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Proton Beam Radiation Targeted Nucleotides with Negligible Effect on Interferon

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Abstract

Background There is increasing evidence that localized irradiation of the tumor may also modify the tumor microenvironment and generate inflammatory cytokines.

Objective This study is aimed to clarify the effect of proton beam radiation on the interferon (IFN-α**,** IFN-β, IFN-γ) and nucleotide.

Methods The Microsoft "The Stopping and Range of Ions in Matter (TRIM-SRIM)" version 1998, and 2003 was used. A model of targeting certain interferon (IFN-α, IFN-β, IFN-γ) as well as the nucleotide pair was created. Each target was subjected to proton radiation of hydrogen [H], helium [He], or carbon [C] at different range of energy seeking for the Bragg's peak**.**

Result The results showed that the cross sections IFN-α, IFN-β, IFN-γ and nucleotide targeted by proton therapy were 0.9776, 0.8317, 0.8297 and 0.7305 [keV/(μg/cm^2)] for hydrogen ion, and 2.3354, 2.3414, 2.3377, 2.0842[keV/(μg/cm^2)] for helium ion, and 8.3032, 8.3198, 8.3109, 7.5394 [keV/(μg/cm^2)] for carbon ion respectively.

Conclusions It concludes that targeting of well precise located tumor with proton beam radiation therapy resulted in nucleotide damage of cancer cell without affecting the immune system in term of interferon surveillance.

Key words Proton, Nucleotide, Interferon

Introduction

Interferons (INFs) are glycoprotein belong to cytokines that released in response to the presence of virus, bacteria, parasites or tumor cells. They activate natural killer cells and macrophages and they increase recognition of infective or tumor cell to T lymphocytes. IFN- γ has pleiotropic effects in the tumor microenvironment, including the inhibition of cell proliferation and angiogenesis [(1)]. They reversed the signal defect in T lymphocytes in patients with melanoma and the synthetic INF-α_{2b} is useful as an adjuvant therapy for high risk melanoma [(1)]. Because abnormally low levels of INF-γ are produced by tumor cells and local T lymphocyte in the glioma, it is a promising adjunct to other immunotherapeutic modalities in the treatment of brain tumors [(2)]. Radiation is an important treatment for the local control of cancer based on its ability to directly kill tumor cells.

However, there is increasing evidence that localized irradiation of the tumor may also modify the tumor microenvironment and generate inflammatory cytokines, which can increase the robustness of the immune response [(4,7)]. Radiotherapy has been demonstrated to cause inflammation, a potentially beneficial state in which IFN-γ is undoubtedly involved as well as it created a tumor microenvironment conducive for T cell infiltration and tumor cell target recognition [(6)]. Interferon-α potentiated the cytotoxicity of X-ray radiation [(8)]. *In vitro* model the production of INF-γ by cells is suppressed by ultraviolet A1 radiation and thereby the immune system is suppressed [(3)]. Recently proton radiation gets

access in management of cancer as a preferable therapeutic modality because fewer harmful adverse reactions, more direct impact on the tumor and increased tumor control. Its effect on the hemopoietic system was generally less pronounced compared to gamma rays and X-rays [9]. Proton radiation was significantly modified the pattern of gene expression in T lymphocytes and highly dependent upon total dose and it may enhance their responsiveness at low dose radiation [10]. This study is aimed to explore the effect of proton radiation on the immune system using the hydrogen, helium or carbon as proton source and interferon as the target in Trim-Srim model.

Methods

This study was carried on in Department of Physiology/Medical Physics, College of Medicine, Al-Mustansiriya University in Baghdad, Iraq. The Microsoft "The Stopping and Range of Ions in Matter (SRIM)" version 1998, and 2003 was used. A model of targeting certain interferon (IFN-α, IFN-β, IFN-γ) as well as the nucleotide pair was created. Each target was subjected to proton radiation of hydrogen [H], helium [He], or carbon [C] at different range of energy seeking for the Bragg's peak. The characteristics of the proton sources and the targets showed in table 1. The stopping power is given (-dE/dx) by applying Bethe-Bloch formula where (– dE) is the energy increment lost in infinitesimal material thickness (dx).

-dE⁄dx = $(2\pi e^4 / m_\circ v^2)$ NB

$$B=Z\left[\ln \frac{m_o v^2 T}{2I^2(1-\beta^2)} - (ln2)\left(2\sqrt{1-\beta^2} - 1 + \beta^2\right) + 1 - \beta^2 + \frac{1}{8}\left(1-\sqrt{1-\beta^2}\right)^2\right]$$

Where $\beta = \frac{v}{c}$, *T* is a constant factor

The total stopping power for electron can be given as a combination of collisional (elastic collision with atomic electrons) and radiative (inelastic collision with nucleus) types of interaction:

[dE/dx]total = [dE/dx] collision+[dE/dx]radiative

The stopping power (S) is given by:

N.S = - (dE/dx)

The quantity of S (keV/μ) is referred to specific energy loss

E: charged particle kinetic energy

-dE: the energy increment lost in infinitesimal material thickness (dx)

N: is number of atom /volume

The specific energy loss is expressed by Bethe-Bloch formula

For heavy charged particle:

$$-\frac{dE}{dx} = \frac{4\pi e^4 z^2}{m_o v^2} NB$$

Where

$$B = Z\left[\ln \frac{2m_o v^2}{I} - \ln\left(1 - \frac{v^2}{c^2}\right) - \frac{v^2}{c^2}\right] - S/2$$

With the following definitions:

v velocity of the charged particle

Z charge of the charged particle

N number density of absorber atoms

Z atomic number of absorber atoms

m electron rest mass

e electron charge

I A parameter, treated as experimentally determined, representing average excitation and ionization potential

B is known as the stopping number (atomic number scaled for stopping)

S is the density correction

Bethe-Bloch formula for electrons:

For heavy particles, orbital electron interactions are only considered since the probability of nuclear interaction resulting in energy loss is much smaller.

$$-\left(\frac{dE}{dx}\right)_r = \frac{NTZ(Z+1)e^4}{137 m_0^2 c^4}\left(4\,ln\frac{2T}{m_0 c^2} - \frac{4}{3}\right)$$

The percent of the energy loss goes to emitted rays is expressed by:

$$(\frac{dE}{dx})_r / (\frac{dE}{dx})\text{total} = EZ/1000$$

Where E is in MeV, where Z is the atomic number of the absorber.

The range of a charged particle can be derived from stopping power formula:

$$R = \int_E^0 dx(cm) = \int_E^0 \frac{dE}{dE} dx = -\int_0^E \frac{1}{dE/dx} dE = \int_0^E \frac{dE}{S}$$

The summal distance elements as kinetic energy goes from *E* down to 0 is the total distance along the incident direction, or the range.

The quantity of stopping power (KeV/(μg/cm^2) is referred to specific energy loss per cross section of targeting molecule. Microsoft Excel 2003 was used for calculations and figures plotting.

Results

Table 2 shows that higher energy is required to achieve the Bragg's peak (-dE/dx) as the atomic number of projected ion is increased. The effect of proton originated from hydrogen source on the INF-α and INF-β is similar in targeting distance but differs in Bragg's peak as well as the targeting cross section (Table2, Figure 1). The Bragg's peak of proton targeting nucleotide is far away than those of interferons with lesser effect on the cross section of nucleotide (Table 2, Figure 1). The results obtained with proton of helium or carbon sources are similar in pattern but not in magnitude to that obtained with hydrogen source in targeting the interferons or nucleotide (Table 2, Figure 1). The cross section of INF-γ targeted by proton of whatever sources (hydrogen, helium or carbon) is less affected than INF-α and INF-β and its targeted depth is more INF-α and INF-β by 100-400 Angstrom. The cross section of nucleotide targeted by proton is less than those observed with interferon despite of higher Bragg's peak and longer projected distance for different sources of proton (Table 2, Figure 1). The spread out cross section of INF-γ targeted by protons in terms of longitudinal and lateral struggling is higher than corresponding INF-α and INF-β (Table 3). Moreover, the spread out effect of proton targeting nucleotide is higher than interferons by 1.3 for all ion sources (Table 3).

Table 1. The constituents of the targets

	IFN-α	IFN-β	IFN-γ	Nucleotide
Density (g/cm^3)	0.98010	0.98276	0.97573	1.1165
Atomic percent (Mass percent)				
C	31.82 (53.69)	32.18 (54.45)	31.55 (53.32)	29.62 (38.41)
H	50.02 (7.08)	49.92 (7.09)	50.01 (7.09)	35.83 (3.90)
N	8.39 (16.52)	8.72 (17.21)	8.87 (17.48)	18.51 (28.0)
O	9.43 (21.21)	8.93 (20.13)	9.32 (20.98)	14.81 (25.58)
S	0.33 (1.5)	0.25 (1.12)	0.25 (1.12)	-
P	-	-	-	1.25 (4.12)

C (carbon), H (hydrogen), N (nitrogen), O (oxygen), S (sulfur), P (phosphate)

Table 2. Effect of proton originated from different ions sources on the interferon and nucleotide

Ion	Target	Energy (KeV)	-dE/dx (KeV/μ)	Depth (μm)	Cross section keV/(μg/cm^2)
H	IFN-α	90	81.27	1.39	0.9776
	IFN-β	90	81.74	1.39	0.8317
	IFN-γ	90	80.96	1.40	0.8297
	Nucleotide	100	81.56	1.52	0.7305
He	IFN-α	550	228.9	3.47	2.3354
	IFN-β	550	230.1	3.45	2.3414
	IFN-γ	550	228.1	3.49	2.3377
	Nucleotide	600	232.7	3.70	2.0842
C	IFN-α	2400	813.8	4.33	8.3032
	IFN-β	2400	817.6	4.30	8.3198
	IFN-γ	2400	810.9	4.34	8.3109
	Nucleotide	2800	842.4	4.77	7.5394

Table 3. The lateral and radial struggle of proton of each target at Bragg's peak

Ion	Target	Longitudinal (μm)	Lateral (μm)	Cross section of damage beyond the target (μm^2)
H	IFN-α	0.1106	0.1514	0.01674
	IFN-β	0.1094	0.1498	0.01638
	IFN-γ	0.1110	0.1520	0.01687
	Nucleotide	0.1271	0.1732	0.02201
He	IFN-α	0.2051	0.2689	0.05515
	IFN-β	0.2029	0.2661	0.05399
	IFN-γ	0.2058	0.2698	0.05552
	Nucleotide	0.2304	0.3020	0.06958
C	IFN-α	0.1879	0.2397	0.04503
	IFN-β	0.1862	0.2373	0.04418
	IFN-γ	0.1885	0.2404	0.04531
	Nucleotide	0.2114	0.2729	0.05769

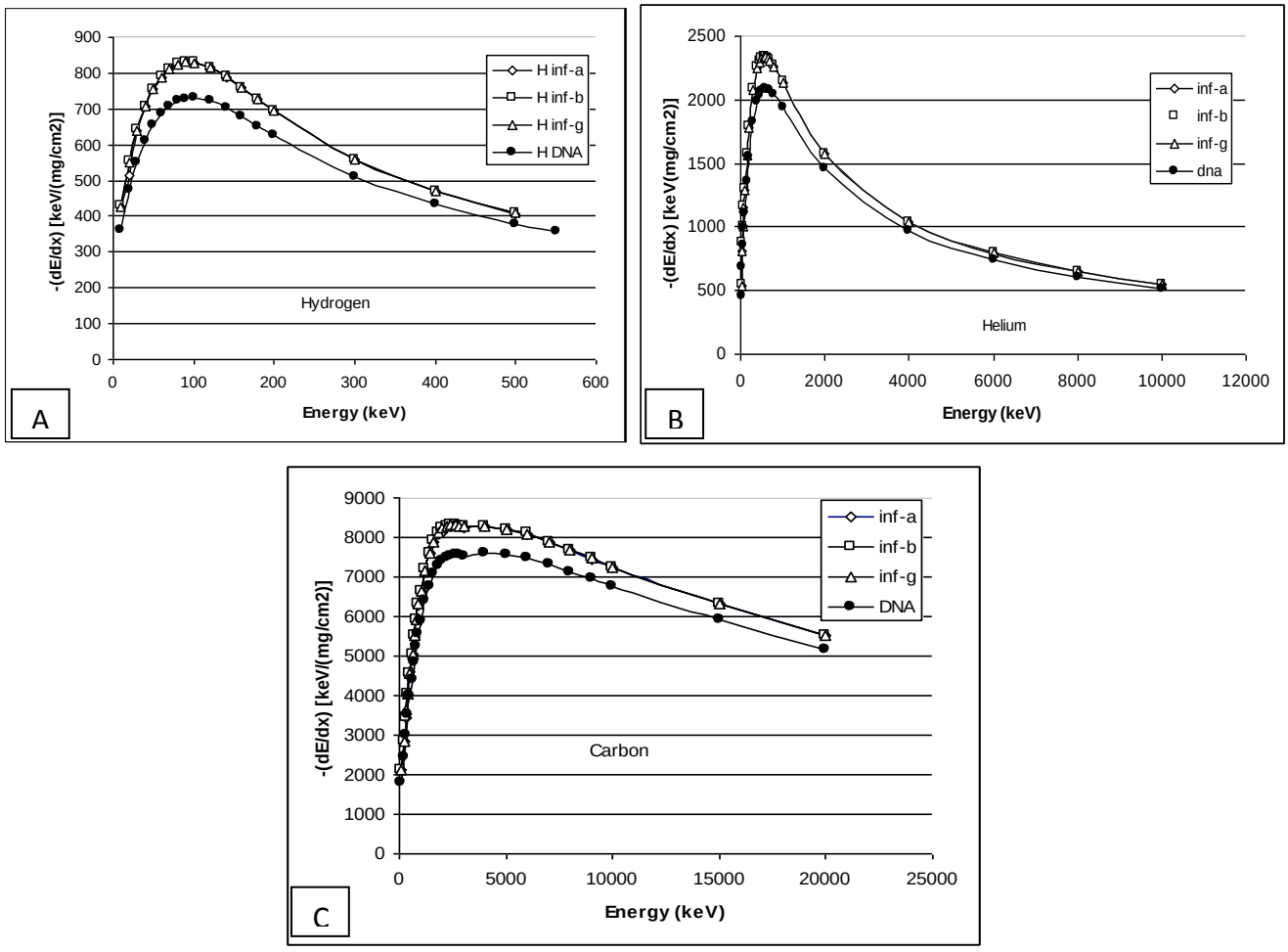

Figure 1. Bragg's peak deposited in different molecules; INF-α, INF-β, INF-γ and DNA targeted by hydrogen [A], helium [B] or carbon [C].

Discussion

The results showed that the Bragg's peak of proton (the maximum energy loss) of nucleotide is differed from that of interferon which means that proton beam radiation targeting the nucleotide will not affect the interferon and thereby not interferes with immune system. Moreover, the spread out effect of proton against the nucleotide at the Bragg's peak was higher by 1.3 fold of interferon at their Bragg's peak which indicated that proton showed selective effect against nucleotide.

Khvostunov et al (2010) found that whole cell nucleus as a function of proton energy shows a distinct peak at 550 keV using biophysical modeling of radiation effects induced by exposure of V79 cells which is approximated to that obtained with helium in this study [(11)]. In vivo, proton beam was found to be more cytotoxic to A549 lung adenocarcinoma cell than gamma radiation [(12)]. Previous studies showed that proton radiation exerts minimal effect on immune system as showed in this study.

The cell death in the splenic white pulp of irradiated whole body ICR mice with proton was lower compared with gamma radiation in spite of an increase damaged DNA [(13)]. Moreover, there is an evidence of using interferon, which is not targeted by proton in this study, in cutaneous melanoma patients to prevent metastasis and recommended to use interferon following proton radiation in patients with high risk of metastasis [(14)].

This study adds more information that endogenous interferon was not affected by proton when the later targeted the nucleotide which means that the immune system is free from the effect of proton radiation as it happens with conventional X-ray radiation [15]. It concludes that targeting of well precise located tumor with proton beam radiation therapy resulted in nucleotide damage of cancer cell without affecting the immune system in term of interferon surveillance.

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