Macrophage Migratory Dysfunction in Cancer

A Mechanism for Subversion of Surveillance

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There is considerable evidence to suggest that macrophages participate in host resistance to the development and spread of cancer. We have, therefore, studied monocyte-macrophage function in humans and animals with neoplasms. Approximately 60% of patients with various types of cancer were found to have abnormal monocyte chemotactic responsiveness *in vitro*, and abnormal chemotaxis was an indicator of poor prognosis in patients with melanoma. By studying patients before and after surgery, it was found that abnormal chemotactic responses normalized within weeks after removal of malignant tumors, indicating that a neoplasm itself might affect the host's monocyte chemotactic responsiveness. Subsequent studies using transplantable neoplasms in mice substantiated this hypothesis in that macrophage accumulation *in vivo* as well as macrophage chemotactic responsiveness *in vitro* was depressed in animals during the early phases of tumor growth. This depression of macrophage function could be attributed to a low-molecular-weight factor contained in murine neoplasms, which when given to normal mice was extremely potent in depressing peritoneal macrophage accumulation and chemotaxis but, paradoxically, enhanced phagocytosis. The serum of tumor-bearing mice also contained potent inhibitory activity for macrophage accumulation. In contrast to the effects on macrophages, granulocyte accumulation *in vivo* and chemotaxis *in vitro* was not depressed by the presence of a neoplasm or the administration of the factor from neoplasms. By rêleasing factors which depress macrophage migratory function, neoplasms may protect themselves from immunologically mediated host destruction during the early phases of tumor growth. (Am J Pathol 88:727–740, 1977)

THE EVOLUTIONARY DEVELOPMENT of complex multicellular organisms has resulted in their dependence upon the highly specialized functions of individual tissues. Principal features of the generation of more complex life forms are increased specialization and integration of cellular functions. Conversely, despecialization of vital tissue function is incompatible with the survival of such organisms. Control of cellular diversity is obviously complex and certainly occurs at many levels. It is our contention that the development of vertebrates comprised of increasingly specialized tissues sharing common and efficient circulatory systems has required the tandem development of a cellular system to protect against

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biologically active environmental factors which, when internalized, could lead to loss of specialized cellular functions. The immune system appears to be an important mediator of this protective function, and its role in preventing microbial invasion is a good example of this supposition. The contention that the immune system also functions to recognize and destroy dedifferentiated cells undergoing uncontrolled replication is less easy to demonstrate but is the major tenet of the concept of immune surveillance against neoplasia.

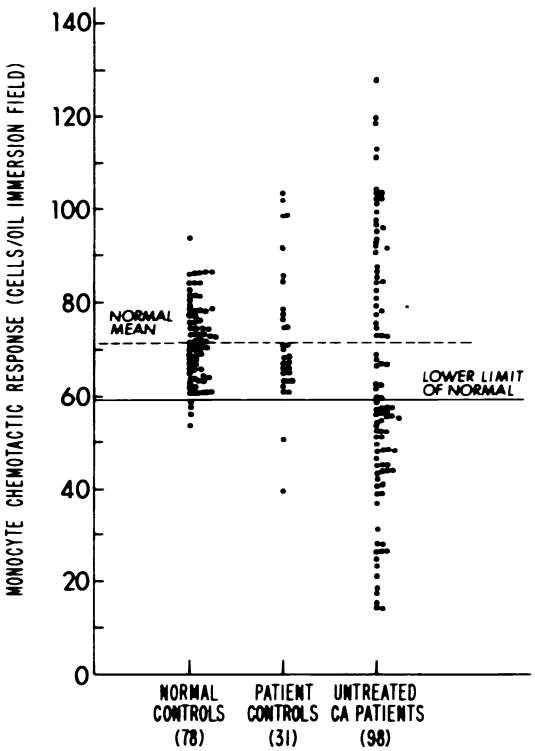
As yet, only indirect evidence supports the role of surveillance against neoplasia as an important immune function. Humans with immune deficiencies or undergoing immunosuppressive therapy have an increased incidence of neoplasms,[1] and it has been demonstrated that cellular-immune reactions occurring within tumors can produce their destruction.[2-5] Arguments against the surveillance hypothesis have cited that T cell–deficient humans and mice do not have an increased incidence of nonlymphomatous neoplasms;[6] however, these observations do not preclude the possibility that macrophages are instrumental for surveillance.

Macrophages are phagocytic wandering cells with tumoricidal capacity [7,8] which actively pervade all tissues of the host. Indeed, their influx into neoplastic sites can result in tumor destruction.[5] It has also been noted that tumors containing the highest numbers of macrophages are least likely to metastasize.[9]

In light of these observations, this laboratory has undertaken studies of monocyte-macrophage function in patients with cancer and has developed an animal model of the study of the effect of transplantable neoplasms and their products on macrophage function.

Studies of Chemotaxis in Patients With Neoplastic Disease

Since macrophages have been shown to be capable of destroying tumors both *in vivo* and *in vitro*, it was important to determine if the ability of monocytes to migrate directionally in response to chemotactic stimuli is impaired in patients with cancer. Over the past several years, this laboratory has studied the monocyte chemotactic responsiveness to a chemotactic lymphokine (LDCF) [10] in a large population of cancer patients, hospitalized patients with nonneoplastic diseases, and in normal individuals.[11,12] The results of these studies, depicted in Text-figure 1, have shown that of 98 patients studied approximately 60% of the patients with cancer had depressed monocyte chemotactic responses when compared to the responses of normal age-matched individuals or hospitalized controls. Subsequently, we have studied the chemotactic responsiveness of an additional 100 cancer patients and have found similar results. Other



TEXT-FIGURE 1—Monocyte chemotatic responsiveness of normal controls, hospitalized patients with nonneoplastic disease, and patients with neoplasms. The lower limit of normal indicates the level below which only 5% of the normal responses fall. The responses of approximately 60% of the patients with cancer (CA) fall below this level. Data from Snyderman and Mergenhagen.[11]

researchers have also found depressed monocyte chemotaxis in cancer patients.[13-15] The extended duration of our investigations has allowed the assessment of the possible prognostic significance of abnormal monocyte migratory function in cancer patients.[16] A longitudinal study of 56 patients with melanoma has revealed abnormal chemotaxis in 36 (64%) patients prior to immunotherapy. Of the abnormal responders, 70% had depressed chemotaxis, while 30% had elevated responsiveness. Immunotherapy with BCG, sensitized autologous lymphocytes, and x-irradiated neuraminidase-treated melanoma cells or surgical removal of the neoplasms both reduced the percentage of patients with abnormal responses, but the best prognosis was found in those patients with normal monocyte chemotaxis prior to therapy (Table 1).[16] Those patients with abnormal chemotaxis, whether depressed or elevated, had a higher mortality rate (44%) when compared to patients whose initial responses were normal (5%). The association of elevated monocyte chemotaxis responses with increased mortality in cancer patients may be explained by recent findings in our animal studies (see below).

The study of patients with breast cancer *in situ*, benign breast masses,

Table 1—Monocyte Chemotactic Responsiveness and Course of Disease in Patients With Malignant Melanoma*

Chemotactic responsiveness at onset of study†	Total No. in group	Extent of disease at conclusion of study		
		Free of disease	Progression of disease	Progression to death
Normal	20	18	1	1
Depressed	25	12	3	10
Elevated	11	5	0	6

P values for the comparison of extent of disease by Chi-square test are depressed versus normal, $P < 0.025$; elevated versus normal, $P < 0.005$; depressed versus elevated, $P > 0.5$.

* Adapted from Snyderman *et al.*[16]

† Patients were grouped according to their initial monocyte chemotactic responsiveness prior to therapy as either normal, depressed, or elevated as defined by the 90% confidence limits of the normal population; then the extent of the disease at the end of the study period was determined for each patient.

and patients with a history of breast cancer but clinically free of disease at the time of testing has yielded an additional provocative finding. Of patients with breast cancer *in situ*, 65% had abnormal responses, while the responses of patients with benign lesions or a prior history of breast cancer with no current active disease were not significantly different from the chemotactic responses of a normal control population.[17] It was also found that the monocyte chemotactic responsiveness of patients with malignant masses was normalized following surgical resection of their tumors (Table 2); this did not occur in patients with benign masses. These findings, together with the fact that normal chemotactic responsiveness was found in patients with a history of breast cancer but with no active disease at the time of testing, indicated that the defect in chemotaxis found in those patients with active disease was acquired and possibly induced by the tumor itself.

Studies of Macrophage Function in Mice With Neoplasms

To determine if neoplasms themselves could induce the alterations seen in human monocyte chemotaxis, we studied the effect of transplantable neoplasms on macrophage function in mice. We have previously shown that the intraperitoneal injection of phytohemagglutinin (PHA) in mice produces a delayed type of inflammatory reaction characterized by an accumulation of macrophages, which reach peak numbers between 24 and 48 hours after injection.[18] C3H mice implanted subcutaneously with any of three syngeneic neoplasms (hepatoma 129, lymphoma 6C3HED, BP8 sarcoma) or an allogeneic (129/J mice) teratocarcinoma were given injections of PHA 5 days after administration of tumor cells. Forty-eight

hours later, the mice were sacrificed, the peritoneal cavities lavaged, and the total and differential leukocyte counts determined on the individual exudates. The administration of the three syngeneic neoplasms dramatically depressed the accumulation of macrophages into the peritoneal cavities of mice in response to PHA injection (Table 3).[19] The implantation of the allogeneic teratocarcinoma, allogeneic spleen cells, syngeneic liver cells, or syngeneic spleen cells caused no depression of macrophage accumulation.[18,19] The *in vitro* chemotactic responsiveness [20] of the macrophages recovered from tumor-bearing animals was also depressed when compared to macrophages from normal mice.[18] The implantation of tumors in mice had no effect on the accumulation of polymorphonuclear leukocytes (PMNs) into the peritoneal cavity in response to either an intraperitoneal injection of PHA or endotoxin.[18]

To determine the mechanism of depression of macrophage function by neoplasms, the four tumors or normal liver and spleen tissues were sonicated and centrifuged, and the cell-free supernatants tested for inhibitory activity of macrophage accumulation *in vivo*. It was found that the supernatants of all neoplasms tested contained a soluble factor capable of

Table 2—Effect of Surgery on the Monocyte Chemotactic Responsiveness of Patients With Operable Tumors

Patient	Diagnosis	Pre-op MCR	Post-op MCR
JON	Melanoma	52.6	62.6
VOL	Melanoma	47.6	76.7
BRO	Melanoma	18.6	70.3
AW	Breast cancer	51.9	69.3
MB	Breast cancer	49.2	78.3
VP	Breast cancer	37.6	88.3
MP	Breast cancer	32.6	81.3
RW	Breast cancer	61.6	106.3
MW	Breast cancer	46.7	114.2
DB	Breast cancer	51.9	91.9
CMQ	Breast cancer	25.9	54.9
DM	Breast cancer	38.6	60.6
MW	Breast cancer	32.9	40.6
RH	Breast cancer	55.9	67.6
SW	Breast cancer	41.3	61.6
VC	Breast cancer	57.6	79.9
GW	Renal adenocarcinoma	21.3	83.3
AG	Renal adenocarcinoma	20.9	86.9
CF	Renal adenocarcinoma	57.6	91.9
Total (N = 19)	Mean ± SD	42.2 ± 13.6	77.2 ± 17.8
		$P < 0.0005$	
Patients with benign breast masses (N = 12)	Mean ± SD	72.0 ± 10.3	73.1 ± 13.7
		$P > 0.4$	
Normal controls (N = 98)	Mean ± SD	72.5 ± 13.5	

MCR = monocyte chemotactic responsiveness.

Table 3—Effect of Implantation of Neoplastic Cells and Their Soluble Products on Macrophage Accumulation *In Vivo**

Source of cells	No. of macrophages† ($\times 10^6$) recovered from peritoneal cavities of mice injected with			
	Intact cells‡		Dialysate§	
	Response	Percent inhibition‖	Response	Percent inhibition‖
Hepatoma 129	1.2 ± 0.3	76	0.4 ± 0.3	91
Lymphoma 6C3HED	1.5 ± 0.3	69	0.2 ± 0.3	96
Sarcoma BP8	1.4 ± 0.4	71	1.8 ± 0.4	62
Teratocarcinoma	3.9 ± 0.5	20	0.6 ± 0.5	87
Liver	5.1 ± 0.7	0	4.6 ± 0.9	2
Spleen	4.0 ± 0.4	18	4.7 ± 0.4	0
No cells	4.9 ± 0.6	—	4.7 ± 0.6	—

* Adapted from Snyderman and Pike.[19]

† The values represent the mean number ± SE of macrophages recovered from the peritoneal cavities 2 days after intraperitioneal injection of 35 μg of PHA into 5 normal mice or 5 mice previously injected in the thigh with the indicated cells or dialysates minus the number of macrophages recovered from the peritoneal cavities of mice similarly treated but not injected with PHA.

‡ Mice were injected subcutaneously with 2.5×10^6 of the indicated cells 7 days before they were killed.

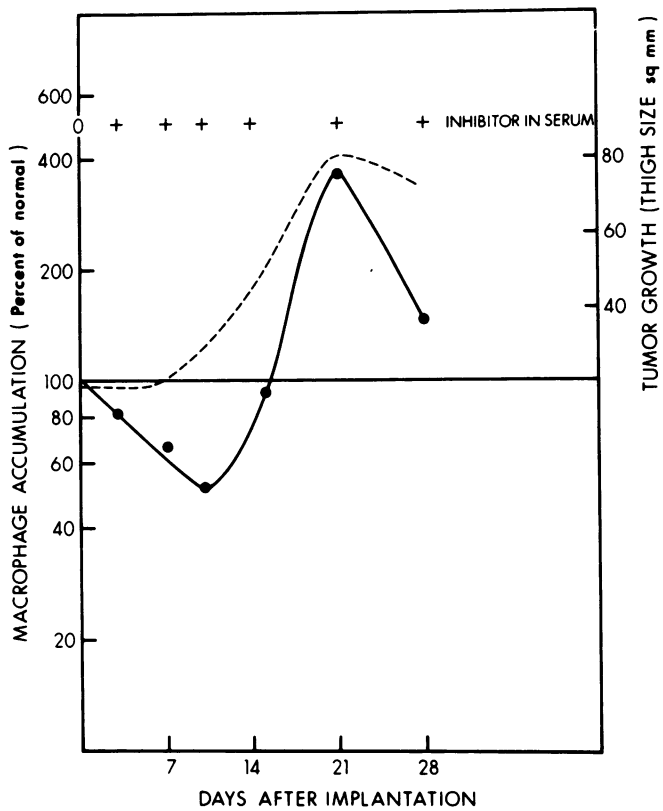
§ Dialysates were obtained by overnight dialysis of 2.5 ml of the supernatant of sonicated cells against 5 ml of RPMI 1640 and 0.2 ml of the indicated dialysate injected in the thighs of groups of 5 C3H mice 3 days before they were killed.

‖ Percent inhibition = $1 - (R_E/R_C \times 100)$ where R_E is the response of mice treated with cells or sonicates and R_C is the response of the control mice.

depressing macrophage accumulation *in vivo*.[19,21] In other studies, we found that the supernatants of sonicated neoplasms contained an inhibitor of macrophage chemotaxis *in vitro*.[19] The inhibitory activity contained in the tumor supernatants had an apparent molecular size of 6,000 to 12,000 daltons as judged by molecular sieve chromatography on Sephadex G-50.[21] To determine if murine neoplasms contained a low-molecular-weight factor capable of depressing macrophage accumulation *in vivo*, the cell-free supernatants derived from sonicated neoplastic cells or normal tissues were dialyzed overnight against twice their volume of tissue culture medium. The dialysates were injected subcutaneously into the thighs of mice. Twenty-four hours later, the mice were given an intraperitoneal injection of PHA and sacrificed 2 days later to determine the number of accumulated macrophages in the peritoneal cavities. The administration of the four tumor dialysates depressed macrophage accumulation in response to PHA by 62 to 96% (Table 3), in contrast to the injection of dialysates from sonicated normal tissues, which had no significant effect on macrophage accumulation.[19,21] The dialysate derived from as few as 10^4

hepatoma cells caused significant depression of macrophage accumulation in response to PHA, and the effect of the inhibitor lasted approximately 4 days following subcutaneous administration. Experiments were performed to determine the effects of the dialysate on the development and growth rate of tumors in C3H mice given injections of low numbers (10^3) of hepatoma 129 cells. The administration of 10^3 tumor cells contained in the hepatoma dialysate derived from 10^6 cells plus subsequent subcutaneous injections of the dialysate every 3 days increased the number of tumor takes from 63% to 100%.[21] The hepatoma dialysate also greatly enhanced the rate of tumor growth. These findings suggested that normal macrophage function is necessary for the efficient retardation of growth of small numbers of neoplastic cells.

We have recently investigated the prolonged effect of neoplasms on macrophage accumulation to determine if the depression seen early after tumor implantation continued throughout tumor growth.[22] In these studies, we also sought to determine if inhibitory activity for macrophage accumulation was detectable in the serum of tumor-bearing mice. Mice were implanted with 2.5×10^6 hepatoma cells subcutaneously in the thigh and at various times thereafter given intraperitoneal injections of either PHA, concanavalin A (con A), or no stimulant. The mice were sacrificed 2 days later, and the harvested macrophages tested for various functional activities. Serum was also obtained from unstimulated tumor-bearing and control animals throughout the study and frozen at −70 C until tested for the presence of inhibitory activity for macrophage accumulation in normal mice. The kinetics of the effect of tumor implantation on macrophage accumulation *in vivo* in response to PHA are shown in Text-figure 2. As can be seen, macrophage accumulation was depressed by Day 3 after tumor implantation and was maximal at Day 10 but rebounded to supranormal levels by Day 21.[22] The kinetics of depression of macrophage accumulation induced by con A was similar to that induced by PHA but occurred earlier and rebounded sooner. Maximal depression was 55% on Day 3 and reached supranormal levels by Day 14. Tumor implantation had no significant effect on the number of resident macrophages in the peritoneal cavities of mice given no inflammatory agent. In contrast to the depression of macrophage accumulation produced by tumor implantation, the *in vitro* phagocytic activity for sensitized sheep erythrocytes of macrophages recovered from mice bearing tumors was enhanced.[22] By 7 days after tumor implantation, phagocytosis by con A–induced cells was 130% of normal. Similarly, the phagocytic activity of PHA-induced macrophages from mice bearing tumors was 150% of normal at the time that



TEXT-FIGURE 2—Kinetics of tumor growth (*dotted line*), its effect on macrophage accumulation in response to PHA (*solid line*), and the appearance of macrophage accumulation inhibitory activity in the serum of tumor-bearing animals (+). Percent of normal = (No. of accumulated macrophages from mice bearing tumors)/(No. of accumulated macrophages from mice not bearing tumors) × 100.

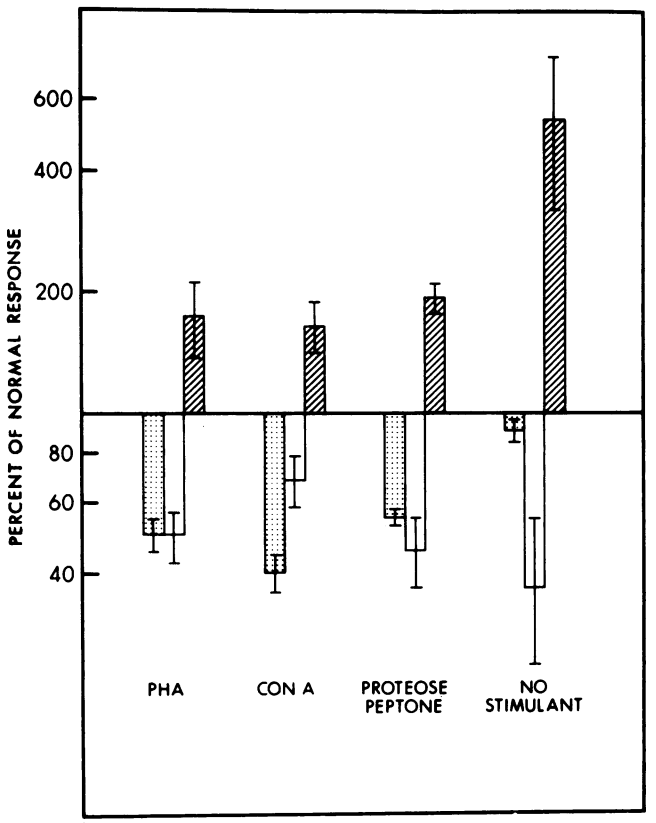
migration into the peritoneal cavity was maximally depressed. Resident peritoneal macrophages from tumor-bearing animals given no stimulant showed the greatest elevation of phagocytic activity (471% of normal at Day 10) compared with peritoneal macrophages from normal mice. The ability of macrophages from tumor-bearing animals to adhere to plastic was not significantly different from normal.[22]

To determine if inhibitory activity for macrophage accumulation was present in the circulation of tumor-bearing mice, serum removed at various times after implantation was diluted 1 : 4 in physiologic saline, and 0.2 ml injected into the thighs of normal mice. Serum drawn from mice before tumor cell implantation was used as a control. Twenty-four hours after injection of serum, the mice were given an intraperitoneal injection of PHA and 48 hours later sacrificed and peritoneal macrophage accumu-

lation determined. Serum obtained from mice before tumor implantation produced no inhibition of macrophage accumulation *in vivo*, but within 24 hours after receiving 2.5×10^6 neoplastic cells, as little as 0.05 ml of the serum obtained from these animals inhibited macrophage accumulation in normal mice by approximately 50%. Inhibitory activity in serum persisted in tumor-bearing animals throughout the entire period studied, despite the fact that macrophage accumulation in the mice rebounded to supranormal levels (Text-figure 2).[22]

To better characterize the effects of the dialysate from sonicated neoplastic cells on macrophage function *in vivo*, groups of mice were injected with the dialysate derived from 2×10^5 hepatoma cells or the equivalent amount of control tissue dialysates and 24 hours later were given intraperitoneal injections of PHA, con A, proteose peptone, or no stimulant.[23] Two or three days later, mice were sacrificed, the peritoneal cavities lavaged, and the number of accumulated cells determined. The recovered cells from mice within each group were then pooled and tested for phagocytic and chemotactic activities *in vitro* and for their ability to adhere to plastic. The administration of the dialysate *in vivo* depressed the accumulation of macrophages into the peritoneal cavity in response to PHA, con A, and proteose peptone when compared to animals treated with no inhibitor or with the control tissue dialysates. The dialysate had no effect on the number of resident macrophages recovered from the peritoneal cavities of mice receiving no intraperitoneal stimulant (Text-figure 3). The injection of the dialysate produced depression of the *in vitro* chemotactic responsiveness of macrophages from all groups of mice to zymosan-activated mouse serum.[23]

In contrast to the inhibition of migratory functions, the injection of the tumor dialysate resulted in enhancement of the ability of macrophages to phagocytize sensitized sheep erythrocytes *in vitro*. The most marked effect was seen in macrophages derived from the peritoneal cavities of mice given no inflammatory stimulant (Figure 3). This finding indicated that the hepatoma factor mimicked the action of implanted neoplastic cells during the initial phase of tumor growth. The injection of control tissue dialysates had no effect on the phagocytic activity of peritoneal macrophages from either stimulated or unstimulated mice. Since the method used for quantification of phagocytic activity depended on the ability of the cells to adhere to the plastic tissue culture plates, we examined the ability of ^{51}Cr-labeled macrophages from mice treated with the hepatoma factor to adhere to such plates following a 3-hour incubation. There was no significant difference in the adherence of macrophages derived from the animals treated with the hepatoma dialysate



TEXT-FIGURE 3—Effect of *in vivo* administration of the hepatoma filtrate (equivalent of 2×10^5 cells) on macrophage accumulation *in vivo* (*dotted columns*), chemotaxis *in vitro* (*open columns*), and phagocytosis *in vitro* (*hatched columns*). Mice were injected subcutaneously with the filtrate and 24 hours later were given intraperitoneal injections of PHA, con A, proteose peptone, or no stimulant. Forty-eight hours later, the mice were sacrificed, and the total and differential cell counts were performed on the peritoneal exudates from individual animals. The cells from mice within groups were then pooled and tested for *in vitro* chemotactic and phagocytic activity. Percent of normal response = (results obtained from mice receiving tumor filtrate)/(results obtained from mice not receiving tumor filtrate) × 100.

when compared to untreated animals or mice injected with control tissue dialysates, regardless of the inflammatory stimulant used.[23]

Discussion

The potential importance of macrophage function for surveillance against the development and spread of neoplasms is becoming increasingly well recognized. Macrophages have potent tumoricidal activity *in vitro*, and their influx into neoplasms *in vivo* can be associated with tumor destruction or increased resistance to metastasis.[5,7-9] Conversely, the inability of a host to rapidly mobilize macrophages to sites of neoplastic

transformation may render that host unable to suppress the development and spread of malignant tumors. Our studies [11,12,16,17] and the studies of others [13-15] have demonstrated that a large portion of humans with cancer *in situ* have abnormal monocyte chemotactic responsiveness. Of patients with abnormal responses, most have depressed chemotaxis but approximately one-fifth have elevated chemotaxis.[11,12] In patients with melanoma, abnormal monocyte chemotaxis is associated with a poor prognosis.[16] Since tumor removal in humans is associated with a rapid normalization of either depressed or elevated chemotaxis, and since patients with a history of cancer but no active disease have normal chemotaxis,[17] it appears that abnormal chemotaxis in cancer patients is secondary to the development of the neoplasm. Studies in mice have allowed a far better understanding of the effects of neoplasms on the host's macrophage function. During the early phases of tumor growth, before it becomes palpable, there is a dramatic depression in the animal's ability to mobilize macrophages to sites of inflammation, whether such inflammation is initiated with PHA or con A.[18,22] The defect in inflammation is cell specific in that granulocyte accumulation is normal.[18] Paradoxically, the resident macrophages recovered from the peritoneal cavities of mice during early tumor growth display markedly enhanced phagocytic activity but depressed chemotactic activity.[22] Similarly, macrophages from stimulated exudates have enhanced phagocytic activity and depressed chemotactic activity *in vitro* but to a lesser degree. During continued tumor growth, the accumulation of macrophages in response to inflammatory stimuli rebounds and becomes supranormal, while the enhanced phagocytic activity diminishes. The rebound in macrophage accumulation occurs despite the continued presence of a circulating factor(s) capable of depressing macrophage accumulation in normal animals. The biologic potency of this factor(s) is evidenced by the observation that only 0.05 ml of serum from a tumor-bearing mouse depresses macrophage accumulation in normal mice.[22] A low-molecular-weight factor from murine neoplastic cells reproduces all the phenomena seen *in vivo* during early tumor growth.[19,21,23] The biologic potency of this factor is evidenced by the fact that the dialysate from as few as 10^4 neoplastic cells produces a significant effect *in vivo*. Other workers have similarly noted depressed macrophage migratory ability in animals with tumors [24,25] and the presence of factors produced by neoplastic cells *in vitro* which inhibit macrophage accumulation and chemotaxis in normal animals.[26]

The paradoxic effects of neoplasms and their dialysates on different macrophage functions are of considerable interest. The data is consistent with the hypothesis that the tumor factor blocks the ability of blood

monocytes to migrate into areas of inflammatory stimuli and causes enhanced phagocytosis and depressed migratory ability of resident tissue macrophages. With time, the host's blood monocytes become refractory to the effects of the factor and, indeed, appear to develop enhanced chemotactic responsiveness.

The time at which the rebound of macrophage migratory function occurs suggests that it may be related to the development of specific T-cell immunity to the neoplasm.[27] Concomitant with this, the "nonspecific" activation of monocytes by T-cell products might make them resistant to the tumor factor(s). By this time, however, the neoplasm is too well established to be destroyed by normal immune mechanisms. The possibility that the factor selectively affects a subset of cytotoxic macrophages is fascinating but as yet unproven.

Regardless of the interpretation of the data in mice, these studies may provide an explanation for the findings of elevated as well as depressed monocyte chemotaxis in cancer patients and the association of abnormal chemotaxis with poor prognosis. During various phases of tumor growth, the host's monocyte-macrophage chemotactic response may first be depressed, then significantly elevated, signalling the continued presence of the neoplasm. These studies suggest that clinically apparent neoplasms may well be those which have developed the ability to subvert the host's native resistance to tumor development. Understanding the mechanisms by which neoplasms affect macrophage function may provide unique new methods to monitor and eventually control tumor growth.

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