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Mini Review

## CIRP may be a New Potential Target in Prostate Cancer - ③

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## ABSTRACT

Cold-Inducible RNA-Binding Protein (CIRP) is a cold-shock protein which can be induced after exposure to a moderate cold-shock in different species ranging from amphibians to humans. Expression of CIRP can also be regulated by hypoxia, UV radiation, glucose deprivation, heat stress and H<sub>2</sub>O<sub>2</sub>, suggesting that CIRP is a general stress-response protein. In response to stress, CIRP can migrate from the nucleus to the cytoplasm and regulate mRNA stability through its binding site on the 3'-UTR of its targeted mRNAs. Through the regulation of its targets, CIRP has been implicated in multiple cellular processes such as cell proliferation, cell survival, and circadian modulation. Recent studies showed that CIRP upregulation is observed in a large number of solid tumors and is regarded as a new oncogene in cancer. In addition, CIRP expression is also upregulated in human prostate cancer and *in-vitro* studies showed that downregulation of CIRP can decrease cell growth and enhance chemosensitivity in prostate cancer cell lines. These results indicate an important role of CIRP in prostate cancer progression. Further study is needed to determine the effects of CIRP *in-vivo* and the clinical prognostic significance of CIRP in prostate cancer.

**Keywords:** CIRP; mRNA stability; Prostate cancer

## INTRODUCTION

CIRP, also called cold-inducible RNA binding protein, is a RNA-binding protein that was first identified as a UV-inducible transcript in CHO cells more than two decades ago [1]. Since then, CIRP was characterized as a cold-shock protein that can be induced after exposure to a moderate cold-shock in different species ranging from amphibians to humans. Expression of CIRP can also be regulated by hypoxia, glucose deprivation, heat stress, H<sub>2</sub>O<sub>2</sub> and inflammatory cytokines [2], suggesting that CIRP is a general stress-response protein. In response to stress, CIRP can migrate from the nucleus to the cytoplasm and regulate mRNA stability through its binding site on the 3'-UTR of its targeted mRNAs [3].

CIRP exerts its function by preferentially targeting translation of specific mRNA transcripts harboring its RNA signature motif in response to cellular stress. In the cytosol, CIRP binds to the 3'-untranslated region (3'-UTR) of RNA transcripts on ribosomal fractions and increases the mRNAs stability, consequently enhancing translation [1,4-6]. Currently, CIRP has been demonstrated to positively regulate the translation of genes involved in DNA repair [1,5,7], cellular redox metabolism [6], adhesion molecules [8], circadian mRNAs [9], reproduction-related genes in testis [4], telomerase components [10], HIF-1 $\alpha$  [11], and a number of transcripts associated with the general translational machinery [11]. In addition to the positively post-transcriptional regulation, a negative role of CIRP in translation has also been reported. In addition; CIRP could also post-transcriptional and negatively modulate expression of the  $\alpha$ -subunits of I<sub>to</sub> channels in cardiomyocytes, affecting cardiac repolarization [12]. Through the regulation of its targets, CIRP has been implicated in multiple cellular processes such as cell proliferation, cell survival, and circadian modulation.

## THE ROLE OF CIRP IN PROSTATE CANCER

CIRP upregulation has been observed in a large number of solid tumors in human, such as colon cancer, central nervous system-related tumors, and liver-pancreas carcinomas, human melanoma, prostate, breast and colon cancers, compared to normal adjacent tissue [11,13], implicating a common role of CIRP in cancer progression. The evidence supporting a key role of CIRP in tumor progression comes from the study that uses tumor xenograft animal models to test the effects of CIRP deficiency on cancer growth. In both melanoma and breast cancer xenograft models, downregulation of CIRP could decrease tumor proliferation, invasion and migration [11]. These data suggest a malignant role of CIRP in cancer, and CIRP has been regarded as a new pro-oncogene in cancer [14], although the

specific role of CIRP upregulation in each kind of cancer still needs to be defined.

Recently studies also implicate a vital role of CIRP in prostate cancer progression. Clinical studies showed that CIRP is overexpression in prostate cancer, with the mRNA upregulation in 36% prostate cancer, and the protein upregulation in 40 to 60% prostate cancer, compared with normal adjacent tissues [11,13]. *In-vitro* studies showed that CIRP is abundantly expressed in prostate cancer cell lines such as PC-3 and LNCaP cells, and knocking down of CIRP by siRNA can significantly inhibit cell growth and colony formation in these cells [15]. In addition, CIRP downregulation can enhance the therapeutic response of prostate cancer cells to chemotherapy *in-vitro* [15]. These results suggest an important role of CIRP in prostate cell proliferation and the therapeutic potential of targeting CIRP in prostate cancer.

Mechanistic study found that downregulation of CIRP of prostate cancer cell lines impedes p53 activation and the subsequent p21 expression, both of which have been shown to render DNA damage repair [15,16], suggesting that CIRP downregulation inhibit DNA repair in prostate cancer. As CIRP can bind to and stabilizes the transcripts of pro-survival genes harboring its RNA signature motif in their 3'-UTR, CIRP may promote tumor growth by coordinating the translation of selected transcripts associated with proliferation and survival in prostate cancer cells, which needs further investigation.

## FURTHER PERSPECTIVE

Although CIRP showed potential role in regulation prostate cancer, further study is needed to determine the role of CIRP *in vivo* and the clinical significance of CIRP in prostate cancer in human. Xenograft animal models of prostate cancer may be valuable to evaluate the effects of CIRP downregulation on tumor growth *in vivo*. Correlation of CIRP expression level with the characters of patients with prostate cancer, such as tumor grade and survival time, may help to identify CIRP as new prognostic markers of prostate cancer progression.

## COMPETING INTERESTS

The authors declare that they have no competing interests

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