СЕКРЕЦИЯ IL-6 И IL-8 КЛЕТКАМИ ГЛИОБЛАСТОМ ЧЕЛОВЕКА, ПРОЛИФЕРИРУЮЩИМИ ПОСЛЕ ОБЛУЧЕНИЯ НА АППАРАТЕ ГАММА-НОЖ

Самойлович М.П.[1, 2], Пиневич А.А.[1, 2], Смирнов И.В.[1], Вартанян Н.Л.[1], Крутецкая И.Ю.[1], Киселева Л.Н.[1], Макаров В.Е.[1], Карташев А.В.[1]

[1] ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия
[2] ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург, Россия

Резюме. Одним из современных методов лечения больных с первичными и рецидивирующими опухолями головного мозга является радиохирургическое облучение на аппарате Гамма-нож, позволяющее за 1-2 сеанса подвести терапевтическую дозу к опухоли, не превышающей 2,5 см в диаметре. Клетки опухоли на периферии этого объема получают меньшие дозы облучения, могут возобновлять пролиферацию и служить источником рецидивов. Увеличение дозы облучения чревато образованием некрозов и ухудшением прогноза. Свойства клеток глиобластом, выживающих и возобновляющих пролиферацию после облучения на установке Гамма-нож, до настоящего времени мало известны. Цель работы состояла в оценке экспрессии IL-6 и IL-8 клетками глиобластом линий A172, R1, T2 и T98G, которые возобновили пролиферацию после сублетального стереотаксического облучения. Клетки облучали однократно в дозах от 6 до 16 Гр, затем культивировали в течение 40 суток, подсчитывая еженедельно количество клеток и определяя таким образом летальную и сублетальную дозы для каждой линии глиобластом. В культурах, возникших в результате пролиферации единичных наиболее радиорезистентных клеток, методом ИФА определяли количество интерлейкинов (нг), секретированных за 96 часов в расчете на 1000 клеток. Клетки всех четырех линий глиобластом секретировали IL-6 и IL-8 в среду культивирования. Максимально высокой продукцией цитокинов, которая ранее не была известна для глиобластом, отличалась линия R1. Высокой продукцией обладала также глиобластома T2. Контраст этим линиям представляла глиобластома A172, наиболее чувствительная к действию цитостатиков и облучения, секреция IL-6 в которой была в 30 раз ниже, чем в клетках R1. Глиобластома T98G, известная своей высокой устойчивостью к действию химиопрепаратов и облучения, также обладала низкой продукцией интерлейкинов. Клетки глиобластом R1, T2 и T98G, возобновившие пролиферацию после облучения, обладали усиленной секрецией IL-6 и, в меньшей

Адрес для переписки:

Самойлович Марина Платоновна
ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ
197758, Россия, Санкт-Петербург, пос. Песочный, ул. Ленинградская, 70.
Тел.: 8 (812) 596-66-53.
Факс: 8 (812) 596-66-53.
E-mail: mpsamoylovich@gmail.com

Address for correspondence:

Marina P. Samoilovich
A. Granov Russian Research Center for Radiology and Surgical Technologies
70 Leningradskaya St
Pesochny, St. Petersburg
197758 Russian Federation
Phone: +7 (812) 596-66-53.
Fax: +7 (812) 596-66-53.
E-mail: mpsamoylovich@gmail.com

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мере, IL-8. Зависимость увеличения продукции цитокинов от дозы облучения для этих клеток не носила линейного характера. Клетки A172 под действием облучения, наоборот, снизили секрецию IL-6 и IL-8. Разнонаправленные изменения в продукции IL-6 и IL-8 клетками разных линий глиобластом были долговременными и сохранялись более месяца. Представленные результаты ставят под сомнение возможность использования показателей продукции IL-6 и IL-8 клетками глиобластом в качестве потенциальных биомаркеров для ранней диагностики, мониторинга терапии, а также в качестве прогностических маркеров течения заболевания.

Ключевые слова: глиобластомы, IL-6, IL-8, Гамма-нож, A172, R1, T2, T98G

IL-6 AND IL-8 SECRETION BY HUMAN GLIOMA CELLS PROLIFERATING AFTER GAMMA KNIFE IRRADIATION

Samoilovich M.P.[a, b], Pinevich A.A.[a, b], Smirnov I.V.[a], Vartanyan N.L.[a], Krutetskaya I.Yu.[a], Kiseleva L.N.[a], Makarov V.E.[a], Kartashev A.V.[a]

[a] *A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*
[b] *St. Petersburg State University, St. Petersburg, Russian Federation*

Abstract. One of the modern methods of treating patients with primary and recurrent brain tumors is radiosurgical irradiation using Gamma Knife, which allows therapeutic doses to be delivered to tumors not exceeding 2.5 cm in diameter in 1–2 sessions. Tumor cells on the periphery of this tissue volume that receive lower radiation doses can resume proliferation and serve as a source of recurrence. The increase of radiation dose may cause necroses formation and a worsening prognosis. The properties of glioblastoma cells that survive and resume proliferation long after stereotactic irradiation are still poorly known. The aim of the work was to evaluate the expression of IL-6 and IL-8 by glioblastoma A172, R1, T2, and T98G cell lines that resumed proliferation after sublethal Gamma Knife irradiation. Cells were irradiated once at doses ranging from 6 to 16 Gy, and then cultured for 40 days. Cell number was counted weekly; lethal and sublethal irradiation doses for each glioblastoma cell line were determined. In cultures descendant from proliferation of single most resistant cells, the level of IL-6 and IL-8 secretion after 96 hours cultivation (ng/1000 cells) was determined by ELISA. The cells of all four glioblastoma lines secreted IL-6 and IL-8 into culture medium. The highest production of cytokines, never before demonstrated for glioblastomas, was discovered in R1 cells. Glioblastoma T2 also had high interleukin production levels. In contrast to these lines, glioblastoma A172 (highly sensitive to the action of cytostatic drugs and radiation) secreted IL-6 at 30 times lower level than R1 cells. Glioblastoma T98G (highly resistant to the action of cytostatic drugs and radiation) also exhibited low interleukins production level. R1, T2, and T98G glioblastoma cells that resumed proliferation after irradiation had increased secretion of IL-6 and, to a lesser extent, IL-8. The dependence of cytokine production increase on irradiation dose for these cells was not linear. In contrast, A172 cells reduced IL-6 and IL-8 secretion under irradiation. The multidirectional changes in IL-6 and IL-8 production by cells of different glioblastoma lines were long-term and persisted for more than a month. The presented results cast doubt on the possibility to use IL-6 and IL-8 production by glioblastoma cells as potential biomarkers for early diagnosis, therapy monitoring as well as prognostic markers of the disease course.

Keywords: glioblastoma, IL-6, IL-8, Leksell Gamma Knife, A172, R1, T2, T98G

The work was performed according to Government Order "Study of resistant tumor cells on glioblastoma cultures in the simulation of stereotactic radiosurgery of recurrent glioblastoma" at the A. Granov Russian Research Center for Radiology and Surgical Technologies (St. Petersburg, Russia).

Introduction

Primary tumors of the central nervous system account for about 2% of all human tumors. Among them, glioblastomas are the most malignant and have the worst prognosis. The formation of tumor cells resistant to therapy is the main reason for glioblastoma recurrence. One of the most modern methods of treatment of patients with primary and recurrent brain tumors is Gamma Knife radiosurgery which allows delivering a full therapeutic dose to the tumor center in 1-2 sessions. The distinctive feature of this radiotherapy method is focusing the photon beam on a small tissue volume not exceeding 2.5 cm in diameter. Tumor cells located on the periphery of this volume receive lower radiation doses. In consequence they

can resume proliferation and serve as an additional source of recurrence. At the same time, increasing the radiation dose can lead to the formation of necroses and a worsening prognosis. The properties of glioblastoma cell populations that survived and resumed proliferation after Gamma Knife irradiation are still poorly known. We are aware of only one work which contains information about the properties of these cells [3].

It was shown that glioblastoma cells that underwent Gamma Knife irradiation have a higher level of integrin beta-1 expression and consequently a higher migratory activity than intact cells. The increased ability of tumor cells to grow by continuation, as well as to form metastases, is precisely associated with the increase in their migratory activity.

Interleukins IL-6 and IL-8 play an important role in the process of carcinogenesis, including gliomagenesis [4]. Immunohistochemical studies have shown that glioblastoma cells can express these cytokines [4, 12]. High IL-8 expression was demonstrated in approximately 80% glioblastoma tissue samples. At the same time IL-8 has been shown to enhance glioma growth by binding to CXCR1 receptor on the cell surface in an autocrine manner [12]. IL-6 has been shown to be directly related not only to tumor growth, but also to manifestations of therapy resistance, in particular, multidrug resistance [5, 7, 14]. The possibility of using inhibitors of these cytokines (antibodies, anti-sense RNA) as drugs to overcome radio- and chemoresistance in tumors of different histogenesis is on the agenda [7, 10]. The aim of the work was to evaluate IL-6 and IL-8 expression by glioblastoma cells that resumed proliferation after sublethal Gamma Knife irradiation.

Materials and methods

Glioblastoma A172, R1, T2, and T98G cell lines were cultured in 12.5 cm^2 plastic vials and 24-well plates at 37 °C, 6% CO_2, and 100% humidity, in α-MEM medium growth medium supplemented with 5% fetal calf serum and 0.5% gentamicin. Cells were cultured until reaching 70-90% confluency and reseeded using 0.25% trypsin-EDTA solution. Glioblastoma cells were irradiated once on a Leksell Gamma Knife® with 201-focused ^{60}Co radiation source at a dose rate of 3.236 Gy/min, 1.17 MeV energy, using a specially designed device for fixation and positioning of cell cultures during precision irradiation (patent for invention No. 2778859). Two hours after irradiation, cells were disseminated into 96-well plates and cultured under normal conditions. During this period the number of live glioblastoma cells in tissue cultures was counted weekly; LD_{100} and sublethal dose values for each cell line were determined.

IL-6 and IL-8 production was evaluated in cell cultures which were progeny of cells that survived and resumed proliferation after sublethal irradiation. Culture medium samples for analysis were collected 30-56 days after irradiation depending on irradiation dose, resumption time, and proliferation rate of surviving cells in different cell lines.

IL-6 and IL-8 secretion was assessed by determining cytokines concentration in the culture medium using Interleukin-6-IFA-BEST and Interleukin-8-IFA-BEST kits (Vector-Best, Russia) according to the manufacturer's recommendations. Cells were disseminated into 24-well plates and after 96 h cultivation culture medium was collected for analysis. Then the number of cells in each well was determined, and the average amount of cytokines secreted into culture medium in ng per thousand cells was calculated.

The data were processed and visualized using R language tools (version 4.1.2). Statistical analysis was performed by creating linear regression models.

Results and discussion

Cells of all glioblastoma lines secreted IL-6 and IL-8 into the culture medium. R1 glioblastoma cells produced the maximum amount of cytokines – 22.3 ng of IL-6 and 9.0 ng of IL-8 per 1000 cells in 96 hours. The secretion of these cytokines by R1 glioblastoma cells has not been previously evaluated, and we are not aware of any studies related to glioblastoma cell lines with such high levels of IL-6 and IL-8 production. T2 glioblastoma has also been tested for the first time and showed high levels of both cytokines secretion. In contrast to these two lines, A172 glioblastoma secreted only 0.06 ng of IL-6 and 1.31 ng of IL-8 per 1000 cells. These data are consistent with the data from other researchers [15]. T98G glioblastoma cells produced average levels of IL-6 and IL-8 – 3.8 ng and 1.25 ng per 1000 cells correspondingly (Figure 1).

The balance of IL-6 and IL-8 production for intact R1, T2, and T98G lines was biased towards IL-6, while IL-8 secretion prevailed in low-secreting A172 line.

Sublethal irradiation of glioblastoma lines R1 and T2 resulted in increased production of IL-6 and IL-8 typical of intact cells. Glioblastoma A172 showed decreased secretion of IL-8 after 9 Gy irradiation (LD_{100} for A172 was 11 Gy), while initially this cell line had the lowest production of both cytokines. Nonlinear dependence of cytokine secretion from radiation dose was observed in R1 and T98G glioblastomas. Thus, for R1 line maximum level of IL-6 and IL-8 was detected in cultures originated from cells irradiated at a dose of 8 Gy. At sublethal dose irradiation of 11 Gy (LD_{100} for R1 cells was 12 Gy) cytokine secretion was lower than after irradiation dose of 8 Gy and did not differ from its level in intact cells. A similar trend was revealed for T98G cells; the peak of IL-6 secretion detected after irradiation dose of 11 Gy. After 14 Gy irradiation, the level of IL-6 secretion by T98G cells

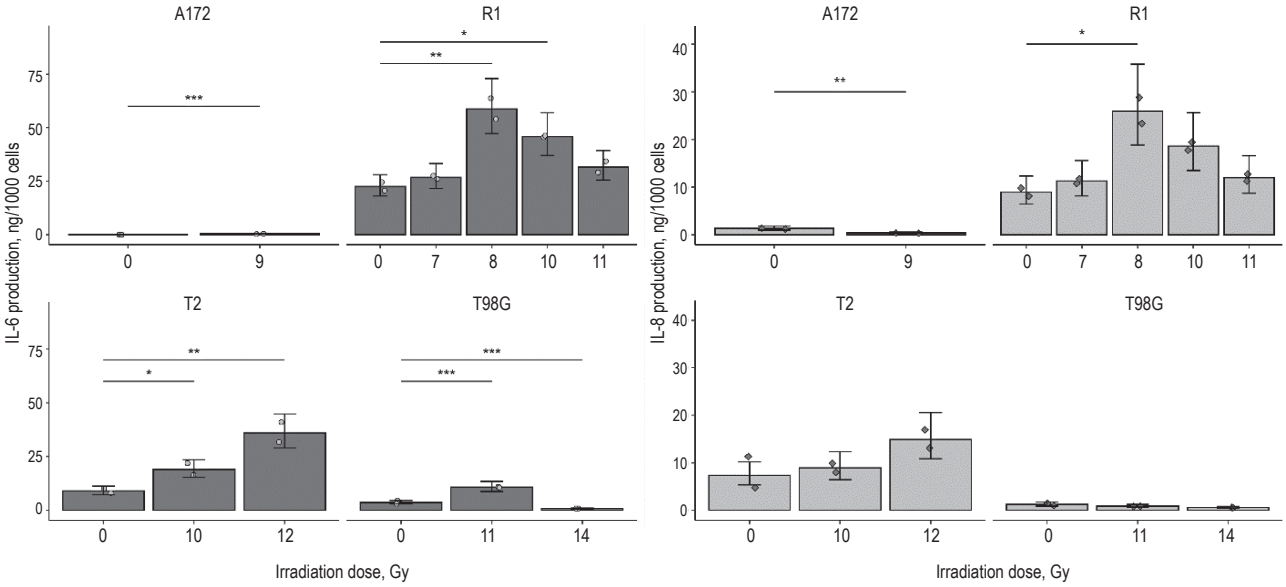

Figure 1. IL-6 and IL-8 level secreted during 96 h cultivation by intact glioblastoma cells A172, R1, T2, T98G, and by cells that resumed proliferation after sublethal Gamma Knife irradiation

Note. Horizontally – irradiation dose (Gy), vertically – amount of interleukins (ng), secreted by cells in 96 hours into the culture medium per 1000 cells. Dots indicate individual values; bars denote the 95% confidence intervals. *, differences are significant at $p < 0.05$; **, differences are significant at $p < 0.01$; ***, differences are significant at $p < 0.001$.

decreased and 16 Gy irradiation caused a complete stop of cell proliferation.

The secretion of IL-6 by T2 glioblastoma cell descendants that survived irradiation was many times higher than that by intact T2 cells. No decrease in cytokine production was observed when irradiation dose was increased up to 12 Gy. The ability of T2 cells to restore proliferation was abolished irradiation dose of 14 Gy.

It can be noted that three out of four studied glioblastoma cell lines, that resumed proliferation after sublethal Gamma Knife irradiation, demonstrated increased interleukin secretion although this effect was not equally dependent on irradiation dose.

The level of IL-6 and IL-8 expression is thought to correlate with the degree of gliomas malignancy [1, 11] but many questions still remain unresolved. In particular, our results suggest that two glioblastoma cell lines, A172 and T98G, have low IL-6 and IL-8 secretion. At the same time, according to the criteria of sensitivity to cytostatic drugs and irradiation, these lines are completely different. Glioblastoma A172 does not express MGMT, is highly sensitive to temozolomide, fotemustine, and radiation, while T98G line actively express *MGMT* gene, multiple drug resistance genes, and is highly resistant to chemo- and radiotherapy [8, 9]. The reasons for these discrepancies are not yet clear. It should be emphasized that in the course of present research, the relapse between glioblastoma irradiation and the assessment of IL-6 and IL-8 production took at least 30 days. Thus, we can conclude that increased cytokine secretion by cells was not due to a short-term effect of irradiation, but persisted for a long time.

Conclusion

Currently, IL-6 and IL-8 are considered as potential biomarkers for early diagnosis and therapy monitoring, as well as prognostic markers of the disease course [2, 6, 13]. From this point of view, the results obtained in the present study on four glioblastoma cell lines exposed to Gamma Knife irradiation serve as a warning against making simple conclusions about the possibility of using IL-6 and IL-8 production as biomarkers for monitoring and prognosis of glioblastoma therapy.

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Авторы:

Самойлович М.П. *– д.б.н., профессор, главный научный сотрудник лаборатории гибридомной технологии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ; главный научный сотрудник кафедры цитологии и гистологии биологического факультета ФГБОУ ВО «Санкт-Петербургский государственный университет» Санкт-Петербург, Россия*

Пиневич А.А. *– к.б.н., старший научный сотрудник лаборатории гибридомной технологии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ; старший преподаватель кафедры цитологии и гистологии биологического факультета ФГБОУ ВО «Санкт-Петербургский государственный университет», Санкт-Петербург, Россия*

Смирнов И.В. *– к.б.н., ведущий научный сотрудник лаборатории гибридомной технологии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Authors:

Samoilovich M.P., *PhD, MD (Biology), Professor, Chief Research Associate, Hybridoma Technology Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies; Chief Research Associate, Cytology and Histology Department, Biological Faculty, St. Petersburg State University St. Petersburg, Russian Federation*

Pinevich A.A., *PhD (Biology), Senior Research Associate, Hybridoma Technology Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies; Senior Lecturer, Cytology and Histology Department, Biological Faculty, St. Petersburg State University, St. Petersburg, Russian Federation*

Smirnov I.V., *PhD (Biology), Leading Research Associate, Hybridoma Technology Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

Вартанян Н.Л. *– к.б.н., старший научный сотрудник лаборатории гибридомной технологии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Крутецкая И.Ю. *– к.б.н., старший научный сотрудник лаборатории гибридомной технологии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Киселева Л.Н. *– к.б.н., научный сотрудник лаборатории генной инженерии ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Макаров В.Е. *– медицинский физик отделения радиохирургии и радиотерапии № 2 ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Карташев А.В. *– к.м.н., врач-радиотерапевт, радиохирург, старший научный сотрудник отделения радиохирургии и радиотерапии № 2 ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Министерства здравоохранения РФ, Санкт-Петербург, Россия*

Vartanyan N.L., *PhD (Biology), Senior Research Associate, Hybridoma Technology Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

Krutetskaya I.Yu., *PhD (Biology), Senior Research Associate, Hybridoma Technology Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

Kiseleva L.N., *PhD (Biology), Research Associate, Genetic Engineering Laboratory, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

Makarov V.E., *Medical Physicist, Radiosurgery and Radiotherapy Department No. 2, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

Kartashev A.V., *PhD (Medicine), Radiotherapist, Radiosurgeon, Senior Research Associate, Radiosurgery and Radiotherapy Department No. 2, A. Granov Russian Research Center for Radiology and Surgical Technologies, St. Petersburg, Russian Federation*

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