MIGRATION ACTIVITY OF SYRIAN HAMSTER PERITONEAL EXUDATE CELLS AT DIFFERENT TIMES AFTER DEPRESSION OF THEIR NATURAL ANTITUMOR RESISTANCE

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Migration activity of hamster peritoneal exudate cells (PEC) on the 9th-13th days after intraperitoneal injection of heat-inactivated tumor cells (strains E-1, GT-11B, STHE-LM^8) is intensified with embryonic hamster cells. In embryonic hamster cells inoculated both normally and spontaneously *in vitro* (strain STHE), no such intensification of migration activity was found [6]. It was shown in the writers' laboratory that injection of tumor cells, inactivated by heating to 56°C and by irradiation, into hamsters depressed their natural resistance (NR) to the tumor, as shown by ability of tumors to grow from single cells when later transplanted into such animals [1, 5]. It has been suggested that there is a connection between the ability of tumor cells to depress NR *in vitro* and their ability to intensify macrophagal migration activity [6].

This paper describes an attempt to discover whether the time at which migration activity of the macrophages changes in animals injected with inactivated tumor cells coincides with the times of most marked depression of their NR, as established by the writers previously.

EXPERIMENTAL METHOD

To depress NR of Syrian hamsters, inactivated cells of strain E-1 (a hamster sarcoma induced by virus SV40) and STHE-LM^8 (a metastatic variant of hamster cells spontaneously transformed *in vitro*: strain STHE [1] were used. The animals also received injections of inactivated STHE cells, not depressing NR of hamsters [1, 5]. Migration activity of PEC was determined by the method described previously [2] at different times in the course of 30 days starting from the first day after injection of inactivated tumor cells. PEC from each experimental and control (intact) hamster were introduced into 4 or 5 capillary tubes and the mean area (for each individual) of the zone of migration (MIZM) and the error of the mean were determined. Besides MIZM, the mean area of the zones of migration for the group (MGZM) also was determined in the control group. The migration index was calculated by the equation [2]:

$$IM = \frac{\text{MIZM in experiment}}{\text{MGZM in control}}.$$

EXPERIMENTAL RESULTS

The writers showed previously that STHE-LM^8 cells differ from the parent cells of strain STHE in their ability to inhibit NR of animals to tumors [5]. In the experiments of series I, therefore, the migration activity of PEC was investigated in animals receiving STHE-LM^8 cells and, at the same time, in hamsters receiving STHE cells (Fig. 1). Migration activity was determined 1, 7, 14, and 20 days after injection of the inactivated cells. The results show that on the first day after injection of the cells migration activity was intensified both in animals receiving STHE-LM^8 cells and in animals receiving STHE cells.

On the following days migration activity in hamsters receiving STHE cells was the same as in the control. Meanwhile, migration activity of PEC of animals receiving STHE-LM^8 cells was significantly increased on the 13-th-14th day after injection, and somewhat reduced on the 20th day. Significant individual differences in migration activity of the PEC of these animals also were noted (Fig. 1).

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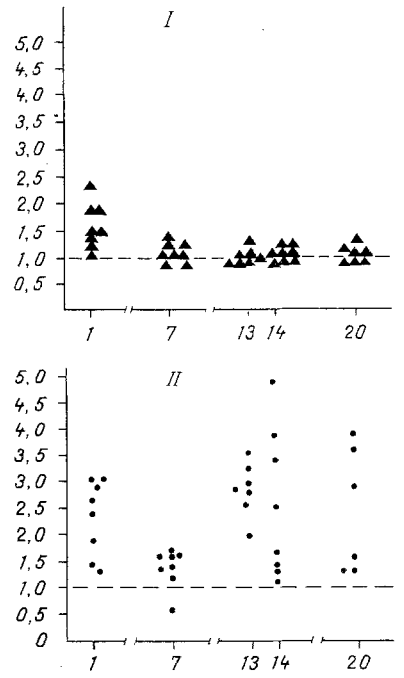

Fig. 1. Migration activity of peritoneal macrophages of hamsters inoculated with heated STHE (I) and STHE-LM^s (II) cells. Each point on graph indicates migration activity of individual animals, expressed in IM.

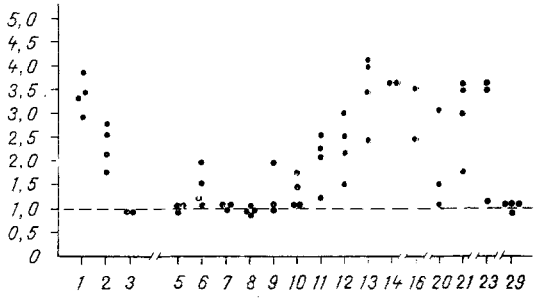

Fig. 2. Dynamics of migration activity of peritoneal macrophages of hamsters inoculated with heated STHE-LM^s cells.

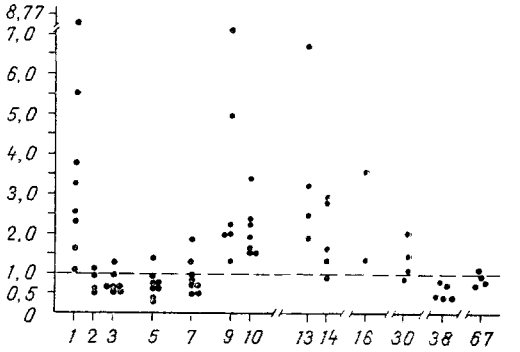

Fig. 3. Dynamics of migration activity of peritoneal macrophages of hamsters inoculated with heated E-1 cells.

Analysis of the data showed that on the 7th day after injection of inactivated STHE-LM^s cells the migration activity of the PEC of the experimental animals was minimal. It was accordingly decided to study in greater detail the time course of changes in migration activity of hamster macrophages after injection of STHE-LM^s cells.

The data in Fig. 2 indicate that 24 h after injection of inactivated STHE-LM^s cells the migration activity of PEC of the experimental animals was 3-4 times greater, and 2 days after injection, about 2-3 times greater than in the control. From the 3rd through the 9th day the migration activity of PEC of these animals was indistinguisable from normal. On the 10th day a weak but statistically significant increase in migration activity of the macrophages was observed, and it continued until the 20th-23rd day after injection of the tumor cells, when it was followed by a return to the normal level on the 29th day. Maximal (3-4 times) intensification of the migration activity of PEC occurred on the 13th-14th day after injection of STHE-LM^s cells into the animals.

In the experiments of series II changes in migration activity of PEC were studied in animals injected with inactivated cells of another tumor strain (E-1). As Fig. 3 shows, after injection of E-1 cells into the hamsters, although migration activity differed from

the results of the previous series of experiments, the difference was not significant. Potentiation of migration activity discovered 24 h after injection was characterized by wide variability of IM of PEC in individual animals (from 1.5 to 9.0). From the 2nd through the 5th day migration activity of the experimental animals did not differ from that in the control, or it was depressed; by the 5th day the number of animals with depressed migration activity was increased. On the 7th day this parameter began to recover in half of the animals, but in one of the seven hamsters migration activity showed a slight increase. From the 9th through the 14th day this activity was increased in 19 of 22 hamsters. Thus despite differences in detail, 24 h after injection of both STHE-LM^8 and E-1 cells a high level of migration activity on the 9th-11th day a high level was restored and lasted in most of the hamsters studied until the 20th-30th day after injection of inactivated tumor cells.

Prostaglandins of type E (PGE), which can enhance or depress this activity of macrophages depending on dose, are known to have a strong influence on migration activity of macrophages: small doses (10^{-8} M) enhance whereas larger doses can depress it [4]. Prostaglandins are synthesized by all types of cells, but in different quantities. The PGE level in cells of malignant tumors is evidently higher than in benign tumor cells, and it is higher in cells of metastasizing then of nonmetastasizing tumors [3]. PGE are produced even more intensively by resident macrophages in response to their activation, and in particular, by suppressor macrophages [7, 8].

The increase in migration activity on the 1st-2nd day after injection of inactivated tumor cells may be due to PGE contained in the injected tumor cells. After injection of inactivated tumor cells, activation of macrophages evidently takes place and is accompanied by PGE production by the macrophages. Possibly on the 3rd-7th day after injection of the tumor cells PGE production by macrophages reaches a maximum, and increased migration activity of the PEC is followed by its depression. The subsequent rise in this parameter on the 14th-20th day may be explained by a gradual fall in the level of PGE production by activated suppressor macrophages. This hypothesis is currently being investigated.

Whatever the mechanism of the phenomenon observed it is evident that a change in functional activity of the macrophages correlates with depression of NR of the animals to the tumor, established previously in response to injection of inactivated tumor cells. This correlation extends both to times of maximal enhancement of migration activity and of maximal depression of NR after injection of inactivated cells and also to the presence or absence of these effects when particular strains of cells (STHE-LM^8 or STHE) are used for injection into the animals.

Depression of NR of animals, important for the appearance and growth of tumors, may thus be connected with a change in functional activity of the macrophages.

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