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Lobaplatin promotes radiosensitivity, induces apoptosis, attenuates cancer stemness and inhibits proliferation through PI3K/AKT pathway in esophageal squamous cell carcinoma

Shupei Pan[a], Yuchen Sun[a], Donghu Sui[d], Tian Yang[a], Shenbo Fu[a], Jizhao Wang[c], Beina Hui[a], Ruxing Xi[b], Chenchen He[a], Xiaozhi Zhang[a,*]

[a] Department of Radiation Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China
[b] The Fourth Department of Gynecological Tumor, The Shaanxi Province Oncology Hospital, Xi'an, Shaanxi, China
[c] The Second Department of Thoracic Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China
[d] GuiZhou EverGreen Pharmaceutical Company Limited, Guizhou, China

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ABSTRACT

Radiotherapy is one of the common treatments for esophageal squamous cell carcinoma (ESCC). Yet, local recurrence led by radioresistance is still not solved. Lobaplatin (LBP) is known to have powerful clinical antitumor activities in various tumors, but its effect in radiotherapy is rarely studied. Here we report that LBP is a promising radiosensitizer for ESCC. We treated ESCC cells with LBP and radiation, both separately and in combination. Untreated cells were set as control groups. We found that LBP inhibited ESCC cell growth and enhanced their radiosensitivity. LBP also impeded the tumor growth *in vivo*. LBP combined with radiation significantly increased ESCC cell apoptosis. Meanwhile, LBP obviously decreased the expression of cancer stem cells biomarker CD271 both *in vitro* and *in vivo*. The molecular mechanism was related to the downregulation of Bcl-2/Bax ratio, PI3K and p-AKT (Ser473) expression. Taken together, our findings indicated that LBP could enhance the radiosensitivity of ESCC cells by increasing radiation-induced apoptosis, attenuating cancer stemness and inhibiting PI3K/AKT pathway. These results provide a foundation for the combined therapy of radiation and LBP for ESCC in clinical practice.

1. Introduction

79% of esophageal squamous cell carcinoma (ESCC) cases in the world take place in Central and South-Eastern Asia, with China alone contributing more than a half in 2012 [1]. Radiotherapy (RT) is a major treatment for ESCC. Even with combined surgery, chemotherapy and RT, the average 5-year overall survival (OS) of ESCC remains less than 20% [2]. Acquired radioresistance results in a high local tumor recurrence rate (around 44%–61%) [3] and this is one of the major reasons for the low OS. Thus, enhancing the tumor radiosensitivty is a vital way to improve the prognosis of ESCC patients.

Lobaplatin (LBP), $C_9H_{18}N_2O_3Pt$, is one of the third-generation platinum antineoplastic drugs. Compared with cisplatin, LBP has less resistance incidence in many solid cancers like lung cancer [4], colorectal cancer [5], and cervical cancer [6–8]. The majority of these reports focus on the antitumor effect of LBP in chemotherapy. Only 9 researches [7–9,10] report about the application of LBP in RT, and the molecular mechanism remains unclear.

Several mechanisms are involved in sensitizing tumor cells to radiation. Among them are the regulation of cell apoptosis and cancer stem-like cells (CSCs). Studies have proved that tumor radiosensitivity can be enhanced by increasing the radiation-induced apoptosis [11,12]. CSCs are a small population of tumor cells with a high self-renewal and tumorigenic capability. Growing evidences indicate that CSCs are resistant to radiation [13–15] and can survive after RT, resulting in the failure of treatment. The cell surface marker CD271 (also called p75NTR) [16] has been reported as human esophageal CSCs biomarker. We demonstrated that ESCC cancer stem cells that survived treatment with LBP or radiation express CD271. PI3K/AKT pathway is of great importance in CSCs, including the maintaining of colony-formation ability and proliferation [17,18]. Meanwhile, targeting PI3K/AKT pathway could significantly reduce the bulk tumor burden and downregulates CSCs metabolism [18,19]. Besides, our previous study [15] proved that targeting the CSCs *via* the inhibition of PI3K/AKT pathway was an available theropy for HPV16 positive ESCC patients. Yet, the role of LBP on CSCs in ESCC is needed to be explored.

* Corresponding author at: Department of Radiation Oncology, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China.
E-mail address: zhangxiaozhi@xjtu.edu.cn (X. Zhang).

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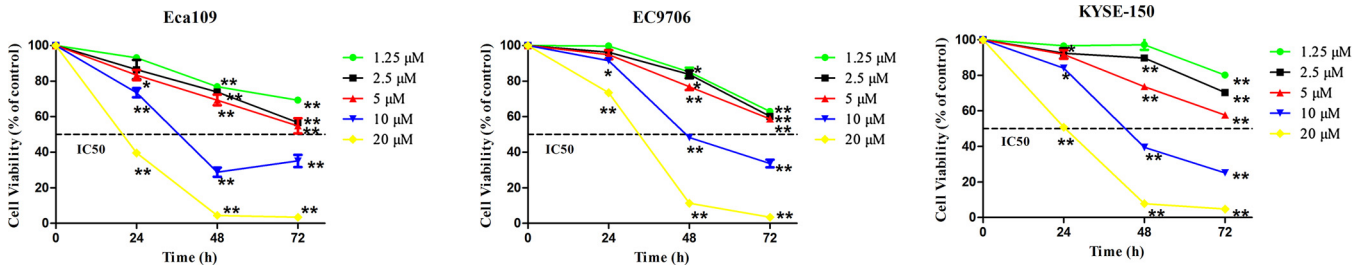

Fig. 1. LBP inhibited the proliferation of ESCC cells including Eca109, EC9706 and KYSE-150 cells. ESCC cells were treated with LBP (0, 1.25, 2.5, 5, 10, 20 μM) for 24 h, 48 h or 72 h, respectively. Proliferation-inhibition rates significantly increased in a time and concentration-dependent manner. $^{*}P < 0.05$, $^{**}P < 0.01$, LBP-treated group compared with the untreated control group, respectively.

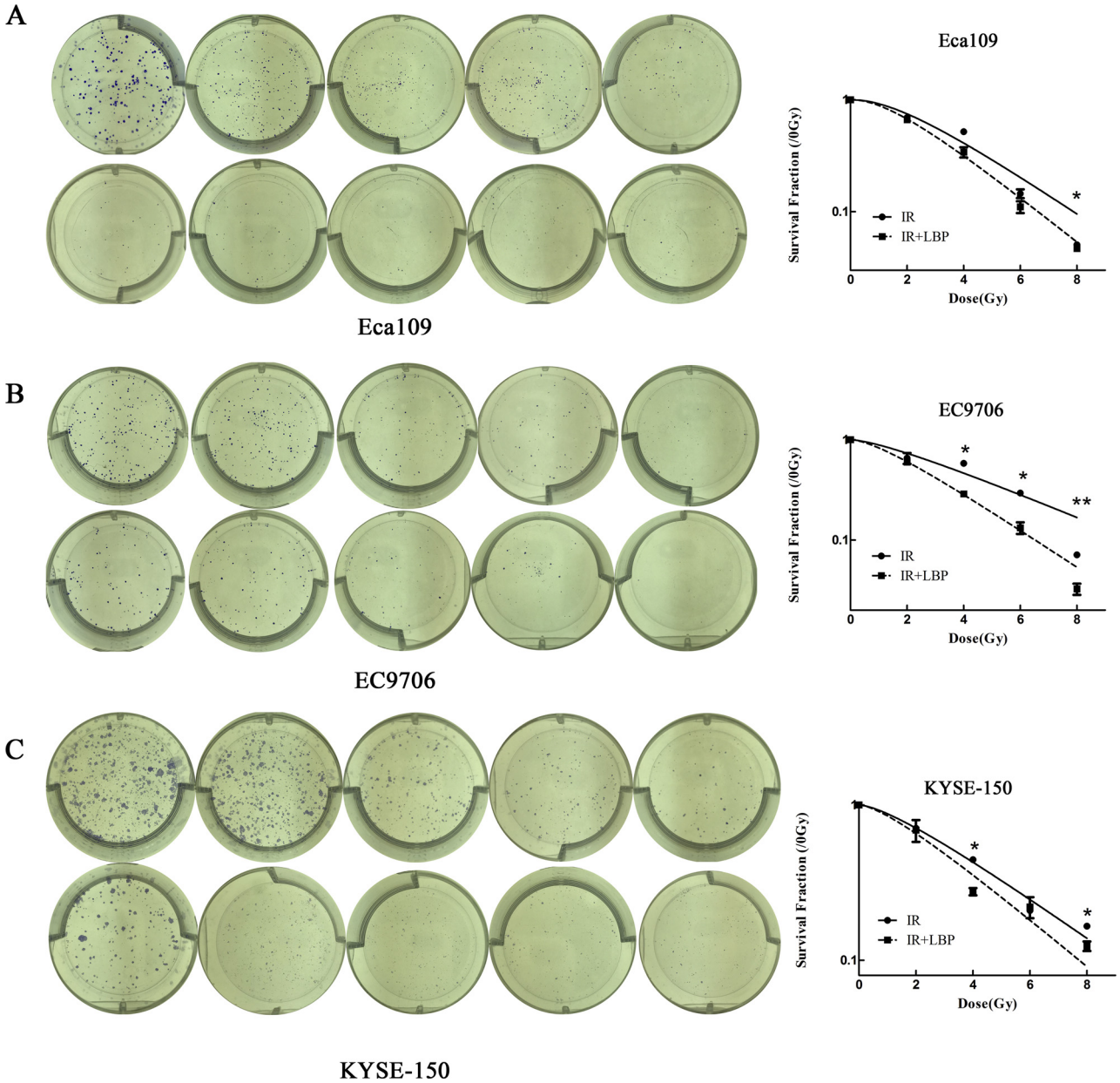

Fig. 2. LBP promoted the radiosensitivity of ESCC cells. Cells were pretreated with LBP (0.01 μM) for 48 h and exposed to 0, 2, 4, 6, 8 Gy of 4 MV X-rays. Colonies were stained and counted after 14 days. The dose-survival curves of ESCC cells were on the right. (A): Eca109, (B): EC9706, (C): KYSE-150. $^{*}P < 0.05$, $^{**}P < 0.01$, LBP-treated group compared with the LBP-untreated control group.