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Original Paper

Spontaneous Development of Plasmacytomas in a Selected Subline of BALB/cJ Mice

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Sixty per cent of BALB/cAnPt mice injected intraperitoneally (i.p.) with tetramethylpentadecane (pristane) develop plasmacytomas (PCs), whereas less than 10% of BALB/cJ develop such tumours. Most other mouse strains are completely resistant. Resistance is dominant over susceptibility in F1 hybrids between BALB/cAnPt and the resistant non-BALB/c strains, suggesting that susceptibility may be due to some genetic defect. (BALB/cAnPtxBALB/cJ)F1 hybrids have a PC incidence of 36–42%. Previously, BALB/cJ has been shown to harbour at least one resistance gene (Potter *et al.*, *Genomics* 1988, Vol. 2, pp. 257–262). On the assumption that BALB/cJ may contain a segregating resistance gene, we crossed BALB/cJ females with pristane-pretreated BALB/cJ males that were found to be carrying PC cells intraperitoneally 5–7 months after pristane treatment. After two selective crosses, 62% of the BALB/cJ subline BALB/cM2/22 developed PC after pristane and 52% after pristane followed by Abelson virus, while unselected controls had an incidence of 11% and 0%, respectively. Moreover, six spontaneous plasmacytomas developed in untreated females of the selected colony. Five of these carried T(12; 15)(F2; D2/3) translocations. The sixth had a T(1; 10)(G; C1) translocation and an interstitial duplication of segment (C1/E3) on one chromosome 5. It may be concluded that pristane treatment is not a prerequisite for the induction of the PC associated Ig/*myc* translocations. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: spontaneous murine plasmacytomas, BALB/cJ mice

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INTRODUCTION

ONLY VERY few mouse strains are susceptible to plasmacytoma (PC) induction by the intraperitoneal implantation of non-metabolisable foreign materials such as pristane, plastics or silicone gel [2, 3]. BALB/c has been the most extensively studied among the susceptible strains. Susceptibility to PC induction varies among BALB/c substrains [4]. Sixty per cent of BALB/cAnPt mice have been reported to develop PC after three 0.5 ml pristane inoculations, whereas less than 10% of BALB/cJ develops PC after the same treatment [5]. BALB/cAnPtxBALB/cJ)F1 hybrids show a PC incidence between 36% to 42% [6]. Most other mouse strains are completely resistant. Resistance is dominant over susceptibility in F1 hybrids between BALB/cAnPt and the resistant non-BALB/c strains, suggesting that susceptibility may have a genetic basis. The mechanism of action of the susceptibility gene is unknown. It has been shown that BALB/cAnPt is defective in the repair of UV damaged 5′ end of c-*myc* [7], and that, in contrast to BALB/cJ, is unable to remove X-ray induced double strand DNA damage *in vitro* [1]. It has been suggested that this may be related to the proneness of BALB/cAnPt to generate Ig/*myc* translocations [1, 7].

Studies on the incidence of PC in backcross and recombinant inbred mice derived from susceptible BALB/c and resistant DBA/2 mice have indicated that resistance and susceptibility are under the influence of several genes [4, 8]. At least two genes have been localised to the distal end of chromosome 4 [9, 10]. Another gene influencing PC susceptibility may be linked to the *Fcgr2* gene in the distal portion of Chr 1 [10].

The presence of pristane in the peritoneal cavity has been shown to create a favourable environment for PC development [11, 12]. Potter and associates [13] have suggested that pristane may facilitate PC development by increasing

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the frequency of chromatin damage. However, this could hardly apply to the inducing effect of other foreign bodies, such as silicone gel or plastic diffusion chambers. An additional or alternative hypothesis stressed the probable role of the foreign body granuloma induced by these agents in the peritoneal cavity. This could act by the release of growth factors and/or by the release of oxidative radicals from the inflammatory cells. The mutagenic effect of the latter might increase the incidence of illegitimate recombinations.

In this study, we describe the selection of a highly PC susceptible BALB/cJ subline by repeated crossing of BALB/cJ females with pristane-treated BALB/cJ males that were diagnosed to have incipient PC cells intraperitoneally 7–8 months after pristane injection.

MATERIALS AND METHODS

BALB/cJ mouse breeding

BALB/cJ pairs were purchased from The Jackson Laboratories (Bar Harbor, Maine, U.S.A.) in the early 1980s. Our BALB/cJ colony was maintained by continuous brother x sister crossing in our animal facility. Randomly chosen 3–4 months old females were mated with pristane-pretreated 8–10 month old BALB/cJ males that showed PC cells intraperitoneally (around 5–7 months post-pristane injection). A proportion of the progeny aged 2–3 months was treated with 3 x 0.3 ml pristane injections or with 0.3 ml pristane + 0.5 ml supernatant containing A-MuLV virus (10^5 focus forming units) and observed for tumour development for 10 months from the first pristane injection. Pristane-treated young males, that were found to carry PC cells in their peritoneal cavity, were crossed with their own untreated sisters. The new substrain was designated BALB/cM2/22. The cumulative PC incidence following pristane or pristane + A-MuLV treatment was compared with the incidence in the parallel unselected subline of BALB/cJ mice after two generations.

Development of spontaneous tumours and diagnosis

A proportion of the progeny from the test-matings and from the control matings received no treatment and were kept under observation for up to 20 months. Six of the 89 untreated mice in the selected group, and none of the 98 unselected BALB/cJ mice, had enlarged abdomens at ages between 5 and 19 months. They were examined by palpation and exploratory paracentesis. Cytosmears were prepared from the ascites or from tumour cell suspensions recovered from sacrificed mice. The ascites was obtained with a 25 gauge needle attached to a 2 ml syringe containing balanced salt solution (BSS) enriched with 5% fetal calf serum (FCS). Cell suspensions were prepared from enlarged spleen or from intraperitoneal tumour masses by mashing the tissue through a metallic net. Cytosmears were prepared and stained with May-Grünwald-Giemsa. Histopathological diagnosis followed the criteria described previously [14]. At least 15–20 characteristic PC cells were counted per smear.

Cytogenetic analysis

Chromosomes were prepared from ascites or from tumour cell suspensions obtained from primary tumour carrying mice. A conventional trypsin Giemsa banding method was used to identify individual chromosomes according to the criteria specified by the Committee on Standardised Genetic Nomenclature for Mice [15]. At least 10 G-banded metaphase plates per tumour were karyotyped.

Immunoglobulin detection

Supernatants from ascites or from overnight cultured tumour cell suspensions were tested for immunoglobulins by using a mouse Ig-typing kit (Amersham, Sweden).

Tumorigenicity

Primary tumours were transplanted i.p. into two untreated and two pristane-pretreated syngeneic recipients. The pretreated mice received 0.3 ml i.p. 3–4 weeks prior to the inoculation. Each mouse received 2 ml of inocula containing 10^7 tumour cells. Mice that failed to develop tumours within 2 months after inoculation were considered negative.

DNA extraction and Southern blot

High molecular weight DNA was prepared from ascitic PC cells and/or from excised tumour tissue according to Sambrook and associates [16]. DNA extracted from the spleen of an untreated BALB/c mouse was used as control. The DNA was cleaved with *Eco*RI, agarose gel electrophoresed and transferred to Amersham Hybond-N membranes. The membranes were washed twice at room temperature with 2 x SSC, 0.1% SDS for 30 min and twice at 65°C with 0.2 x SSC, 0.1% SDS for 30 min and further hybridised as previously described [17]. A [^{32}P]-labelled *c-myc* exon 3 fragment (300 bp) was used as probe. The membranes were exposed to Fuji X-ray film.

RESULTS

PC incidence after pristane treatment

Table 1 shows the cumulative tumour incidence after the injection of pristane (TEPC), and pristane followed by Abelson virus (ABPC) in first and second generation descendants from two pristane-treated males (BALB/cM2 and BALB/cM34), in comparison with the unmanipulated subline. The total incidence of TEPC tumours was 62% in the selected mice, compared to 11% in the unmanipulated subline. This difference is of the same magnitude as between the relatively susceptible BALB/cAnPt and the relatively resistant BALB/cJ subline. The total incidence of ABPC tumours was 52% in the selected and 0% in the unmanipulated mice. The incidence of ABPC tumours in the selected subline was much higher than the usual ABPC incidence (approximately 20%) in the susceptible BALB/cAnPt mice [18]. The TEPC tumours developed after shorter latency periods in the selected compared to the unselected subline. The higher PC-susceptibility of the selected subline is further emphasised by the appearance of spontaneous plasmacytomas in the selected, but not in the unselected subline, as described below.

Tumour development in untreated mice

Six untreated mice of the selected BALB/cM2/22 subline developed PCs, described below (Table 2). A sixth mouse (a 16 month old female) had haemorrhagic ascites containing a few plasmacytoma cells, but no tumour tissue was found.

SMPC-1. An untreated, 6-month old BALB/c female had an enlarged abdomen 3–4 weeks after the third normal delivery, but no palpable fetuses. Haemorrhagic ascites was

Table 1. Tumour incidence and latency periods in descendants from pristane-pretreated BALB/cJ males (M2 and M34) and from untreated BALB/cJ males (control)

		TEPC*			ABPC†			
		Incidence		Latency	Incidence		Latency	
Pristane-pretreated male	Progeny generation	I‡	(%)	PP§	I	(%)	PP	PV‖
BALB/cM2	1	10/18	(56%)	185 ± 45	4/10	(40%)	64 ± 13	42 ± 13
	2	9/24	(38%)	82 ± 19	6/14	(43%)	80 ± 16	58 ± 20
BALB/cM34	1	13/15	(87%)	213 ± 53	8/10	(80%)	66 ± 14	47 ± 17
	2	12/14	(86%)	171 ± 47	8/16	(50%)	67 ± 16	47 ± 16
Cumulative		44/71	(62%)	163 ± 66	26/50	(52%)	126 ± 70	104 ± 70
Control		4/35	(11%)	241 ± 45	0/15	(0%)		

*Tumours induced by 3 × 0.3 ml pristane i.p. injections. †Tumours induced by pristane (0.3 ml) + A-MuLV virus (10^5 focus forming units). ‡No. of tumours/no. of mice. §Days after first pristane injection (X ± S.D.). ‖Days after A-MuLV infection.

present, containing large plasmacytoid cells with intensely blue stained cytoplasm and eccentric non-pyknotic nuclei with a clear perinuclear zone (hof), detected on cytosmears (Figure 1).

SMPC-2A and SMPC-2B. A 5-month old BALB/c female developed ascites that contained a high concentration of PC cells. The autopsy revealed tumour masses dispersed in the omentum that resembled a granuloma macroscopically. The uterus was slightly enlarged and contained a yellow (egg-yolk like) fluid. The smears from the intrauterine liquid revealed exclusively PC cells. Cell suspensions prepared from omental tumour masses + ascites (SMPC-2A) as well as a cell suspension prepared from intrauterine fluid (SMPC-2B) were transplanted independently.

SMPC-3. An 18-month old female (littermate of the female that developed SMPC-1), developed ascites. Large numbers of lymphoma and PC cells were found on cytosmears in the peritoneal fluid, with very few macrophages. The mouse was very ill and was sacrificed. On autopsy, extensive tumour masses were observed, dispersed in the peritoneal cavity, together with focal enlargement of Peyer's patches on the intestinal wall.

SMPC-5. A 19-month old female had a palpable spleen without ascites. The mouse was sacrificed and the autopsy revealed many white spots covering the surface of the spleen. The smear prepared from the spleen revealed very few enlarged plasmacytoid cells and a predominance of lymphoma cells. Spleen cell suspensions were inoculated i.p. into two pristane-pretreated BALB/c females. Haemorrhagic ascites developed after 30 days. After 2 sequential passages, the ascites contained a mixture of lymphoma cells and characteristic plasmacytoma cells. During further passages, the PC cells overgrew the lymphoma cells.

SMPC-6. An 11.5-month old female showed progressive accumulation of ascites that contained PC cells. On autopsy, tumour masses were found in the ventral wall of the peritoneal cavity.

Other spontaneous tumours

Two spontaneous B lymphomas were diagnosed by histological and immunological methods in the selected subline: *SLy-BALB-1* lymphoma was isolated from the enlarged spleen of an 8-month old BALB/c female and *SLy-BALB-2* lymphoma compromised the mesenteric lymph nodes of an untreated 12-month old BALB/c female.

Cytogenetic analysis

The cytogenetic results (Table 2) revealed the presence of reciprocal T(12; 15)(F2; D2/3) translocations in SMPC-1,

Table 2. Histomorphology and main cytogenetic changes of spontaneous BALB/c plasmacytomas

Tumour	Mouse sex/age*	Site of tumour	Histomorphology	Cytogenetic abnormalities
SMPC-1	F/203	Ascites	Plasmacytoma	rcpt(12;15), Ts11 (Hyperdiploid)
SMPC-2A	F/157	Ascites	Plasmacytoma	rcpt(12; 15) (Diploid)
SMPC-2B	F/157	Uterus	Plasmacytoma	rcpt(12; 15) (Diploid)
SMPC-3	F/569	Mesenteric granuloma	Lymphoma + plasmacytoma	T(1; 10), Ts5 (Near tetraploid)
SMPC-5	F/594	Spleen	Lymphoma + plasmacytoma	rcpt(12; 15), Ts 11, Ts1 (Hyperdiploid)
SMPC-6	F/345	Ascites	Plasmacytoma	rcpt(12; 15), Ts 11 (Hyperdiploid)

*Age (days) at the time of histological diagnosis.
F, female; rcpt, reciprocal.

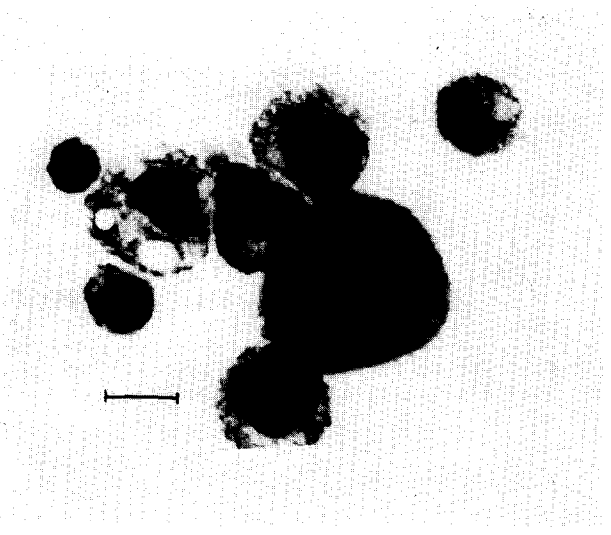

Figure 1. Characteristic plasmacytoma cell on a May-Grünwald-Giemsa stained smear prepared from ascites of a primary spontaneous plasmacytoma carrying mouse (bar, 10 μ).

Table 3. Transplantability of spontaneous plasmacytomas and a spontaneous B-cell lymphoma to pristane-treated and untreated syngeneic mice

Tumour	Transplant generation	Tumour frequency in transplant recipients: Pristane-treated*	Untreated†
SMPC-1	0‡	2/2	0/2
	1	2/2	
SMPC-2A	0	2/2	0/2
SMPC-2B	0	2/2	0/2
	1	2/2	
SMPC-3	0	2/2	0/2
	1	2/2	
SMPC-5	0	2/2§	0/2
	1	2/2§	
	2	2/2	
SMPC-6	0	2/2	0/2
	1	2/2	
SLy-BALB-1	0	2/2	2/2
	1	2/2	2/2

*Pristane (0.3 ml) i.p. 2–4 weeks prior to the inocula. †Observation period was 2–3 month postinoculation. ‡Cell suspensions from primary tumour. §Mainly B-cell lymphoma cells were observed in the early passages.

SMPC-2A, SMPC-2B, SMPC-5 and SMPC-6. The karyotype of SMPC-3 showed two chromosome markers—one was a T(1; 10)(G; C1) translocation [the reciprocal T(10; 1) was missing], while the other marker arose by interstitial duplication of the (C1/E3) segment on one chromosome 5. This segment was thus represented in three copies (Figure 2). No MPC associated translocations were detected in SMPC-3. The tumour SLy-BALB-1 was tetraploid (data not shown).

Immunoglobulin production

SMPC-1 and -6 produced $IgG_3\kappa$. The two SMPC that derived from a single mouse produced different immunoglo-

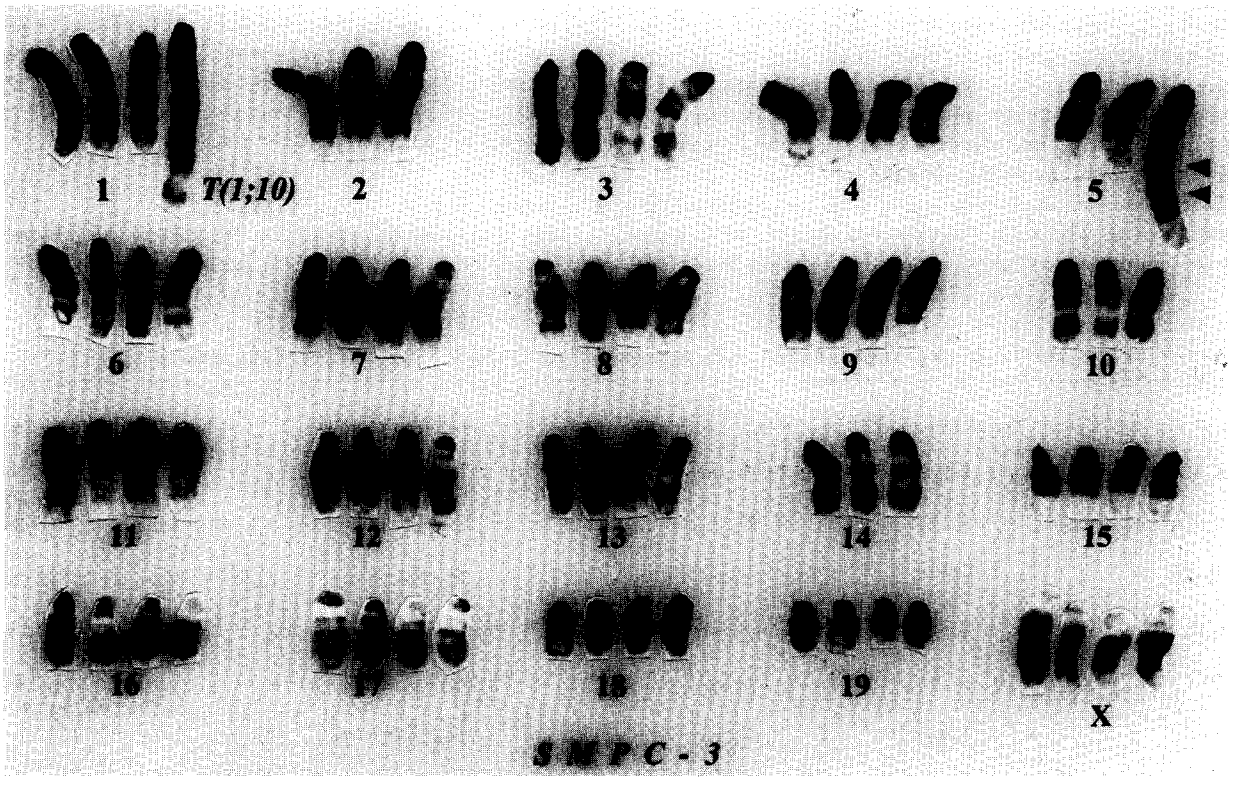

Figure 2. A representative G-banded karyotype of a spontaneous plasmacytoma (SMPC-3) carrying a T(1; 10)(G; C1) translocation and an interstitial duplication of the (C1/E3) segment on one chromosome 5 (arrows).

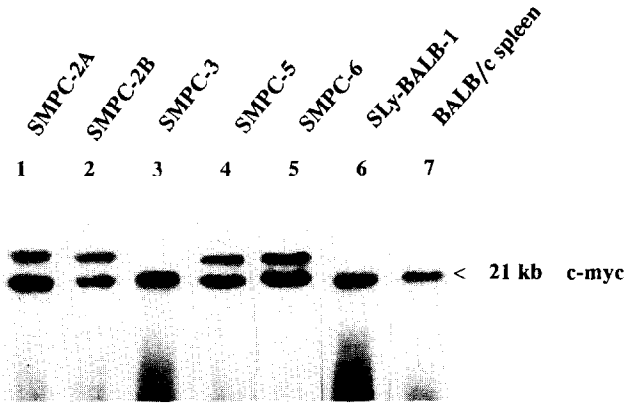

Figure 3. Southern blot of *Eco*RI-cleaved DNA from spontaneous plasmacytomas SMPC-2A, SMPC-2B, SMPC-3, SMPC-5, SMPC-6, and from spontaneous lymphoma SLy-BALB-1. Spleen DNA from a normal BALB/c mouse was used as control (lane 7). 21 kb = germ line c-*myc* band.

bulins; SMPC-2A produced $IgG_{2a}\kappa$ and SMPC-2B produced $IgG_{2b}\lambda$, suggesting independent clonal origin. SMPC-3 and 5 produced $IgG_{2a}\kappa$.

Growth and tumorigenicity

Table 3 shows the results of the tumorigenicity test in pristane-pretreated and untreated recipients. All tumours grew in pristane-pretreated mice. The same inocula of 10^7 cells failed to grow in untreated syngeneic mice. Transplanted cells from SLy-BALB-1 grew in both treated and in untreated syngeneic mice.

*Rearrangement of c-*myc *gene*

Five spontaneous plasmacytomas were analysed for c-*myc* rearrangement by Southern blotting. *Eco*RI-cleaved DNA was hybridised with a c-*myc* exon 3 probe. The probe detects a 21 kb c-*myc* germline band in the control sample (Figure 3, lane 7). A clearly re-arranged band was identified in SMPC-2A, SMPC-2B, SMPC-5 and SMPC-6 tumours. Both SMPC-3 and SLy-BALB-1 lacked PC translocations and showed only the 21 kb c-*myc* germline band.

DISCUSSION

Susceptibility to PC induction varies among BALB/c substrains. Sixty per cent of BALB/cAnPt mice have been reported to develop PCs after three 0.5 ml pristane inoculations, whereas less than 10% of the BALB/cJ substrain develops PCs after the same treatment [4]. Susceptibility has been determined by assessing the incidence of PCs that appeared within one year after the start of the treatment [5, 6].

Earlier findings in EμIL-6 transgenic mice indicated that BALB/c mice are genetically prone to generate Ig/*myc* translocations [19]. In C57BL/EμIL-6 transgenic mice, benign plasmacytosis but no plasmacytomas have been observed [20]. IL-6 is known to stimulate plasmacyte proliferation. In the construct used, it was linked to an immunoglobulin heavy-chain enhancer and was thus expressed in the entire B-cell system. When the BALB/c genetic background was introduced into these mice, by one F1 cross and one subsequent backcross to BALB/c, plasmacytomas appeared that had rearranged c-*myc* genes and typical Ig/*myc* translocations [19].

Juxtaposition of c-*myc* and the IgH-switch has been detected by a PCR assay in preneoplastic lesions of pristane-treated BALB/cAnPt mice, 30 days after pristane administration [21, 22] and more recently in the Peyer's patches of untreated BALB/cAnPt mice (unpublished data). This suggests that the Ig/*myc* translocation is an early initiating step in the genesis of PC. Interestingly, the incidence of PCR-detected translocations in preneoplastic tissue (8/20 mice, 40%) was clearly higher than the incidence of PCs (20%), both obtained after a single pristane injection. This suggests that the translocation may not be sufficient by itself to generate autonomous tumours but additional changes may be required. A similar conclusion was previously reached [23] on the basis of similar experiments with Eμ-*myc* transgenic mice. Even though these mice developed 90–95% lymphomas, the tumours were mono- or oligoclonal, consistent with a requirement for additional genetic changes. As such, it is noteworthy that three of our SMPCs were characterised by trisomy 11, also detected in pristane or pristane + Abelson virus induced PCs [24]. The mechanism by which this trisomy appears to be selectively favoured during PC development is not known.

The physiological mechanism responsible for BALB/c susceptibility to PC induction has not been clarified. In an earlier study, we exposed reciprocal BALB/c ↔ DBA/2 chimeras to pristane alone or combined with Abelson virus and found that PCs arose exclusively from BALB/c cells in both reciprocal combinations. This was taken to indicate that at least part of PC susceptibility was determined at the level of the target cell itself [14]. The relevant genetic variable may be the propensity of the cells to undergo Ig/*myc* translocations. Alternatively, this could be one of several relevant factors. It has been suggested that BALB/c B lymphocytes have a deficient DNA repair mechanism, as indicated by the rapid removal of UV-induced DNA damage in the c-*myc* locus in splenic B lymphoblasts derived from DBA/2N, but not in B lymphoblasts from BALB/cAn mice [7]. If so, translocations would also be expected to occur spontaneously. In previous studies, we have found that *in vitro* A-MuLV infected BALB/c spleen cells, transferred into pristane-treated syngeneic recipients, give rise to donor type PCs after a short latency period [25]. We concluded that translocation carrying cells may pre-exist in untreated BALB/c mice [25]. Our finding of spontaneous plasmacytomas with different translocations that have arisen in untreated BALB/c mice, aged between 6 and 19 months, is consistent with this pattern.

Spontaneous B-cell lymphomas have been described in old BALB/cAn mice [26, 27]. Slavin and Strober [28] described a spontaneous B-cell leukaemia (BCL_1) that had arisen in the spleen of a 24-month old BALB/c female. After transplantation, BCL_1 tumour cells grew in neonatal and sublethally irradiated (500 r) mice, but not in untreated adult BALB/c mice. An *in vitro* cell line established from this tumour secreted IgM and showed a reciprocal T(4; 15) translocation. The 15D2/3 breakpoint was consistent with the site of the c-*myc* gene in the typical T(12; 15) translocation [29].

All SMPCs carried T(12; 15) translocation, except one which carried a T(1; 10)(G; C1) translocation. It may be noted that a PC resistance gene has been mapped linked to the *Fcgr-2* gene that resides in the 1G breakpoint region on Chr 1 [10]. Two other genes located in the region affected by this translocation, namely *c-myb* and *mdm-2* on Chr 10, were not rearranged on Southern blot analysis (data not shown). The significance of this translocation is under further investigation.

Ig/*myc* translocations, homologous to those seen in murine PCs and differing only with regard to minor detail, have been found in human Burkitt's lymphoma and spontaneous rat immunocytoma. These tumours develop spontaneously in the absence of any introduced, external agent. It is, therefore, hardly surprising that spontaneous PCs can occur in untreated BALB/c mice.

The high frequency of pristane-induced PCs in our BALB/cM2/22 subline suggests that we may have selected a new or a pre-existing mutant from the original BALB/cJ population. The BALB/cM2/22 subline had a highly increased incidence of pristane-induced PCs (62%), and in addition developed six spontaneous PCs that appeared in female mice aged 4–19 months. The fact that they have arisen without the introduction of pristane or other foreign bodies into the abdominal cavity argues against two frequently held ideas: (i) that pristane is required to induce DNA damage, e.g. by favouring the generation of reactive oxygen radicals released by inflammatory cells, and (ii) that pristane or other foreign bodies are needed to induce an intraperitoneal granuloma that promotes PC development through the release of growth factors and lymphokines. Our finding of six spontaneous plasmacytomas in untreated BALB/c mice does not support the first of these two ideas, and is consistent with the occurrence of Ig/*myc* translocations in untreated BALB/c mice (unpublished data). It also shows that the cells may progress to fully fledged plasmacytomas in the absence of an induced granuloma.

The spontaneous PCs were not fully autonomous, as shown by the fact that they were transplantable to pristane-pretreated but not untreated syngeneic recipients. A similar phenomenon has been observed previously in plasmacytomas generated in IL-6 transgenic mice with a BALB/c background that were only transplantable to pristane pretreated BALB/cA-*nu/nu* mice [19]. This indicates that a tumour-promoting micro-environment, not reproduced in the peritoneal cavity of untreated syngeneic mice, may be required for spontaneous PC development. In the EμIL-6 transgenic mice, IL-6 (produced by the transgenic) may be the relevant factor. In our case, some conditioning factors may be provided by the peritoneal environment of ageing females but not males.

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