

Original article

Radiosensitivity of prostate cancer cells is enhanced by EGFR inhibitor C225[☆]

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Abstract

Purpose: To determine the direct effects of the epidermal growth factor receptor (EGFR) inhibitor C225 on the radiosensitivity of human prostate cancer cells.

Experimental design: Human prostate cancer DU145 cells were irradiated with ⁶⁰Co (1.953 Gy/min) at various doses in the presence or absence of C225. The cellular proliferation and cell-survival rate were evaluated by MTT and colony-forming assays after irradiation. The cell-cycle distribution, cell apoptosis, and MAPK expression were investigated using FCM. The expression of Cyclin D1, CDK2, CDK4, and Survivin were determined by RT-PCR.

Results: The RBE in the C225 group compared with that in the control group was 1.39. Cells treated with C225 and irradiated at 4 Gy predominantly exhibited G₀/G₁ phase arrest and significant decrease in the fraction of cells in the S phase in comparison with those in the control cells, respectively. An evidently higher apoptosis rate on irradiation at 4 Gy was observed in C225-treated cells compared with that in the control cells. Decreased cell proliferation and increased cell death were further supported by the down-regulation of cyclin D1, CDK2, CDK4, and survivin in C225-treated DU145 cells, as determined by RT-PCR. Furthermore, C225 significantly inhibited the phosphorylation of P38-MAPK in DU145 cells.

Conclusions: The EGFR inhibitor C225 increased the radiosensitivity of DU145 cells through antiproliferative effect, inhibition of clonal growth, G₀/G₁ phase arrest, apoptosis induction, and inhibition of EGFR-signaling pathways by the down-regulation of MAPK activation. © 2010 Published by Elsevier Inc.

Keywords: EGFR inhibitor; Prostate cancer cells; Cell proliferation; Apoptosis

1. Introduction

Growth factors control cellular proliferation and differentiation and are important for the initiation and maintenance of neoplastic transformation. Transforming growth factor- α (TGF- α) and epidermal growth factor (EGF) and its specific receptors, the epidermal growth factor receptors (EGFRs), have been implicated in the development and progression of the majority of human epithelial cancers, including prostate cancer [1–3]. TGF- α and EGF and/or EGFR are expressed at high levels in prostate cancers,

which are generally associated with advanced disease and poor prognosis [4,5]. EGFR activation is not only critical for cell proliferation but EGFR-mediated signals also contribute to other processes that are crucial to cancer progression, including angiogenesis, metastatic spread, and the inhibition of apoptosis [6,7]. The high expression of EGFR is also associated with resistance to cytotoxic drugs or ionizing radiation, as determined in several preclinical models.

EGFR activation may prevent apoptosis induced by radiation in cancer cells. This may be clinically relevant because it could represent a mechanism via which cancer cells escape radiation-induced cell death. A large body of experimental and clinical work supports the view that the EGFR is a relevant target for cancer therapy. Different pharmacological and biological approaches have been developed for blocking EGFR activation and/or function in cancer cells.

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