

The up-regulation of cysteine-rich protein 61 induced by transforming growth factor beta enhances osteosarcoma cell migration

Jun Chen · Yang Song · Jing Yang ·
Li Gong · Peng Zhao · Yong Zhang ·
Haichuan Su

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Abstract Overexpressed cysteine-rich protein 61 (Cyr61) is believed to enhance osteosarcoma (OS) cell metastasis, but the mechanism of Cyr61 overexpression in OS is not clear so far. In this study 33 OS samples were analyzed by immunostaining and focused on two parts: the correlation between overexpression of Cyr61 and OS metastasis; the mechanism of regulating Cyr61 expression in OS. Twenty-five out of 33 cases (75.76 %) with metastasis showed high expression of Cyr61. Furthermore, Cyr61 expression in Saos-2 cells was reduced by siRNA, and lower expression of Cyr61 in Saos-2 cell resulted in a cell migration deficiency and had no effect on cell proliferation. Particularly, Cyr61 expression was significantly increased in Saos-2 cells in response to different dosages of transforming growth factor beta (TGF- β), indicating that the expression of Cyr61 is TGF- β dependent. A transwell assay showed that Saos-2 cells stimulated with TGF- β had a greater capacity for migration than the control cells. The p38 MAPK-specific inhibitor SB203580 was able to reduce Cyr61 expression and inhibit the migration of Saos-2 cells stimulated with TGF- β . These results obtained provide new evidence that

overexpressed Cyr61 plays a key role in the metastasis of OS cells and Cyr61 is a potential target downstream of TGF- β /p38 MAPK to regulate cell migration.

Keywords Osteosarcoma · Cyr61 · TGF- β · p38 MAPK · Migration

Introduction

Osteosarcoma (OS) is the most common primary malignancy of the bones and is a major disease that results in the death of adolescents and young adults because of tumor recurrence and multiple organs metastasis [1–3].

Cyr61 (cysteine-rich protein 61), a member of the CCN growth factor family which includes six small secreted cysteine-rich proteins that are responsible for multiple biological activities [4–6], is overexpressed in advanced breast adenocarcinoma, pancreatic cancer and gastric cancer, thus it is believed to play a critical role in cancer metastasis [7–10]. Through the analysis of clinical samples, a high level of Cyr61 expression has been found in patients with OS metastasis [11]. Results of cytology experiments and OS metastasis animal model are consistent with clinical analysis. Mice intratibially injected with Cyr61-overexpressing Saos-2 cells showed an increase in number and outgrowth of lung metastases and consequently have a shorter survival than mice injected with control Saos-2 cells, while Cyr61 silencing inhibited OS cell invasion and migration in vitro as well as lung metastases in vivo in mice [12].

However, little is known about the mechanisms regulating Cyr61 overexpression in OS cells. In previous studies, TGF- β has been proven to induce Cyr61 expression in primary cultures of murine osteoblasts and enhance OS proliferation by activating TGF- β type I receptor

Jun Chen and Yang Song have contributed equally to this study.

J. Chen · Y. Zhang (✉)
Institute of Osteosarcoma, Tangdu Hospital of Fourth Military
Medical University, Xi'an, China
e-mail: zhangyongtdgk@yeah.net

Y. Song · J. Yang · H. Su (✉)
Department of Oncology, Tangdu Hospital of Fourth Military
Medical University, Xi'an, China
e-mail: haichuan-su@gmail.com

L. Gong · P. Zhao
Department of Pathology, Tangdu Hospital of Fourth Military
Medical University, Xi'an, China