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EDITORIAL

Circular RNA: The main regulator of energy metabolic reprogramming in cancer cells

To acquire the necessary energy from a frequently energy-poor microenvironment and use this energy to maintain viability and generate new biomass is a common feature of cancer cell metabolism.[1,2] The alterations in cancer-associated metabolic enzymes and metabolites have exerted far-reaching influence on cancer genetics/epigenetics,[3,4] cancer development,[5,6] and therapeutic resistance.[7] Therefore, cancer-associated energy metabolism pathways are potential targets for cancer therapy.[8]

One of the possible therapeutic targets is AMP-activated protein kinase (AMPK). As an important sensor of cellular energy status, it monitors the energy metabolism and regulates cellular glycolysis, lipolysis, and fatty acid oxidation (FAO).[9] When cells are deficient in energy, AMPK is activated and turns off energy-consuming metabolic activity (anabolism), while at the same time, it turns on metabolic activities that generate energy (catabolism).[10] AMPK is a core regulator of cellular metabolism and its activity is strictly regulated. Previous studies have demonstrated that liver kinase B1 (LKB1), calmodulin-dependent protein kinase kinase 2 (CaMKK2) and transforming growth factor beta-activated kinase 1 (TAK1)[11] are upstream regulators of AMPK. In addition, some small molecules such as 5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR), A-769662, etc. can also activate AMPK.[12]

In recent years, noncoding RNAs, as an emerging class of functional molecules, have attracted more and more attention. Long noncoding RNAs and circular RNAs (circRNAs) are two major groups of noncoding RNAs. Long noncoding RNA has already previously been reported to be involved in the regulation of AMPK.[13] However, whether circRNA is involved in AMPK regulation is still unknown. In a study recently published in *Cell Metabolism*, entitled "CircACC1 regulates assembly and activation of AMPK complex under metabolic stress", Li *et al.*[14] has demonstrated that circACC1, a circRNA, is an activator of AMPK whose expression is increased by cancer-associated stress conditions and its main function is to promote glycolysis and FAO.

To determine whether circRNA could implicate lipid metabolism, the authors selected six circRNA candidates whose host genes are associated with lipid metabolism from 1444 validated circRNAs. They examined these circRNAs in colon cancer cell lines by broad functional screening and found that expression inhibition of circACC1 could lead to significant lipid accumulation. To further confirm this finding, the authors constructed circACC1-overexpression cell model using normal human hepatocytes. In contrast with the colon cancer cell lines mentioned above, circACC1 exogenous expression resulted in decreased lipid accumulation. Moreover, lipidomic analyses showed that the constituent metabolite levels were significantly increased after circACC1 silencing. Given acetyl-CoA carboxylase (ACC1), the parental gene of circACC1, encodes a lipid metabolism regulator, the authors examined whether circACC1 affected the expression/activity of ACC1. They found that circACC1 silencing did not influence the mRNA level of ACC1; however, overexpression of circACC1 could antagonize ACC1 by promoting AMPK phosphorylation. As the functions of AMPK include energy homeostasis maintenance and remedying low adenosine triphosphate (ATP) levels by promoting FAO and glycolysis, the authors hypothesized that circACC1 could enhance FAO and glycolysis by promoting AMPK activity. The following extracellular acidification and oxygen consumption assays confirm their hypothesis.

In order to study how circACC1 affected AMPK signaling, the authors determined whether circACC1 was directly interacting with AMPK subunits by using RNA pulldown assays. The results revealed that circACC1 could directly bind to AMPKβand γfunctional domains. Additionally, the subsequent immunoprecipitation assays demonstrated that the direct binding of circACC1 to AMPK β and γ domains was involved in holoenzyme assembly, stability, and activity of AMPK. As AMPK signaling plays an important role in sensing and responding to changes in energy status, the authors examined how energy metabolic stress (serum removal) influenced the expression and functions of circACC1 by a series of biological experiments. They found that serum-deprivation activated the c-Jun N-terminal kinase (JNK)-c-JUN signaling pathway. The activation of the transcription factor c-JUN causes the ACC1 gene to produce less linear ACC1 mRNA but more circACC1, thereby, the upregulation of circACC1 expression imparts significant effects on cancer cell proliferation, promotes FAO and glycolysis in an AMPK-dependent manner.

This study identified a JNK-c-JUN-circACC1-AMPK pathway which is associated with cancer cell survival under nutrient-deficient conditions. This exciting finding enriches our understanding about the involvement of circRNA in energy metabolism regulation. It is worth noting that advanced colorectal cancer patients with low activation levels of AMPK in primary cancer tissues were associated

with poor prognosis after chemotherapy plus bevacizumab (a vascular endothelial growth factor antagonist).[15] This seems to contradict the view of the study by Li *et al*. who suggests that cancer cells gain survival advantages by upregulating AMPK activity. In fact, bevacizumab can induce AMPK activation leading to glucose depletion and ATP depletion in cancers.[16] Thus, the role of anti-cancer therapy in cancer metabolism reprogramming needs to be considered when treating cancers.

Disclosure

The author declares no competing interests.

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