DISTURBANCE OF FUNCTION OF VASCULAR AND PLATELET COMPONENTS OF THE HEMOSTASIS SYSTEM DURING TUMOR GROWTH

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Malignant neoplasms cause an increased tendency toward blood clotting and thrombus formation. In turn, the hemostasis system exerts an influence on tumor growth and metastasization. For instance, the formation of oncogenic-thromobogenic emboli and their retention in the vessels of the microcirculation depend on the functional state of the vessel wall and of the platelets [5, 6]. It has recently been shown that the antithrombogenic activity of the vessel wall is depressed in cancer patients [1]. Tumors in animals and, in particular, metastasizing tumors, have been shown to aggregate platelets [3, 9].

The aim of this investigation was to study disturbances of the vascular and platelet components of the hemostasis system in rats during growth of a metastasizing tumor RA-2.

EXPERIMENTAL METHOD

Experiments were carried out on 95 noninbred male rats weighing 200-250 g. The RA-2 tumor was transplanted intramuscularly, by grafting a piece of tumor tissue measuring 1 mm^3 in the region of the thigh. Platelet aggregation was determined [4] on an aggregometer ("Chronolog," USA), spontaneous intravascular platelet aggregation was determined as in [10], and the antiaggregating [8] and anticoagulant [2] activity of the vessel wall was estimated. Blood was taken from the abdominal aorta under pentobarbital anesthesia. The results were subjected to statistical analysis by Student's test and by analysis of variance.

EXPERIMENTAL RESULTS

As Table 1 shows, ADP-induced platelet aggregation was intensified on the 9th day after transplantation of the tumor on average by 12%, and reached a maximum (mean 45%) on the 15th day; it was somewhat lower on the 24th day, when its value was on average 14% higher than in healthy animals.

Growth of the tumor was accompanied by increased functional activity of the platelets, which reached a maximum during the first 2 weeks of tumor development. On the 9th day, for instance, the index of intravascular platelet aggregation was increased on averaged by 2.4 times, and on the 15th day by twice compared with the control. Later, until the 30th day of observation, functional activity of the platelets declined.

The antiaggregating activity of the vessel wall of the animals was judged by the degree of inhibition of ADP-induced platelet aggregation after incubation with a segment of the abdominal aorta. Significant reduction of the antiaggregating activity of the vessel wall was recorded on the 15th day (by 15%), and to a lesser degree, on the 24th day of tumor growth. A tendency was found toward reduction of the anticoagulant activity of the vessel wall, determined as the concentration of anththrombin III, entering the blood from the vascular wall.

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TABLE 1. State of Vascular and Platelet Components of Hemostasis System in Rats with Tumors (M ± m)

Experimental conditions	ADP-induced platelet aggregation, %	Index of intravas. platelet aggreg.	Anti-aggreg. activity of vessel wall, %	Anticoagulant activity of vessel wall, %
Control	39,1±2.4	1.4±0.1	93.6±0.54	16,2±1,7
Time after tumor transplantation, days:				
9	51,5±1,05*	3.4±0,25*	91.6±1,05	—
15	73,8±4,7*	2,9±0.33*	78,7±2,64*	—
24	53,7±1,3*	2,2±0.23*	90,8±1,08*	13,7±0,9
30	—	1,5±0,23	90,2±1,96	—

Legend. *$p < 0.05$.

The results thus indicate that the vascular and platelet components of the hemostasis system undergo considerable changes in rats with tumors. The antiaggregating properties of the vessel walls are due mainly to prostacyclin – an active product of endothelial synthesis. It was shown previously [o] that prostacyclin prevents metastasization of tumor cells. For instance, injection of prostacyclin into mice before intravenous injection of tumor cells reduced metastasis formation in the lungs on average by 70%, whereas simultaneous injection of prostacyclin with theophylline, which blocks the breakdown of cAMP and reduces the aggregating activity of platelets, reduced the number of metastases on average by 93%. Depression of antithrombin III synthesis by the vascular endothelium also leads to elevation of the thrombogenic potential of the vessel wall. Cells of malignant tumors, which possess marked procoagulant and adhesive activity, cause platelets to adhere to their surface and aggregate them, and are then covered with fibrin, leading to the organization of an oncogenic-thrombogenic embolus. Although such am embolus is still not a metastasis, disturbance of the functional properties of the vascular wall facilitates its penetration into the extravascular space and increases the likelihood of formation of a metastatic focus. In turn, platelets increase the viability of tumor cells, by releasing growth factor and, by adhering to their surface, they promote physical protection of cancer cells and thereby increase the degree and rate of implantation of tumor cells in the vascular wall [7].

Depression of the antiaggregating activity of the vascular wall and enhancement of platelet function can thus play a crucial role not only in the development of a primary tumor focus, but also in the process of dissemination of cancer cells in the animal body and the development of metastases.

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