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Research Article

Correlation Between Peripheral Blood Cells and their Membrane Charge Depending on the Radicality of Surgical Removal of Glioblastomas

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Abstract

Study of processes occurring in tumor tissues during tumor progression in the postoperative period investigated by studying inflammation of tumor and non-tumor nature. Verapamil hydrochloride, as shown in our studies, changes the transmembrane potential of tumor and peripheral blood cells of the tumor-bearing organism. Previously shown that adding verapamil hydrochloride to blood cells without plasma in a dilution of 10,000 times increases the indices of surface plasmon resonance (SPR) indirectly determines blood cell aggregation level on Plasmon device for malignant gliomas. A dilution of verapamil hydrochloride by 100 times this indices increases in case of traumatic brain injuries or other inflammatory processes of a non-tumor nature. The work used these two dilutions for correlation between the cellular transmembrane potential mediated by SPR indices and quantitative changes in the cellular pool derived from mesenchymal stem cells. As is known, peripheral blood cells are an active mechanism in the tumor microenvironment, which affects its progression in the postoperative period. For the first time, it was separated SPR indices on the blood of patients *in vitro* with total and subtotal tumor removal, confirmed by clinical examinations. This approach makes possible clearly distinguish the mechanisms of progression by participation of blood cells

Keywords: *Glioma; Blood Cells; SPR Indices; Radicalism of Tumor Removal*

Introduction

The inflammatory process is closely associated with the progression of malignant tumors of all types [1], including brain gliomas. The diversity of cellular fractions in peripheral blood depends on the growth patterns of malignant neoplasms is poorly understood. Most blood cells have several functions in the peripheral bloodstream, both in the processes of protection against numerous infectious factors and their destruction, and in repair and regeneration processes to restore damaged body tissues. In these processes, in addition to mature peripheral blood cells, bone marrow mesenchymal stem cells may be involved in regeneration processes.

Monocytes can develop into specialized cell species and therefore function as mature stem cells of mesenchymal origin [2-4].

Previous studies have shown the dependence of peripheral blood cells number from the charge of cells membranes [5,6].

Of significant interest is the search for laboratory markers that it characterized by information content and public availability in order to improve the prediction of the course of the disease, decipher the mechanisms of tumor progression and search for effective therapy for malignant tumors, including brain gliomas.

Currently, many works present such markers in the form of relationships between different cellular blood fractions to predict the course of the disease [7] and many others. The research base on the dependence of cells number from the values of the transmembrane potential of blood cells. Of particular interest are the features of changes in cellular composition depending on the relatively radical removal of tumors during surgical interventions. The radicalism of tumor removal, as shown in our studies, is determined by the blood cell aggregation level measured using the physical SPR phenomenon [8-10].

Purpose of the Study

The purpose of the study was to search a correlation between the cellular number of peripheral blood leukocytes and the SPR indices taking into account of total and subtotal removal of glioblastomas.

Objective of the Study

To study the correlation *in vitro* between peripheral blood cells and it charge as a possible indicator of the prevalence of reparative or regenerative processes in complete or incomplete surgical removal of glioblastomas that will further determine the rate of recurrence of glioblastomas.

Materials and Methods

Explored 14 patients with primary glioblastomas before surgery and on the 7th day after surgery in which the radicalism of glioblastoma removal was analyzed *in vitro*.

The method for determining SPR indices on blood cells is described in detail in a previous work [11]. SPR indices were the same when studying leukocyte and erythrocyte fractions. Addition of verapamil hydrochloride (0.25% solution; Farmak), diluted at 10,000 times to blood cells, demonstrates the opposite effect on the SPR indices, compared to that without the addition of verapamil hydrochloride. This methodological approach makes it possible to analyze the degree of tumor malignancy, and therefore, the radicalism of tumor removal during surgery. Diluting verapamil hydrochloride 10,000 times and adding it to blood cells makes it possible to determine the level of SPR in tumor-associated inflammation. A 100-fold dilution of verapamil hydrochloride makes it possible to determine the level of SPR in normal inflammation during wound healing.

The SPR indices of cells without the addition of non-ionic water and with the addition of water were used as controls, because the drug verapamil hydrochloride was dissolved 100 and 10,000 times with the same volume of water. Water added to blood cells changed the SPR indices. Cell membranes were not destroyed when water was added in a ratio of 1:10.

The number of blood cells was determined in the same blood samples using an automatic hematological analyzer Mindray-3000.

Monocytes were detected in the pool of Mid cells of the peripheral bloodstream.

Statistical studies

Using the “OriginPro 8.1” package statistical studies were performed.

Absolute value r_{xy}	The tightness (strength) of the correlation
Less than 0.3	Weak
From 0.3 before to 0.5	Moderate
From 0.5 before 0.7	Noticeable
From 0.7 before 0.9	High
More than 0.9	Very high

Table 1: *Indices of the Chaddock scale [12].*

Results

In the general group of patients with glioblastoma before surgery, a negative noticeable correlation of granulocytes with SPR indices was found when a solution of verapamil hydrochloride (dilution at 100 times) was added to blood cells in a volume ratio of 1:10 (verapamil: water) (Table 2).

	SPR indices	WBC	Lym	Mid	Gran
		12.4 ± 3.86	**3.17 ± 1.225**	**1.4 ± 1.410**	**8.4 ± 3.684**
Control	1.2748 ± 0.3233	0.12527	0.21319	0.42432	-0.21319
100	1.24561 ± 0.34769	-0.21758	-0.09011	0.14365	-0.5033
10.000	1.40165 ± 0.37079	0.11209	0.23956	0.42653	-0.27912

Table 2: *indices in the general group of 14 patients before surgery (Correlation with a 10,000-fold dilution of verapamil).*

Links: SPR indices in control with the addition of non-ionic water;

100 - SPR indices (verapamil dilution at 100-fold);

10.000 - SPR indices (verapamil dilution at 10,000-fold).

After surgery on the 7th day in the same patients, a negative noticeable correlation of SPR indices with leukocytes, lymphocytes, granulocytes was found when non-ionic water was added to the cells as a control, and there was a correlation with granulocytes in the control (Table 3).

	SPR indices	WBC	Lym	Mid	Gran
		13.5 ± 7.66	**2.4 ± 1.115**	**1.07 ± 0.8250**	**10 ± 6.442**
Control	1.2211 ± 0.38502	-0.62266	-0.52214	-0.48275	-0.6652
100	1.2409 ± 0.35185	-0.33563	-0.11912	-0.05331	-0.49311
10.000	1.4416 ± 0.42678	-0.05721	0.0708	-0.09163	-0.11674

Table 3: *Indices in the general group of 14 patients on the 7th day after surgery (correlation with a 10,000-fold dilution of verapamil).*

From the data obtained, it is difficult to understand to which process such changes in the correlation between the SPR indices and the leukocyte pool relate, since before and after surgery in the general group, tumor cells closely interact with the inflammatory process. If the general groups of patients before and after surgery divided depending on the increase or decrease in SPR indices associated with the radicalism of tumor removal, one can judge the correlation and change in the cellular composition of leukocytes in the absence of a tumor after surgery and the associated tumor-associated inflammation.

In subsequent studies, the general group divided into two subgroups. The 1st subgroup consisted of 7 patients whose SPR indices after surgery were lower than before surgery. Before surgery, there was a positive noticeable correlation of SPR indices with Mid cells when water was added as a control. A positive noticeable correlation with SPR indices with the addition of diluted verapamil 10,000-fold with leukocytes and lymphocytes, as well as a high positive correlation with Mid cells (Table 4).

	SPR indices	WBC	Lym	Mid	Gran
		13 ± 3.06	3.8 ± 1.3626	1.4 ± 1.235	7.8 ± 2.209
Control	1.4469 ± 0.24238	0.42857	0.28571	0.53571	-0.03571
10.000	1.5863 ± 0.33409	0.5	0.5	0.71429	0.07143

Table 4: *Indices in a group of 7 patients before surgery with total tumor removal (Correlation with a 10,000-fold dilution of verapamil).*

After the operation, is no noticeable correlation of SPR indices with blood cells (Table 5).

	SPR indices	WBC	Lym	Mid	Gran
		14.7 ± 7.16	3.1 ± 1.1544	1.1 ± 0.454	10.6 ± 6.337
Control	1.19619 ± 0.31074	0.10714	0.25226	0.01802	0.10714
10.000	1.35247 ± 0.3548	0	0.12613	-0.01802	0

Table 5: *Indices in a group of 7 patients after surgery with total tumor removal (Correlation with a 10,000-fold dilution of verapamil).*

In the 2nd subgroup after surgery, SPR indices were higher than before surgery (subtotal removal). Preoperative SPR indices in all cases significantly correlated only with lymphocytes. There was a negative noticeable correlation of SPR indices with lymphocytes (Table 6).

	SPR indices	WBC	Lym	Mid	Gran
		11.7 ± 4.69	2.6 ± 0.7044	1.3 ± 1.66	9.04 ± 4.86
Control	1.10273 ± 0.31418	-0.32143	-0.89286	0.21622	-0.21429
10.000	1.21697 ± 0.32664	-0.32143	-0.82143	0.09009	-0.28571

Table 6: *Indices in the group of 7 patients before surgery with subtotal tumor removal (correlation with a 10,000-fold dilution of verapamil).*

After the operation, negative noticeable correlation of SPR indices in control with all types of cells and lack of correlation with the addition of verapamil diluted 10,000 times to blood cells. A negative noticeable correlation of SPR indices was noted with Mid cells in cell control, when water was added to the cells. There was a high negative correlation between SPR indices and granulocytes in controls, and there was no correlation with the 10,000 (Table 7).

	SPR indices	WBC	Lym	Mid	Gran
		12.9 ± 8.64	2.1 ± 1.312	1.1 ± 1.12	9.8 ± 6.99
Control	1.24613 ± 0.47241	-0.85714	-0.67857	-0.5766	-0.8571
10.000	1.53083 ± 0.5002	-0.10714	0.21429	0	-0.1071

Table 7: *Indices in a group of 7 patients after surgery with subtotal tumor removal (correlation with a 10,000-fold dilution of verapamil).*

The next stage of the study was the division of the general group of patients depending on the SPR indices with the 100-fold verapamil dilution before surgery compared with the indices after surgery.

Before surgery was noticeable positive correlation between SPR indices with 100 times verapamil dilution and Mid cells in control. There was a negative noticeable correlation of SPR indices with granulocytes (Table 8).

	SPR indices	WBC	Lym	Mid	Gran
		13.4 ± 3.67	**3.4 ± 1.3899**	**1.2 ± 1.122**	**8.7 ± 3.417**
Control	1.31337 ± 0.3339	-0.03333	0.31667	0.57741	-0.46667
100	1.3199 ± 0.37643	-0.36667	0.03333	0.38494	-0.75
10.000	1.4211 ± 0.37651	-0.18333	0.35	0.66109	-0.56667

Table 8: *Indices in the group of 9 patients before surgery with total tumor removal (correlation with a 100-fold dilution of verapamil).*

After surgery, a negative noticeable correlation was present in all cells except Mid cells in control and verapamil dilution in 100-fold (Table 9).

	SPR indices	WBC	Lym	Mid	Gran
		15.8 ± 8.56	**2.7 ± 1.06**	**1.4 ± 0.89**	**11.6 ± 7.501**
Control	1.1131 ± 0.3844	-0.6862	-0.65828	-0.31477	-0.60252
100	1.2087 ± 0.3585	-0.62762	-0.51481	-0.00874	-0.64436
10.000	1.4172 ± 0.3784	-0.0251	-0.00844	-0.02623	0.05858

Table 9: *Indices in a group of 9 patients after surgery with total tumor removal (correlation with a 100-fold dilution of verapamil).*

Before surgery, the very high negative correlation was with lymphocyte and a 100-fold dilution of verapamil (Table 10).

	SPR indices	WBC	Lym	Mid	Gran
		9.8 ± 4.08	**2.8 ± 0.89**	**0.7 ± 0.469**	**6.3 ± 2.96**
Control	1.1798 ± 0.3728	-0.2	-0.4	0.31623	-0.2
100	1.0990 ± 0.3137	-0.4	-0.8	-0.31623	-0.4
10.000	1.4135 ± 0.4470	0.4	0.2	0.63246	0.4

Table 10: *Indices in the group of 4 patients before surgery with subtotal tumor removal (correlation with a 100-fold dilution of verapamil).*

After the surgery, there was no correlation between SPR indices and Mid cells. There was a negative high correlation with leukocytes in control and it absence with the addition of verapamil. Positive high correlation present in lymphocytes only with the addition of verapamil 100 - fold dilution. Granulocytes had a very high negative correlation in control (Table 11).

	SPR indices	WBC	Lym	Mid	Gran
		11.1 ± 1.126	**2.2 ± 0.607**	**0.6 ± 0.15**	**8.2 ± 1.19**
Control	1.35752 ± 0.35752	-0.8	0.2	-0.2582	-1
100	1.3132 ± 0.37727	0.2	0.8	0.2582	-0.4
10.000	1.53987 ± 0.61859	-0.4	0.4	0.2582	-0.8

Table 11: *Indices in a group of 4 patients after surgery with subtotal tumor removal (correlation with a 100-fold dilution of verapamil).*

Discussion

The work presents additional information to the generally accepted theory of growth and progression of malignant human tumors. They are evidence of participating in the pathogenesis of growth and progression of malignant tumors, for the example of glioblastoma, peripheral blood cells of mesenchymal origin (from the bone marrow). Some fractions of these cells have not only generally accepted protective characteristics of inflammatory genesis, but also have the properties of stem cells involved in tissue regeneration in the postoperative period. Chronic inflammation observed during the period of tissue regeneration after removal of the tumor prevents the morphogenesis of newly proliferating cells with stem potential (monocytes, lymphocytes and others), resulting in a chaotic tissue growth in a remote tumor. In the process of evolution, at least two mechanisms were formed in the body that prevent tumor regression, known as apoptosis and epithelial-mechanical transition [13]. These two mechanisms protect the regeneration processes from the inflammatory process in the adult organism. In the early embryonic period there is no inflammation, as a result of which the cells are quickly divided in the first trimester of pregnancy, but tumor growth does not arise. The work shows the differences in the cellular ensemble during regeneration with a complete removal of the tumor and in the case, when a small number of glioblastoma cells remains in the postoperative tissue. As shown in the work, these processes are influenced by a membrane charge of participating cells, which determines the nature of tissue restoration: inflammatory reparation, or regeneration with the participation of cells with stem potential.

Conclusion

The main conclusion from the work is the discovery, for the first time, of the cellular number dependence from SPR indices.

The SPR indices when verapamil diluted 10,000-fold is added to blood cells indicates micro inflammation associated with tumor growth. With total removal of glioblastoma, the correlation of SPR indices with Mid-blood cells disappears after surgery, indicating its connection with the presence of a tumor. With subtotal removal of the tumor, there is no correlation before surgery, but it appears after surgery, which may indicate a connection between Mid-cells and the onset of regeneration of the remaining tumor tissue, i.e. tumor relapse. The SPR indices when verapamil diluted 100-fold is added to blood cells indicates inflammation associated with healing of the surgical wound, i.e. tissue reparation. Correlation of the SPR indices with other cells, such as leucocytes, lymphocytes and granulocytes is more common with total tumor removal, indicating the predominance of the inflammatory process. This mechanism can influence the processes of tissue regeneration in the tumor microenvironment, with or without tumor progression, depending on the radicalism of tumor removal, cellular charge and it number.

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