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CD44 collaborates with ERBB2 mediate radiation resistance via p38 phosphorylation and DNA homologous recombination pathway in prostate cancer

Ji-wei Ma[a,f,1], Xiao Wang[d,1], Lei Chang[e], Xue-yun Zhong[f], Haiyan Jing[a], Xiaolong Zhu[g], Shaoxiang Wang[c,*], WeiWei Xiao[b,*]

[a] Department of Pathology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan 250021, China
[b] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou 510060, China
[c] College of Pharmacy, Shenzhen University School of Medicine, Shenzhen 518061 China
[d] Department of Pharmacy, The Second Clinical Medical College (Shenzhen People's), Jinan University, Shenzhen 518020, China
[e] Department of Gynecology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China
[f] Department of Pathology, School of Medicine, Jinan University, Guangzhou 510632, China
[g] Department of Surgery, Shandong Provincial Hospital Affiliated to Shandong University, Jinan 250021, China

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ABSTRACT

CD44, a glycoprotein, has been reported to have relationship with resistance to radiation in prostate cancer (Cap) cells. However, its molecular mechanism remains unknown. In this study, we demonstrated that inhibited CD44 enhanced the radiosentivity in Cap cells. It has been hypothesized that CD44 combine with ERBB2 and activate downstream phosphated protein to mediate DNA damage repair. Therefore, we conducted a detailed analysis of effects of radiation by clonogenic assay and immunofluorescence stain for p-H2AX foci. The downstream of CD44/ERBB2 and DNA damage repair proteins was detected by western blot. The results reveal that CD44 interacted with ERBB2, the downstream of CD44/ERBB2 was p-p38 when Cap cells were irradiated. Among the pathways, homologous recombination (HR) related proteins Mre11 and Rad50 were involved in CD44/ERBB2/p-p38 mediated radioresistance in Cap. In conclusion, CD44 could stabilize ERBB2 and co-activate p-p38 expression then promote the DNA damage repair by HR pathway, which finally contribute to the radioresistance of CaP.

1. Introduction

Prostate cancer (Cap) is the most common cancer of urinary system in elderly men. Treatment modalities of Cap include radical resection of prostate cancer, hormonal therapy, chemotherapy and radiotherapy [1–3]. Although surgery combined with endocrinotherapy is suitable for most Cap patients, some of them are insensitive [4,5]. Radical or palliative radiotherapy are also needed for a portion of Cap patients [6]. Radiotherapy is also an effective salvage option for recurrent CaP patients [7].

CD44, a glycoprotein transmembrane receptor, which combines with hyaluronic acid (HA) mainly mediates cellular adhesion and invasion function [8]. In recently years, accumulating studies focus on CD44 as a stem marker in breast cancer, prostate cancer, squamous cell carcinoma and pancreatic cancers [9–12]. It has been reported that strong expression of CD44 is the only independent prognostic factor for radiation resistance in head and neck squamous cancer [13]. De Jong et al. reported that expression of CD44 in mRNA and protein levels was both correlated with response to radiotherapy in larynx cancer [14]. Phillops TM et al. reported that the CD44 + /CD24- breast cancer cells harbor resistance to radiation than other subtypes [15]. More importantly, it has been reported that a variant of CD44 called CD44v6 which resistance to radio/chemotherapy through EMT pathway in prostate cancer [16]. However, the classic hyaluronic acid (HA)-CD44-MMPs pathway may not be suitable for explain the mechanism of CD44-mediated radioresistance.

CD44 is a co-receptor of ERBB2 and activates both Rac1 and Ras signaling that is required for human ovarian tumor progression and could also activate CXCR4 to promote gastric tumor metastasis [17]. Overexpression of ERBB2 promotes tumor progression through

* Corresponding authors.
E-mail addresses: wsx@szu.edu.cn (S. Wang), xiaoww@sysucc.org.cn (W. Xiao).
[1] Contributed to this work equally.

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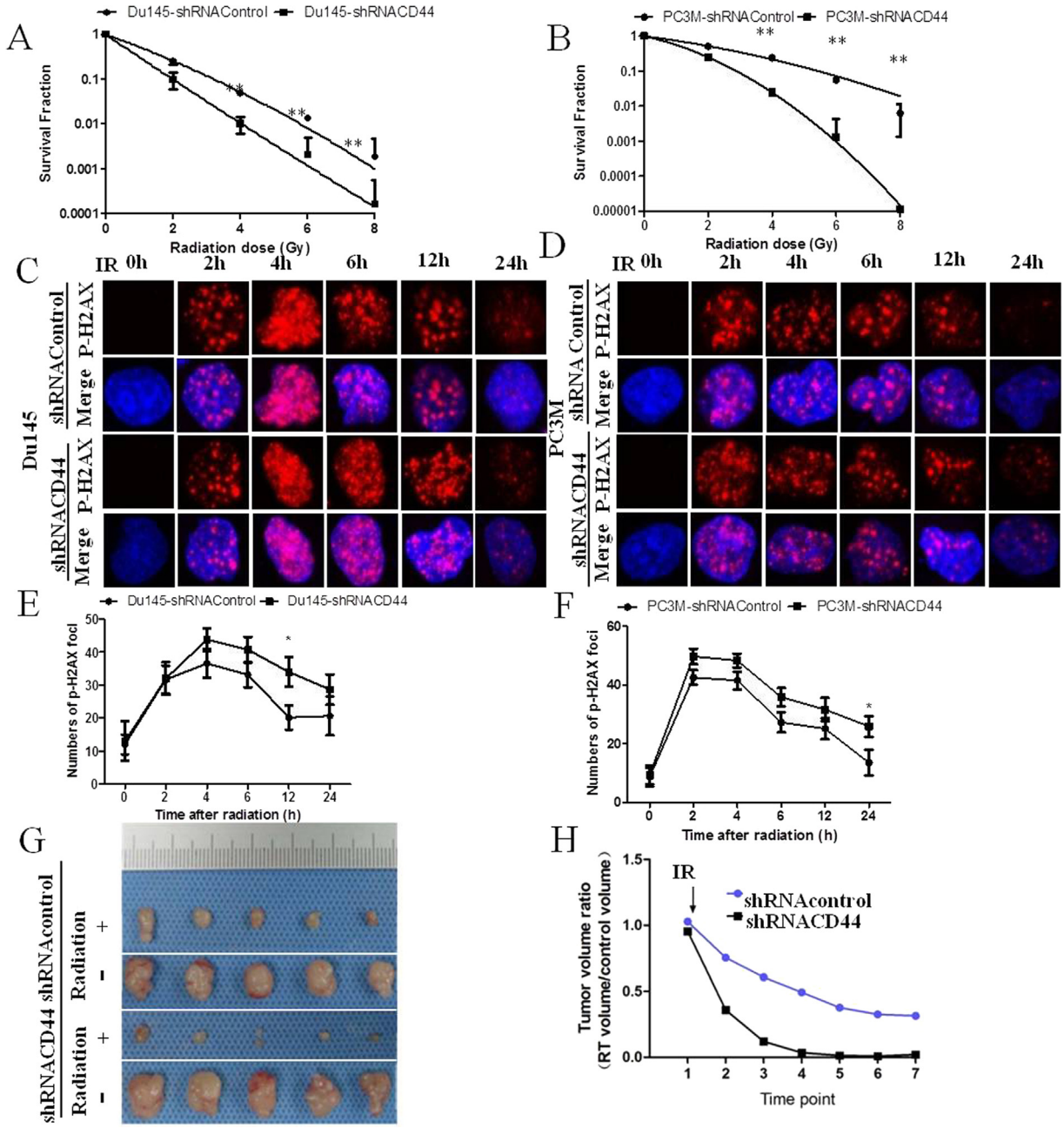

Fig. 1. Inhibition of CD44 enhanced radio-sensitivity on Cap *in vitro* and *in vivo*. A-B: The survival fraction of Cap and its CD44 knock down cells after radiation treatment. (n = 3) C-D: Cap and its CD44 knock down cells with immunofluorescence staining for phosphorylation of H2AX after the cells received radiation treatment. E-F: Quantification of phosphorylation of H2AX foci numbers in Cap cell received radiation treatment. G: The transplanted tumors of Cap after radiation treatment. H: The transplanted tumors volume ratio of radiation treatment groups and control groups in Cap and its CD44 knock down cells. Magnification × 40 in C-D. * ($p < 0.05$) and ** ($P < 0.01$) indicate significant difference between the Cap cell and its CD44 knock down cells.

activation of the RTK and Ras-Raf-Mek1/2-ERK1/2 signaling pathways [18,19]. It has also been reported that ERBB2 mediated radioresistance of breast cancer through phosphating AKT and MAPK and subsequently activating transcription factors including NF-kB and c-myc [20].

In this study, we investigated that whether coexpression of CD44 and ERBB2 involved in the radioresistance of CaP cells and its mechanism.

2. Materials and method

2.1. Cell lines and cell culture

The human CaP cell line Du145 was obtained from Shanghai Institute of Cell Biology, the Chinese Academy of Sciences, China. PC-3M was kindly presented by Pro. Yong Li, Faculty of Medicine, University of New South Wales, Australia. These cell lines were cultured in RPMI-1640 medium (Life Technologies, Paisley, Scotland, UK) with 10% fetal bovine serum (FBS).

2.2. Decrease the expression of CD44 by transfecting CD44 shRNA

Cap cells were cultured up to 70% confluence, and then transfected CD44 shRNA with lentiviral vector (Jikai Gene, China) in a RPMI-1640 medium. After transfection (about 24 h), the medium was repleaced with a fresh complete medium. When transfected cells were grown up to 100%, culture medium was changed with 2 μg/ml puromycin in

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