Journal of Cancer Therapy, 2014, 5, 1362-1365
Published Online December 2014 in SciRes. http://www.scirp.org/journal/jct
http://dx.doi.org/10.4236/jct.2014.514136

Inhibition of Radiation-Induced Lung Adenocarcinoma Cell Metastasis by Adenovirus of PIAS3 Overexpression Driven by Radiation-Inducible Promoter (*Ad-pig3RRP-PIAS3*)

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Received 26 September 2014; revised 23 October 2014; accepted 18 November 2014

Abstract

Radiotherapy is one of important approaches for pulmonary adenocarcinoma. However, many studies have shown that radiation can also enhance the ability of tumor cells metastasis, although the lung adenocarcinoma could be killed. The increased metastasis induced by radiation is associated with the activation of *STAT*3 in lung adenocarcinoma cells. Based on the importance role of *STAT*3 in cell proliferation and survival, we can construct an adenovirus vector of *PIAS*3 overexpress driven by radiation-induced promoter to inhibit the activation of *STAT*3 specifically. In this way, when *STAT*3 was activated by radiation, the expression of *PIAS*3 will be increased at the same time; this lead to the inhibition of invasion and metastasis caused by *STAT*3 in lung adenocarcinoma cells. These researches are expected to develop a novel target and method for radiotherapy and molecular therapy of lung adenocarcinoma.

Keywords

Radiation, Adenocarcinoma, Metastasis, Promoter, *PIAS*3

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How to cite this paper: Gao, L., *et al.* (2014) Inhibition of Radiation-Induced Lung Adenocarcinoma Cell Metastasis by Adenovirus of PIAS3 Overexpression Driven by Radiation-Inducible Promoter (*Ad-pig3RRP-PIAS3*). *Journal of Cancer Therapy*, **5**, 1362-1365. http://dx.doi.org/10.4236/jct.2014.514136

1. *STAT*3—Key Target of Radiation-Induced Metastasis in Lung Adenocarcinoma

In the current study, it was indicated that radiation can promote the metastasis of pancreatic cancer cells [1] [2], glioma cells [3] [4], hepatoma carcinoma cells [5], breast cancer cells [6], melanoma cells [7], ductal carcinoma cells [8] and lung adenocarcinoma cells [9], although the tumor cells can be killed. Radiation was found to activate the phosphorylation of *STAT*3 which resulted in the increase of invasion of A549 cells [9]. By using special inhibitor to block radiation-induced *STAT*3 activation, the increase of invasion and migration of A549 cell induced by radiation can be reduced significantly [10]. All above comes down to one point: *STAT*3 plays a key role in radiation-induced invasion and metastasis and is a potential target of therapy in lung adenocarcinoma.

2. *PIAS*3—Specific *STAT*3 Inhibitor Protein

*PIAS*3 (protein inhibitor of activated *STAT*3) is one of *PIAS* (including *PIAS*1, *PIAS*2, *PIAS*3 and *PIAS*4) family members, which can inhibit *STAT*3 specifically [11]. As an endogenous inhibitor of *STAT*3, *PISA*3 is expressed at high level in many normal human tissues and cells, while shows a very low level or even no expression in the tumor tissues and cells. Dabric [12] found that protein expression with *PIAS*3 is in a low level which affected survival upon mesothelioma patients and indicated *PIAS*3 as having potential for development into a novel therapeutic target. When the expression of *PISA*3 has been silenced, the activity of *STAT*3 increased continuously, which resulted in the significant increasing of growth and proliferation of tumor. Our group study showed that the expression of *PISA*3 is in a low level, and is not affected by γ-ray radiation. As the radiation-induced activation of *STAT*3 plays an important role on invasion and metastasis of A549 cells, it can be inferred that *PIAS*3 also played a prominent role in the invasion and metastasis of lung adenocarcinoma cells via *STAT*3.

3. *PIG*3—Radiation Sensitive Gene

*PIG*3, one of *PIG* family members regulated by p53 protein, participated in oxidative stress of cells and cell apoptosis pathway mediated by radiation. Our study group has drawn a conclusion that the expressions of *PIG*3 in mRNA and protein level were enhanced 15 to 20 times by radiation in a dose-dependent manner from 0 to 10 Gy. Other group also discovered that the *PIG*3 gene expression was enhanced by radiation in AHH-1 and HPBL cells [13]. These results demonstrated that the promoter region of *PIG*3 gene contains a radiation-sensitive region, which could activate the gene expression of downstream when the cells were irradiated. It indicated that we can turn-on or turn-off the gene expression by controlling the radiation at any time.

4. Adenovirus Drug—An Effective Gene Therapy Means

Adenovirus has no genetic toxicity to the human body because adenovirus DNA does not integrate into the host cell genome. Adenovirus drugs are wildly considered to be safe and effective, with the launching of gendicine, which is the first commercial adenovirus gene therapy product and have been used in clinical for many years. Yu M. [14] reported that Recombinant adenovirus-*p*53 is effective for pulmonary metastasis in hepatocellular carcinoma. Jinluan Li [15] reported that Recombinant adenovirus-*p*53 (Gendicine) enhances radiosensitivity of a pancreatic carcinoma cell line. The future of adenovirus drugs is attractive and vast.

5. Discussion

Based on the fact that *PISA*3 can inhibit the activation of *STAT*3 specifically, we can utilize recombinant adenovirus vector which can be administrated in clinical to transfer the radiation-sensitive *PISA*3 gene into cancer cells. Under these circumstances, when *STAT*3 was activated by radiation, the expression of *PIAS*3 would be increased at the same time. So while radiation is utilized to kill tumor cells, meanwhile, the invasion and metastasis induced by radiation will be prevented effectively in lung adenocarcinoma cells. The vector will have no function until the cells transfected with it are exposed to radiation. Therefore, if the normal tissue cells, which will not be irradiated during radiotherapy, intake the vector, the PIAS3 expression should not be initiated. This eliminates the potential effect of vector on normal tissue cells. On the basis of these findings, we intend to identify the radiosensitive region of *PIG*3 promoter, and subsequently clone this region into the adenovirus expression vector of *PIAS*3, in order to construct a radiosensitive adenovirus vector encoding *PIAS*3 (*Ad-pig*3*RRP-PIAS*3).

Based on the function of *PIAS*3 on inhibiting cell proliferation [16] [17] and the response of *STAT*3 to radiation [18] [19], we will further investigate the inhibiting effect of *Ad-pig*3*RRP-PIAS*3 on metastasis which is induced by radiation in lung adenocarcinoma cells and the correlation mechanism. From a new perspective, a novel target and treatment means which combined molecular target therapy with radiotherapy will be explored in lung adenocarcinoma.

Acknowledgements

This work was supported by The National Natural Science Foundation of China (fund NO are 31340051, 81202151 and 81001216), Head Young Scholar Scientific Research Foundation of National Institute for Radiological Protection, China CDC (fund NO is 201101) and a Military Fund of China (CWS12J082).

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