Eur J Cancer Clin Oncol, Vol. 21, No. 1, pp. 119–125, 1985.
Printed in Great Britain.

0277-5379/85$3.00+0.00

Autochthonous Murine Tumors: Effects of Viral or Ultraviolet Induction, Immunogenicity and Transplantation on Intratumoral Macrophages and Systemic Inflammatory Responses*

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Abstract—*Macrophage tumoricidal activity requires a constant influx of macrophages but many transplanted cancers inhibit macrophage inflammatory responses. In this paper we address the issue of whether or not autochthonous tumors induced by either mammary tumor virus (MTV) in C3H/He mice or ultraviolet (u.v.) radiation in C3H/He or BALB/c mice also depress macrophage responses. Anti-inflammatory activity was not observed either prior to or during growth of these autochthonous tumors. Rather, the opposite was observed: strongly immunogenic u.v.-induced tumors which were rejected upon transplantation to syngeneic hosts had enhanced macrophage responses and more intratumoral macrophages than those mice whose tumors were transplantable. Transplantation of MTV-induced tumors selected for more aggressive tumors which had fewer intratumoral macrophages. In both MTV- and u.v.-induced tumors inflammatory responses of mice bearing serially transplanted tumors often differed from mice with autochthonous tumors. Our results demonstrate that anti-inflammation is probably not required for emergence and growth of these autochthonous tumors, that strongly immunogenic tumors may actually enhance macrophage responses and that the effect of tumor bearing on macrophage inflammation is a characteristic of the tumor, including its site and host of origin, its immunogenicity and its transplant generation.*

INTRODUCTION

COMPELLING evidence suggests that macrophages are anti-cancer cells [1, 2] but that the state of macrophage activation necessary for tumor killing is short-lived [3]. Thus a constant influx of macrophages is required to maintain the tumoricidal state [4]. However, tumor bearing depresses macrophage accumulation at inflammatory sites [5, 6]. As these anti-inflammatory effects were described originally for transplanted tumors, attention has focused on the relevance of these observations for autochthonous tumor growth.

Patients with cancer of diverse histologic types have decreased monocyte chemotaxis [7, 8] and polarization of normal monocytes is inhibited by carcinomatous pleural effusions of man [9]. Concordantly, mice bearing virally induced lymphoreticular neoplasms have decreased macrophage inflammatory responses [10, 11]. Macrophage responses are inhibited by the chemical carcinogen 3-methylcholanthrene and mice with defective macrophage responses have a higher incidence of tumors than mice with normal responses [12]. However, MCA-induced autochthonous tumors generally lack anti-inflammatory activity while transplanted tumors rapidly acquire this capability [12]. We report now on two additional autochthonous tumors. The rationale for examining a virally induced carcinoma was to determine if the previous observations made on hematogenous tumors were generally applicable to virally induced cancers of

Accepted 15 July 1984.
*Supportd by grants 3.603-80 from the Swiss National Science Foundation, FOR 183-AK-81 and 227-AK-82 from the Swiss Cancer League and CA 2251-07 from the National Cancer Institute, U.S.A.
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other histologic types. This experiment was performed with tumors induced in C3H/He mice by the Bittner mammary tumor virus. Ultraviolet light-induced tumors of skin were examined because these autochthonous tumors are strongly immunogenic [13] and it has been speculated that immunogenicity may be a factor in mediating tumor-associated anti-inflammation [14]. Further, the latent period for u.v.-induced tumors is shortened by silica treatment which depletes macrophages [15], lengthened by pyran copolymer activation of macrophages [15] and correlated with emergence of T suppressor (T_s) cells that appear to exert non-specific immuno-regulatory effects [16]. These observations suggested that u.v. light might depress macrophage responsiveness shortening tumor latency while the immunogenicity of the resulting tumor afforded an opportunity to examine the hypothesis that immune responses might be involved in tumor-associated anti-inflammation.

MATERIALS AND METHODS

Animals

Specific pathogen-free inbred BALB/c and C3H/He mice with and without milk-transmitted mammary tumor virus (MTV) were obtained from MRC Laboratory Animals Centre, Surrey, U.K. Experiments were begun when the mice were 3 months of age. Representative mice were tested and found free of lactic dehydrogenase (LDH) virus.

u.v. light-induced skin tumors

BALB/c and MTV-negative C3H/He mice both of male sex were irradiated according to the method of Kripke [13]. A total of four Westinghouse FS40 sunlamps arranged in two banks were used to deliver light over the wavelength range of 280 to 340 nm. The lights were 20 cm above the shelf holding the mouse cages. Mice were shaved with electric clippers once per week, removing hair from the tail to the nape of the neck and lateral to the midline. Mice were exposed three times per week for 1 hr.

Virus-induced mammary tumors

Milk-transmitted MTV induces tumors in about 70% of female mice. MTV-negative female mice which do not develop tumors were used as controls.

Tumor transplantantion

Tumor suspensions were prepared from disaggregated mammary tumors and transplanted to syngeneic C3H/He MTV negative mice by injecting 2×10^7 viable cancer cells s.c. into the lateral aspect of the thigh. u.v. light-induced skin tumors were transplanted as described by Kripke [13] in the manner used to determine the high antigenicity of these tumors. Autochthonous tumors were excised, washed, cut into 1-mm^3 fragments containing about 10^8 cells and transplanted s.c. into the thighs of syngeneic recipients by means of a trocar. Recipients were inspected weekly for evidence of tumor growth. Transplantation rejection was defined as no tumors in any of six recipient mice within 6 months of transplantation. Serial transplantation was performed similarly.

Tumor analysis

Tumor tissue was finely minced and disaggregated by incubating for 30 min in a mixture of 0.25% trypsin containing 20 μg DNase and 20 μg collagenase per g tissue. Then the tissue was passed through a fine meshed screen and the cells collected by centrifugation in a siliconized tube and washed twice. Differential cell counts were performed on cytocentrifuge-prepared slides stained with Wright's Giemsa. The content of intratumoral macrophages was determined by morphology and verified by histochemical staining for non-specific esterase.

Tumor immunogenicity

Tumors were transplanted to the thighs of syngeneic recipients and after the tumors were readily detectable they were excised. After a rest period of 8–10 days, groups of six mice each were rechallenged with increasing numbers of tumor cells in suspension. Concurrently, an equal number of uninoculated mice were challenged as non-immune controls. Mice were observed for up to 4 months for outgrowth of tumors. The dose of tumor cells that resulted in tumor takes in 50% of recipient animals was determined for each group. Immunogenicity was defined as the base 10 logarithmic difference in tumor dose required for 50% takes between control and tumor-excised rechallenge mice.

Quantitation of inflammation

Macrophage accumulation in the peritoneal cavity was measured 48 hr after injection of 200 μg of PHA-P (Difco Laboratories, Detroit, MI). Total cell yield was determined using a hemocytometer and differential cell counts made on cytocentrifuge-prepared slides stained with Wright's Giemsa. Macrophage yields were corrected for resident macrophages. Macrophage inflammatory responses in subcutaneous tissues were evaluated by the accumulation of macrophages on nitrocellulose filters [17]. The filters were removed after 48 hr, stained and the number of macrophages counted in ten oil immersion fields.

Statistics

Differences between two means were evaluated using Student's *t* test at a significance level of 0.05.

RESULTS

MTV-induced C3H/He mouse mammary carcinoma

This tumor arises between 6 and 12 months of age (peak incidence at 9 months) in mice infected with mammary tumor virus (MTV). We tested for the effect of the virus on macrophage responsiveness by comparing age- and sex-matched MTV-positive mice with cesarian section-derived, foster-nursed MTV-negative mice. Both groups of non-tumor-bearing mice were tested after 3, 6 and 9 months of age. As summarized in Table 1, MTV caused no alteration in macrophage accumulation either to s.c.-inserted nitrocellulose filters or to i.p. PHA-P. However, older mice in contrast to young mice had greater numbers of resident peritoneal macrophages and more macrophages responding to PHA-P.

Tumor presence was readily detectable by palpation and the inflammatory response of mice bearing autochthonous tumors was tested when tumors were first detected, intermediate in size and quite large. Age-matched MTV-negative mice were tested concurrently. Autochthonous mammary tumors did not alter macrophage inflammatory responses either to i.p. PHA-P or to s.c. inserted filters (Table 1). A separate group of tumor-bearing mice not tested for inflammation were examined for their content of intratumoral macrophages. The numbers of macrophages within tumors increased dramatically from around 11 million for small tumors to 186 million for large tumors, but this increase in macrophages was proportional to tumor growth as the ratio of macrophages to tumor cells did not differ between small-, intermediate- or large-sized tumors. Thus tumor bearing did not appear to alter the capacity of macrophages to respond to inflammatory stimuli either at a site distant to the tumor or within the tumor.

Tumors were transplanted to syngeneic, MTV-negative mice and the latent period prior to tumor detection declined upon successive transplantation. Further, the time to death for first generation tumors averaged 60 days while for fifteenth generation transplants it averaged 24 days. Excision-rechallenge tests revealed that the tumors were essentially non-immunogenic at generation 2 and that after 15 transplant generations they were only weakly immunogenic (+1). As summarized in Table 1, successively transplanted tumors did not inhibit macrophage

*Table 1. Macrophage inflammatory responses during induction and growth of autochthonous and transplanted virus-induced mammary tumours of C3H/He mice**

Mice with	Subcutaneous inflammation MTV-	Subcutaneous inflammation MTV+	Peritoneal Inflammation MTV-	Peritoneal Inflammation MTV+	Intratumoral macrophages ($\times 10^6$)
No tumors:					
3 months	79 ± 7	74 ± 9	52 ± 7	51 ± 6	
6 months	91 ± 8	99 ± 7	65 ± 7	61 ± 7	
9 months	91 ± 6	92 ± 8	79 ± 6‡	75 ± 8‡	
Autochthonous tumors					
Small (0.3 g)		96 ± 5		71 ± 1	11 ± 2 (7.5%)
Intermediate (1.7 g)		93 ± 3		70 ± 4	65 ± 9 (9.1%)
Large (4.2 g)		86 ± 6		65 ± 9	186 ± 28 (10.6%)
Transplanted tumors†					
Generation: 1		73 ± 8		66 ± 6	176 ± 22 (9.8%)
5		89 ± 9		76 ± 5§	132 ± 13 (8.4%)
10		90 ± 8		77 ± 4§	79 ± 9 (4.2%)
15		112 ± 5§		94 ± 1§	71 ± 13 (4.0%)

*Data are reported as mean ± S.E. on 6–12 determinations. Subcutaneous inflammation is reported as macrophages/oil immersion field and peritoneal inflammation as macrophage yield $\times 10^5$. Mean age of mice bearing autochthonous tumors was 8.6 months. Transplanted tumor bearers (age 3 months) were tested when tumors were between 3 and 5 g. Tumor bearing did not alter either the total or differential cell counts in the peripheral blood. MTV+ indicates mice infected with mammary tumor virus. MTV- indicates cesarian section-derived non-infected mice.

†Tumor immunogenicity was determined at generations 2 and 15. Tumor takes at generation 2 required 5×10^7 tumor cells in control and 1×10^8 in excision-rechallenged recipients (tumor immunogenicity ±) and at 15 it required 1×10^6 vs 1×10^7 tumor cells respectively (tumor immunogenicity + 1).

‡Significant difference between age 3 and 9 months.

§Significant difference between tumor bearers and age-matched MTV-negative non-tumor-bearing control mice.

inflammatory responses. In fact, after 15 transplantation generations macrophage responses actually were enhanced during late tumor growth. A similar effect was observed when tumor bearers were tested 2 days after transplantation. However, the content of intratumoral macrophages decreased from an average of 9.8% for first-generation tumors to 4.0% at the fifteenth generation. This decline in the percentage of intratumoral macrophages might be interpreted as a local inhibition of macrophage response to the tumor.

u.v. light-induced skin tumors

Ultraviolet light induces skin tumors in BALB/c and C3H/He mice after about 16 weeks of radiation treatment. In both mouse strains tumor incidence averaged 80%, with a mean latency of 32 weeks. During the latent period inflammatory responses were measured using s.c.-inserted nitrocellulose filters. Since only four filters could be inserted in the same anatomical region, half of the mice were tested between 2 and 12 weeks while the remainder were tested between 16 and 24 weeks. In irradiated C3H/He mice the macrophage inflammatory response over the belly was normal while the response on the back was consistently elevated (Table 2). In BALB/c mice macrophage accumulation on filters inserted over the belly was often depressed while the response was normal in the region of u.v. light exposure. We concluded that dorsal u.v. radiation did not depress macrophage responses in the region where tumors subsequently developed.

Nearly all tumors in C3H/He mice arose on the back whereas BALB/c tumors arose on both the back and ear at a ratio of 1.8:1. Inflammatory responses were tested when ear tumors reached 0.2- 0.6 g or when back tumors were 1-2 g. Each mouse was given an i.p. injection of PHA-P and 2 days later the yield of peritoneal macrophages was determined. The tumors were excised and transplanted to syngeneic recipients. Tumors arising on the back of C3H/He and BALB/c mice upon transplantation were rejected equally (39%) in both mouse strains. The data on inflammatory responses obtained in autochthonous hosts were collated based upon transplantation acceptance or rejection and are summarized in Table 3.

BALB/c mice bearing transplantable, autochthonous back tumors had normal inflammatory responses while mice whose tumors were rejected had significantly greater yields of elicited peritoneal macrophages. Nearly all tumors arising on the ear were transplantable and none altered macrophage responses. In C3H/He mice with autochthonous tumors the peritoneal exudate response was increased regardless of whether the tumors upon transplantation were accepted or rejected, but the difference was significant only for rejected tumors. However, the macrophage content of C3H/He transplantable tumors was significantly less than tumors which were rejected. We concluded that mice bearing autochthonous tumors whose immunogenicity was sufficient for transplantation rejection had increased macrophage inflammatory responses and a higher content of macrophages within their tumors. In contrast, mice bearing autochthonous tumors whose immunogenicity was sufficiently weak as to permit transplantation acceptance had normal macrophage inflammatory responses.

Randomly selected tumors were transplanted to 3-month-old syngeneic recipients and inflammatory responses measured after the tumors had reached 3-5 g. Tumors were transplanted through

*Table 2. Effect of dorsal u.v. radiation to BALB/c and C3H/He mice on inflammatory responses prior to tumor emergence**

Duration irradiation (weeks)	C3H/He mice: site of filter		BALB/c mice: site of filter	
	Belly	Back	Belly	Back
0 (control)	79 ± 4	76 ± 3	74 ± 6	77 ± 4
2	80 ± 6	70 ± 4	73 ± 7	105 ± 5‡§
4	86 ± 3	93 ± 6‡	68 ± 5	72 ± 6
8	82 ± 7	112 ± 6‡§	48 ± 5‡	79 ± 5§
12	80 ± 4	98 ± 7‡	47 ± 5‡	70 ± 7§
16-20	79 ± 7	N.D.	63 ± 8	69 ± 7
24-28	83 ± 6	N.D.	59 ± 4	71 ± 4

*Each experiment consisted of 24 irradiated mice and 12 control non-irradiated mice tested concurrently. Since the values for control mice did not vary during the course of the experiment, they are reported as one value. A separate group of irradiated mice were tested by filter placement only on the belly. Their response was identical to that reported above for the belly response of mice who also received filters on the back.

†Data are reported as macrophages/oil immersion field (mean ± S.E.).

‡Significant difference from non-irradiated control.

§Significant difference between belly and back.

15 generations and the results are summarized in Table 3. BALB/c mice that received tumors arising on the back had normal macrophage responses at all generations tested and these tumors were weakly immunogenic. In contrast, C3H/He mice that received back tumors had elevated macrophage responses and moderately immunogenic tumors. Upon serial transplantation, both the macrophage response and tumor immunogenicity increased. Recipients of the moderately immunogenic BALB/c ear tumors had normal macrophage responses at the first transplant generation but exhibited a 40% inhibition of macrophage responses and decreased tumor immunogenicity after 15 transplant generations. Thus inflammatory responses of mice with transplanted tumors did not always correspond to mice with autochthonous tumors. The transplanted tumors were associated with inhibited, normal or enhanced macrophage responses, depending upon site and mouse strain of tumor origin, transplant generation and tumor immunogenicity.

DISCUSSION

Impairment of macrophage inflammatory responses was not detectable in the autochthonous host during growth of either MTV-induced mammary carcinomas or u.v. light-induced skin tumors of mice. These results are concordant with plutonium-induced autochthonous tumors in rats which also do not depress macrophages [14]. Further, infection by an oncogenic virus (MTV) did not influence macrophage responsiveness prior to tumor emergence. While u.v. radiation depressed macrophage responses over the belly of BALB/c mice, these responses were normal in C3H/He mice but increased over the radiation-exposed back. The yields of thioglycollate-elicited peritoneal macrophages are reportedly normal in mice receiving 2 or 4 months of u.v. radiation [18]. Thus inhibition of macrophage responses is probably not measurable either during induction or growth of MTV- or radiation-induced autochthonous tumors. These results contrast with other studies in which autochthonous tumors are associated with macrophage impairment including histiocytic lymphoma in SJL/J mice [10], T cell leukemia in AKR mice [11] and human cancers of various types as measured by skin abrasion, monocyte chemotaxis, monocyte maturation or monocyte polarization [7–9, 19, 20]. Collectively, the data suggest that autochthonous tumors differ in their effects on macrophages which may reflect the host of origin, the type of test employed, the mechanism of tumor induction, tumor immunogenicity and type of cancer produced.

Studies with MTV were initiated to determine if virally induced carcinomas compromise macrophage responses similar to lymphoreticular

Table 3. Macrophage inflammatory responses in mice bearing u.v. light-induced autochthonous and transplanted tumors

Determination	BALB/c mouse tumors: origin and transplantation			C3H/He mouse tumors: origin and transplantation	
	Back rejected	Back accepted	Ear accepted	Back rejected	Back accepted
Autochthonous tumors					
Incidence	12	20	18	11	16
Latency (months)	8.0	8.6	7.2	8.1	8.0
Macrophage content	N.D.	N.D.	N.D.	16 ± 3%	6.5 ± 1.5%†
Peritoneal inflammation* in mice with:					
No tumors (age 11 months)	38 ± 4	41 ± 3	41 ± 3	71 ± 4	71 ± 4
Autochthonous tumors	53 ± 3‡	41 ± 5	41 ± 7	93 ± 5‡	85 ± 7
No tumors (age 3 months)		41 ± 3	41 ± 3		42 ± 4
Transplanted tumors					
Generation 1		34 ± 5	48 ± 6		59 ± 6‡
Generation 15		40 ± 5	29 ± 3‡		78 ± 7‡
Tumor immunogenicity					
Generation 2		+2	+3		+3
Generation 15		+1	+1		+6

*Peritoneal inflammation is reported as macrophage yield × 10^5. Mice received u.v. radiation treatment beginning at 3 months of age. Tumors appeared at a mean age of 11 months and were transplanted to non-irradiated syngeneic recipients of age 3 months. Data were obtained when tumors were 3–5 g in size.
†Significant difference from tumors which were rejected.
‡Significant difference from non-tumor-bearing control.

neoplasms. Since they did not, one interpretation of the results relates to the fact that histiocytic lymphomas of SJL/J mice and T cell leukemias of AKR mice are caused by type C oncornoviruses that contain the low-molecular-weight hydrophobic envelope protein p15E whereas MTV is a type B virus lacking p15E. p15E is immunosuppressive [21] and has been identified as the anti-inflammatory component present in extracts of Friend, Moloney and Rauscher viruses [22]. However, extracts of MTV are not anti-inflammatory [22] and these results are consistent with our data on intact animals infected with MTV. Cianciolo *et al.* [23] reported anti-inflammatory activity in the plasma, urine and homogenates of MTV-induced mammary tumors but similar preparations from our animals failed to show anti-inflammatory activity.

Although p15E has anti-inflammatory activity, it is not the only mediator of anti-inflammation associated with tumor bearing. For instance, mice bearing P-815 mastocytoma cells exhibit anti-inflammation directed against macrophages [24] but these cells failed to react to a monoclonal antibody against p15E [25] and tumor-associated anti-inflammatory factors have been isolated with molecular weights less than 2000 [26]. Since some of these factors may be of host rather than tumor origin, a relationship between immunogenicity and anti-inflammation has been suggested. Nolibe *et al.* [14] observed that plutonium-induced pulmonary tumors were neither detectably immunogenic nor associated with anti-inflammation and we observed that chemically induced tumors acquire anti-inflammatory activity upon transplantation analogous to the increased immunogenicity associated with tumor transplantation [12].

If an immunogenic cancer is required for macrophage impairment, we reasoned that the strongly immunogenic u.v.-induced tumors of skin should impair macrophage responses. However, mice whose tumors were rejected upon transplantation had enhanced elicited peritoneal macrophage responses and a higher content of intra-tumoral macrophages than those mice whose tumors were transplantable. Thus strong tumor immunogenicity appears to be associated with enhanced, not impaired, macrophage responses.

Upon serial transplantation, u.v.-induced ear tumors in BALB/c mice acquired anti-inflammatory activity similar to results reported for chemically induced tumors [12]. This behavior does not appear to be due to viral contamination during transplantation or a laboratory artifact since BALB/c recipients of serially transplanted u.v.-induced back tumors had normal inflammatory responses. Further, macrophage responses were enhanced with serially transplanted u.v.-induced back tumors in C3H/He mice but the same mouse strain serially transplanted with mammary tumors had normal responses.

In conclusion, we have shown that mice infected with MTV or bearing autochthonous mammary tumors do not have depressed macrophage inflammatory responses, suggesting that not all oncogenic viruses inhibit macrophages and that the latter is not a universal requirement for tumor growth. Secondly, we have demonstrated that strong tumor immunogenicity such as exists in u.v. light-induced autochthonous skin tumors may enhance macrophage responses despite progressive tumor growth. Thirdly, serial transplantation can result in tumors with anti-macrophage effects which are not laboratory artifacts since different tumors arising in the same mouse strain behave differently upon transplantation to syngeneic recipients.

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