Asian Journal of Andrology (2014) 16, 788–789

www.asiaandro.com; www.ajandrology.com

Open Access

LETTER TO THE EDITOR

Prostate Cancer

Cyr61: a potential therapeutic target for prostate cancer

Chang-Ming Lin[1,2], Chao-Zhao Liang[1]

Asian Journal of Andrology (2014) **16**, 788–789; doi: 10.4103/1008-682X.128517; published online: 11 April 2014

Dear Editor,

We read with great interest in the recent paper by Terada *et al.*,[1] named "Cyr61 is a potential prognostic marker for prostate cancer" published in *Asian Journal of Andrology* and the paper by Schmitz *et al.*[2] entitled "Cyr61/CCN1 affects the integrin mediated migration of prostate cancer cells (PC-3) *in vitro*". These elegant studies have revealed that Cyr61 has a clear impact on the PC-3 cell migration through alteration of the functions of integrin.

Until date, prostate cancer (PCa), the most common non-cutaneous male cancer, affects middle-aged or older men. Siegel *et al.*[3] estimated that PCa, the second leading cause of death of 29 720 in the United States, is the largest number of newly diagnosed cancer cases of 238 590 in 2013. However, the exact molecular mechanism of PCa controlling proliferation and tumorigenesis remains unclear.[4] It is well-known that integrins are heterodimeric transmembrane receptors, consisting of α and β subunits, which play a distinctly important role in cell migratory activities in term of the metastatic cascade of tumor cells. Schmitz *et al.*[2] demonstrated that clone cells exhibit a higher expression of α5 integrin subunit than wild type cells. In addition, the study showed that the lack in Cyr61 mediated integrin activation in the clone cells appears to equilibrated by a higher receptor expression due to α5β1 is the main fibronectin (FN) receptor. As we all known that the α5β1 integrin, common binding partners of β1 and α5 subunit, make a great contribution to regulating PCa growth.[5] Notably, Pal *et al.*[6] showed that FN bind PC-3 cells induces signaling pathway such as focal adhesion kinase/phosphoinositide-3-kinase (PI3K)/Akt/nuclear factor-kappa B through α5β1 integrin, leading to upregulation of matrix metalloproteinases-9 (MMP-9) and MMP-1, which was associated with PCa tissue or in the blood from PCa patients.[7] On the other hand, α5β1 is a downstream of type I insulin-like growth factor-I receptor (IGF-IR), which plays an important role in mitogenesis, angiogenesis, transformation, apoptosis, and cell motility.[5] IGF-IR also generates intensive proliferative signals, leading to carcinogenesis in prostate tissue.[8] Taken together, α5β1 integrin may play a crucial role in Cyr61 mediated regulation of PC-3 cells.

Of note, Cyr61 is a potential and clinically useful biomarker for PCa, Terada *et al.*[1] demonstrated that Cyr61 is highly expressed in early stage PCa or prostatic intraepithelial neoplasia and is a useful tissue biomarker for the detection of PCa in biopsy samples. Moreover, Schmitz *et al.*[2] confirmed that Cyr61 can affect the integrin function in cell migration, and insist on the issue of tumorigenicity of Cyr61 and add novel insight into the Cyr61-dependency of PC-3 cells. Previous data suggested that Cyr61 acts as a tumor-promoting factor and a key regulator in cancer progression.[9] Overproduction of Cyr61 was high in PC-3 cells through activation of the PI3K/Akt signaling, while knockdown of Cyr61 expression induces upregulation of proapoptotic molecules. Pharmacologic studies have emerged that zoledronic acid (ZOL) is an aminobisphosphonate able to have an antitumor effect on hormone-refractory PCa. Marra *et al.*[10] observed the effects of Cyr61 on ZOL-inhibited PC-3 cells. After treating with ZOL, downregulated-Cyr61 potentiated more powerful growth inhibition than control PC3 cells. Besides, downregulation of Cyr61 increased the percentage of cells in S-phase and the effects induced by ZOL on PCa cell motility and invasion. Furthermore, Lee *et al.*[9] have confirmed an antiapoptotic role of Cyr61 protein in PC-3 cells.

In summary, based on the study of Terada *et al.*,[1] Schmitz *et al.*[2] and other available data given therapeutic potential for PCa, these findings may suggest a valuable role for Cyr61 in the development of PCa. However, the mechanisms of interaction between them still poor understand. Additional studies are required, not only in animals, but in humans to further illustrate the clear relationship between PCa and Cyr61. Defining the often chief contribution of Cyr61 to PCa and identifying the mechanisms by which they alter the pathogenesis of disease is a rapidly expanding area of study and will add valuable information to our understanding of the kinetics, pathology and biology of PCa.

AUTHOR CONTRIBUTIONS

CML drafted the manuscript. CZL provided important intellectual advice and helped to revise the manuscript. Both authors reviewed and approved the final manuscript.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ACKNOWLEDGMENTS

This project was partly supported by grants from the National Natural Science Foundation of China (No. 81370856 and No. 81170698), the Natural Science Foundation of Anhui Province of China (No. 1208085 mh138) and Doctor Program Foundation of Ministry of Education of the China (No. 20113420110003).

[1]Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China; [2]Department of Urology, The Central Hospital of Maanshan, The Affiliated Hospital of Wannan Medical College, Maanshan, China.
Correspondence: Dr. CZ Liang (liang_chaozhao@163.com)
Received: 14 November 2013; Revised: 11 December 2013; Accepted: 19 February 2014

REFERENCES

1 Terada N, Kulkarni P, Getzenberg RH. Cyr61 is a potential prognostic marker for prostate cancer. *Asian J Androl* 2012; 14: 405–8.
2 Schmitz P, Gerber U, Jüngel E, Schütze N, Blaheta R, *et al*. Cyr61/CCN1 affects the integrin-mediated migration of prostate cancer cells (PC-3) *in vitro*. *Int J Clin Pharmacol Ther* 2013; 51: 47–50.
3 Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013; 63: 11–30.
4 Liu Y, Song H, Pan J, Zhao J. Comprehensive gene expression analysis reveals multiple signal pathways associated with prostate cancer. *J Appl Genet* 2014; 55: 117–24.
5 Sayeed A, Fedele C, Trerotola M, Ganguly KK, Languino LR. IGF-IR promotes prostate cancer growth by stabilizing $\alpha5\beta1$ integrin protein levels. *PLoS One* 2013; 8: e76513.
6 Pal S, Ganguly KK, Chatterjee A. Extracellular matrix protein fibronectin induces matrix metalloproteinases in human prostate adenocarcinoma cells PC-3. *Cell Commun Adhes* 2013; 20: 105–14.
7 Hadler-Olsen E, Winberg JO, Uhlin-Hansen L. Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and therapeutic targets. *Tumour Biol* 2013; 34: 2041–51.
8 Ozkan EE. Plasma and tissue insulin-like growth factor-I receptor (IGF-IR) as a prognostic marker for prostate cancer and anti-IGF-IR agents as novel therapeutic strategy for refractory cases: a review. *Mol Cell Endocrinol* 2011; 344: 1–24.
9 Lee YJ, Lee DM, Lee SH. Production of Cyr61 protein is modulated by extracellular acidification and PI3K/Akt signaling in prostate carcinoma PC-3 cells. *Food Chem Toxicol* 2013; 58: 169–76.
10 Marra M, Santini D, Meo G, Vincenzi B, Zappavigna S, *et al*. Cyr61 downmodulation potentiates the anticancer effects of zoledronic acid in androgen-independent prostate cancer cells. *Int J Cancer* 2009; 125: 2004–13.

How to cite this article: Lin CM, Liang CZ. Cyr61: a potential therapeutic target for prostate cancer. *Asian J Androl* 11 April 2014. doi: 10.4103/1008-682X.128517. [Epub ahead of print]