how can we identify the exact moment to inhibit the tumor via host autophagy regulation? Is there a risk in the reversal of cancer cell growth in host autophagy inhibition? In addition, the long-term effects of autophagy on normal host cells should also be considered. Some cells are stimulated by certain factors, such as inflammatory cytokines, which can exacerbate arginine metabolism, cause autophagy, and even display a trend of malignant transformation of normal cells (14).

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Footnote

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References

1. Cancer Research UK. Available online: https://www.

cancerresearchuk.org/health-professional/cancer-statistics/worldwide-cancer#heading-One
2. Kalyanaraman B, Cheng G, Hardy M, et al. A review of the basics of mitochondrial bioenergetics, metabolism, and related signaling pathways in cancer cells: Therapeutic targeting of tumor mitochondria with lipophilic cationic compounds. Redox Biol 2018;14:316-27.
3. Peters GJ, Raymond E. Contemporary reviews on cancer treatment. Cancer Chemother Pharmacol 2016;77:3-4.
4. Levy JM, Towers CG, Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer 2017;17:528-42.
5. Sun T, Li X, Zhang P, et al. Acetylation of Beclin 1 inhibits autophagosome maturation and promotes tumour growth. Nat Commun 2015;6:7215.
6. Poillet-Perez L, Xie X, Zhan L, et al. Autophagy maintains tumour growth through circulating arginine. Nature 2018;563:569-73.
7. Bean GR, Kremer JC, Prudner BC, et al. A metabolic synthetic lethal strategy with arginine deprivation and chloroquine leads to cell death in ASS1-deficient sarcomas. Cell Death Dis 2016;7:e2406.
8. Patil MD, Bhaumik J, Babykutty S, et al. Arginine dependence of tumor cells: targeting a chink in cancer's armor. Oncogene 2016;35:4957-72.
9. Riess C, Shokraie F, Classen CF, et al. Arginine-Depleting Enzymes - An Increasingly Recognized Treatment Strategy for Therapy-Refractory Malignancies. Cell Physiol Biochem 2018;51:854-70.
10. Kremer JC, Prudner BC, Lange SE, et al. Arginine Deprivation Inhibits the Warburg Effect and Upregulates Glutamine Anaplerosis and Serine Biosynthesis in ASS1-Deficient Cancers. Cell Rep 2017;18:991-1004.
11. Robainas M, Otano R, Bueno S, et al. Understanding the role of PD-L1/PD1 pathway blockade and autophagy in cancer therapy. Onco Targets Ther 2017;10:1803-7.
12. Wang Z, Shi X, Li Y, et al. Blocking autophagy enhanced cytotoxicity induced by recombinant human arginase in triple-negative breast cancer cells. Cell Death Dis 2014;5:e1563.
13. Levy JM, Towers CG, Thorburn A. Targeting autophagy in cancer. Nat Rev Cancer 2017;17:528-42.
14. Xia XJ, Gao YY, Zhang J, et al. Autophagy mediated by arginine depletion activation of the nutrient sensor GCN2 contributes to interferon-γ-induced malignant transformation of primary bovine mammary epithelial cells. Cell Death Discov 2016;2:15065.

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