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CircECE1 activates energy metabolism in osteosarcoma by stabilizing c-Myc

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Abstract

Background: Osteosarcoma (OS) is the most common malignant bone tumor and has a poor prognosis. The potential involvement of circular RNAs (circRNAs) in OS progression remains unexplored.
Here, we report that *CircECE1*, a circular RNA derived from human *ECE1*, plays a critical role in energy metabolism in OS.

Methods: The RIP chip sequence assay was performed to confirm *CircECE1*, through overexpression or knockdown of *CircECE1* to verify its function in 143B and U2OS. RNA immunoprecipitation and immunoprecipitation were used to verify *CircECE1*'s regulation of protein c-Myc and co- immunoprecipitation was used to verified the competitive binding relationship between *CircECE1* and SPOP. The influence of *CircECE1* on energy metabolism was evaluated by seahorse experiment, western blot, and immunohistochemistry.

Results: We found that *CircECE1* is highly expressed in OS tissues and cells and that *CircECE1* knockdown suppresses tumor proliferation and metastasis both in vitro and in vivo. Further, *CircECE1* significantly promotes glucose metabolism in OS cells in vitro and in vivo. Mechanistically, *CircECE1* interacts with c-Myc to prevent speckle-type POZ-mediated c-Myc ubiquitination and degradation. C-Myc inhibits thioredoxin binding protein (*TXNIP*) transcription and subsequently activates the Warburg effect.

Conclusions: *CircECE1* regulates the Warburg effect through the c-Myc/TXNIP axis. CircECE1 mediated signal transduction plays a important role in OS process and energy metabolism. These findings may identify novel targets for OS molecular therapy.

Keywords: Osteosarcoma, *CircECE1*, C-Myc, Glucose metabolism, TXNIP

Background

Although osteosarcoma (OS) is a rare malignancy, it has the second highest incidence and mortality among malignant bone tumors. OS is most common during childhood and adolescence [1, 2]. It is characterized by direct formation of osteoid tissue and uncontrolled proliferation of bone-related mesenchymal cells and is highly aggressive; 75% of OS cases have invasion of nearby tissues [2, 3]. Although neoadjuvant therapy and wide tumor excision have improved survival, the clinical outcomes and survival rates of OS patients are still unfavorable due to early lung-targeted metastasis. Hence, a better understanding of the biological characteristics and molecular mechanisms of OS carcinogenesis is urgently needed.

With the development of RNA high-throughput sequencing technology and advances in biotechnology, many noncoding RNAs have been found to perform a variety of biological functions in the human body and to participate in the occurrence and development of tumors and other diseases. Circular RNAs (circRNAs), an enigmatic subclass of endogenous long noncoding RNAs that regulate genes at the transcriptional or

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