การเกิดมะเร็งต่อมน้ำเหลืองและมะเร็งพลาสมาไซโตมาในหนูเอสทีเอสเอ จากการกระตุ้นโดยพริสเตนและไวรัสวีเอเบิลมิค

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Pristane Plus *v-abl/myc* Induced Lymphoma and Plasmacytoma Development in STS/A Mice

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Abstract

The STS/A (STS) mouse is a highly resistant strain for radiation-induced hematopoietic and mammary gland neoplasms while BALB/cHeA mouse is susceptible. The BALB/c mouse strain is also sensitive to peritoneal plasmacytoma (PCT) induction by a variety of agents, including plastic implants, paraffin oils, pristane and pristane plus *v-abl/myc*, with different latency periods, incidences and effectiveness.

The objective of this study was to investigate the susceptibility of the STS mouse to pristane plus *v-abl/myc* induced plasmacytomagenesis.

Materials and methods: Ten mice from a control group were intraperitoneally injected with pristane only and the other ten mice were injected with pristane followed by *v-abl/myc*. All mice were investigated routinely for ascitis and tumor formation up to 100 days. Histologic slides were prepared from harvested tumor samples as well as CD138 immunofluorescence staining for plasma cells detection.

Results: Four of ten mice in pristane plus *v-abl/myc* group developed ascites and showed evidence of lymphoid malignancies. Three of the ten mice had mixed tumors (lymphoma and PCT) and one of ten had lymphoma. None of the control STS mice developed a tumor. The average latency period of tumor development in STS mice was 90 days which was longer than pristane plus *v-abl/myc* plasmacytomagenesis in BALB/c and congenics. The relative risk of tumor resistance of a control group compared to the test group was 1.67 (95% confidence interval (CI): 1.005-2.765).

Conclusion: The STS mice were not completely tolerate to pristane plus *v-abl/myc* plasmacytoma induction but an average latency period of tumor formation was longer than the BALB/c and congenics mouse strain. This extended period indicated some resistances in the STS genetic background.

Keywords: lymphoma, plasmacytoma, mouse tumor induction, mouse chromosome 11, *v-abl/myc*

Introduction

Inbred mouse strains have been developed for use in cancer research since the 19th century to explain the existence of genetic factors influencing the incidence of cancer. Inbred strains of mice differ widely in susceptibility to different types of tumor. One example is the STS/A mouse strain. This strain is resistant to radiation-induced thymic lymphomagenesis while other strains such as BALB/cHeA (BALB/c) are sensitive (Okumoto, Nishikawa, Imai, & Hilgers, 1989, pp. 135-139). This type of tumor resistance in STS mice was confirmed by the work of Kamisaku and colleagues in which radiation bone marrow chimeras were constructed in the reciprocal resistant donor (STS strain) host of susceptible mice (B10

strain), as well as other reciprocal donor-host combinations of susceptible and resist strains. Both STS bone marrow transplant-susceptible hosts and STS donor-resistant hosts manifested a low incidence of thymic lymphomas compared to other groups, which were susceptible donor-resistant host strains and susceptible donor-susceptible host strain chimeras (Kamisaku, Aizawa, Tanaka, Watanabe, & Sado, 2000, pp. 1105-1111) indicating that the resistance to lymphomagenesis resides in the bone marrow hematopoietic cells rather than in the host's environment. Genetic control of radiation-induced lymphomagenesis in strains BALB/c and STS had been studied by using a set of CcS-recombinant congenic strains each of which carries a unique random set of segments encompassing 12.5% of the genome of STS strain on the genetic background of BALB/c (Demant, 2003; Demant, & Hart, 1986). The tests of CcS strains indicated that susceptibility to radiation-induced T and B cell lymphomas is controlled by separate sets of multiple genes, some of which have been mapped (Piskorowska, et al., 2011; Szymanska, et al., 1999).

STS mice were found to be completely resistant to both spontaneous and mouse mammary tumor virus (MMTV)-induced mammary tumors (Hilgers, & Arends, 1985). This strain was also reported to be resistant for hormone-induced mammary gland carcinogenesis (van der Gugten, Ropcke, van Nie, & Hilgers, 1985, pp. 3448-3453). The resistance of the STS strain to hormone-induced mammary gland carcinogenesis was confirmed by the very low incidence of mammary tumors after hypophysial isografts implantation, while O20, C3Hf, and BALB/c strains were highly susceptible to prolactin mediated carcinogenesis and C57BL and TSI strain females were intermediately susceptible (van der Gugten, & Ropcke, et al., 1985). However, STS mice carry susceptible alleles at several loci for susceptibility to induced mammary tumors (Quan, et al., 2012, pp. 631-643). In contrast to T cell lymphoma and MMTV-induced mammary tumors, STS mice are highly susceptible to carcinogen-induced colon tumors, while BALB/c mice are relatively resistant. Using the CcS strains, 14 colon cancer susceptibility loci were mapped (Demant, 2003) and one of them was identified as *Ptprj* (protein tyrosine phosphatase receptor type J), encoding a receptor-type protein tyrosine phosphatase. In human colon, lung and breast cancers *PTPRJ* showed frequent deletion, allelic imbalance in loss of heterozygosity (LOH) and missense mutation (Ruivenkamp, et al., 2002, pp. 295-300).

Mouse plasmacytoma can be induced in several ways and the intraperitoneally injecting by pristane (2,6,10,14-tetramethylpentadecane), a common component of many mineral oils, has been extensively used. Pristane provokes the formation of chronic inflammation follow by a plasma cell tumor development (Potter, 2003). Many strains have been shown to be resistant to pristane induced plasmacytoma including AL/N, B10D2, C57BL/6, C57BL/Ka, C58Lw, C3H, CBA, DBA/2, NH, NZC, SJL and SWR (Potter, & Wiener, 1992). Only a few strains including BALB/c and NZB/B1 congenic mice are susceptible to peritoneal PCT induction and showed a high incidence of PCT after an intraperitoneal inoculation of liquid paraffin or pristane (Murphy, & Bolgos, 1985; Warner, 1975).

Mouse PCT, rat immunocytoma and human Burkitt lymphoma were the first B lineage tumors shown to result from *c-myc*-activating chromosomal translocations. Pristane-induced mouse PCTs develop very slowly with a mean latency period of 220 days (Ohno, et al., 1984; Potter, 2003; Potter, & Wax, 1983). In pristane plus Abelson Murine Leukemia Virus (A-MuLV)-induced PCTs with *c-myc/Ig*

translocations, the mean latency period decreases to 89 days (Ohno, et al., 1984; Potter, & Wiener, 1992). The highest incidence and the shortest latency period, average 45 days, was found by pristane pretreatment of BALB/c or BALB/c congenic mice, infected with *v-abl/myc* retrovirus (Wiener, Coleman, Mock, & Potter, 1995, pp. 1181-1188). This helper-free *v-abl/myc* retrovirus was initially developed by Largaespada and colleagues in 1992 (Largaespada, et al., 1992, 811-819). The viral construct contained *c-myc* and *v-abl* gene, an oncogene with a transforming activity for fibroblasts, pre-B lymphocytes and other cells of hematopoietic lineages (Wong, et al., 1995, pp. 6535-6544). These findings were confirmed in 2010 by the same group who found the trisomy of Chr 11 was always associated with accelerated pristane+*v-abl/myc*-induced PCT development in a unique BALB/c congenic mouse strain, T38HxBALB/c (Wiener, Schmalter, Mowat, & Mai, 2010, pp. 847-858).

Because most mouse strains are resistant to PCT induction, we hypothesized that the STS mouse strain, which is resistant to a variety of tumors including hematopoietic tumors, might be resistant to PCT induction. Our control group consisted of ten STS mice injected with pristane only, while our experimental group had ten STS mice injected with pristane plus *v-abl/myc*. Three months after induction we found that STS mice from the experimental group were not fully resistant to pristane plus *v-abl/myc* PCT induction, as 40% of the mice developed either lymphoma or mixed lymphoma/PCT.

Materials and Methods

Ethics statement. The experimental procedures were in compliance with the Canadian Council on Animal Care with the approval of Research Ethics Review Board of the University of Manitoba (protocol number 07-002/1/2/3).

Tumor induction and clinical assessment. At 7-9 weeks of age, seven male and three female STS mice of the experimental group were given a single intraperitoneal (i.p.) injection of pristane (0.3 ml, Sigma-Aldrich, St. Louis, MO, USA). Five days later, the *v-abl/myc* virus was given through an i.p. injection (1 ml at a viral titre of $\sim 10^3$ PFU/ml) (Neoclone®, Madison, WI, USA). Mice were regularly observed for the development of ascites or any sign of tumor development. Another seven male and three female age-matched mice were injected with 0.3 ml of pristane only. These mice were used as a control group. The mice were sacrificed to assess tumor development at the endpoint of 100 days post virus, which is the longest latency period previously observed for pristane plus *v-abl/myc* mouse PCT development (90 days post virus) (Wiener, et al., 2010, pp. 847-858), or earlier if the mice showed ascites development. Physical examination was performed on every mouse. Ascites fluid was harvested along with oil granulomas or any other pathologic tissue.

Histological slide. Following the harvest of ascites fluid, histology staining was performed as follows: the slides were fixed with methanol (Fisher Scientific, Fair Lawn, NJ, USA) for 10 minutes at room temperature and stained by modified Giemsa (GS-500, Sigma-Aldrich, St. Louis, MO, USA) for 15 minutes. All excess staining was removed by washing with cold tap water. The slides were photographed using Axioplan2, Axiocan Ico3 (Carl Zeiss) microscope.

Immumofluorescence. A CD138 staining was performed on smear slides which were fixed with methanol. The fixed cells were washed 3 times with 1X PBS, and blocking was done for 30 mins at RT with 0.5 mg/ml IgG1 anti-mouse (02231D,

Pharminogen) diluted in PBS to the concentration of 0.1 mg/ml. Incubation of primary antibodies using 1:100 dilution of mouse monoclonal anti-CD138/syndecan-1 (Cell Marque, CA, USA) was done for 1 hour at RT in a humidified atmosphere. This was followed by an incubation in a 1:200 dilution of Cy3 Goat anti-mouse IgG secondary antibody (A10521, Invitrogen/Gibco, ON, Canada) in 3% bovine serum albumin (BSA) diluted in 4X Saline-sodium citrate (SSC) buffer, for 45 min at RT in humidified atmosphere. After washing 3 times with 1X PBS, slides were counterstained using DAPI and mounted in Vectashield (Vector Laboratories, CA, USA) with cover slips. Fluorescent images were taken using an Axio Imager Z1 (Carl Zeiss, Toronto, Canada) microscope.

Statistic analysis. The incidence of tumor absence from a control group and test group were calculated. The ratio of tumor resistance incidence from a control group was compared to the test group (Relative risk, RR) and corresponding 95% confidence interval (CI) were analyzed.

Results

Four of ten pristane+*v-abl/myc*-induced STS mice (40% of experimental group) developed B-cell lineage tumors and all of them developed ascites. In this group, two female and one male STS had mixed tumor phenotypes (lymphoma and PCT), another one female developed lymphoma. Oil granulomas were found in every tumor-carrying mouse. Independent of sex, three of four tumor mice (30% of experimental group) had mixed tumor phenotypes and the latency periods were 84-98 days. The fourth mouse developed lymphoma with a latency of 80 days. The average latency period of tumor development in pristane-*v-abl/myc*-induced STS mice group was 90 days (Table 1). Enlarged spleens were also found in two of the four tumor carrying mice. Oil granulomas were also found in an additional two mice from the experimental group but they did not show any evidence of tumor formation at the time of harvest (Table 2). The control group of pristane only induced-STS mice did not develop any tumors (Table 1).

Table 1 Tumors induced with pristane+*v-abl/myc* in STS mice.

STS mice	Treatment	Tumor development (%)			Average latent period
		Tumor Type			
		Lymphoma	PCT	Mixed	
Control group	Pristane only	0 (0/10)	0 (0/10)	0 (0/10)	-
Experimental group	Pristane+*v-abl/myc*	10 (1/10)	0 (0/10)	30 (3/10)	90 days

PV: post-*v-abl/myc* infection

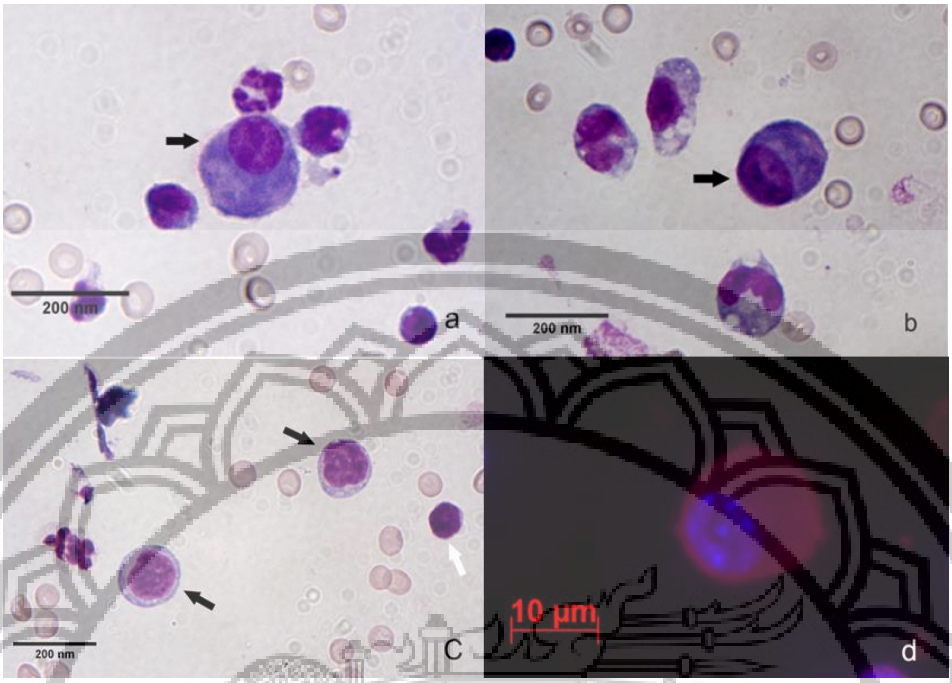

Figure 1 Plasmacytoma cells (black arrows) show morphologic features, oval shape with an eccentric nucleus composed of coarsely clumped chromatin, densely basophilic cytoplasm (a) and a clear area in cytoplasm suggesting the Golgi apparatus (b). Lymphoma cells (black arrows) show an irregular nuclear contour and a larger size in comparison to a normal lymphocyte (white arrow) (c). Positive immunofluorescence staining of anti-CD138 monoclonal antibody and a Cy3 labeled secondary antibody was confirmed the plasma cell type of a neoplastic cell (d).

Histologic slides from ascites fluid of the mixed PCT-lymphoma tumor mice (Figure 1a-c) showed PCT cells (Figure 1a-b) and lymphoma cells (Figure 1c) present in the peritoneal cavity. The same smear slides were used for an immunofluorescence staining of CD138 which is a surface protein specific to plasma cells. CD138 staining was found along the plasma membrane and in the cytoplasm because of a partial permeabilization from the methanol fixation step (Figure 1d).

Table 2 Incidence and latent period of tumor development in STS mice.

Mice no.	Method of induction	Tumor/Type	Oil granuloma	Ascitis	Other organ	Gender	Latency in days (PV)
1	Pristane alone	No	No	No	Normal	Male	-
2	Pristane alone	No	No	No	Normal	Male	-
3	Pristane alone	No	No	No	Normal	Male	-
4	Pristane alone	No	No	No	Normal	Male	-
5	Pristane alone	No	No	No	Normal	Male	-
6	Pristane alone	No	No	No	Normal	Male	-
7	Pristane alone	No	No	No	Normal	Male	-
8	Pristane alone	No	No	No	Normal	Female	-
9	Pristane alone	No	No	No	Normal	Female	-
10	Pristane alone	No	No	No	Normal	Female	-
11	Pristane + *v-abl/myc*	No	No	No	Enlarged spleen	Male	-
12	Pristane + *v-abl/myc*	No	Yes	No	Normal	Male	-
13	Pristane + *v-abl/myc*	No	Yes	No	Normal	Male	-
14	Pristane + *v-abl/myc*	PCT and Lymphoma	Yes	Yes	Enlarged spleen	Male	98 days
15	Pristane + *v-abl/myc*	Lymphoma	Yes	Yes	Normal	Female	80 days
16	Pristane + *v-abl/myc*	PCT and Lymphoma	Yes	Yes	Normal	Female	84 days
17	Pristane + *v-abl/myc*	PCT and Lymphoma	Yes	Yes	Enlarged spleen	Female	98 days
18	Pristane + *v-abl/myc*	No	No	No	Normal	Male	-
19	Pristane + *v-abl/myc*	No	No	No	Normal	Male	-
20	Pristane + *v-abl/myc*	No	No	No	Normal	Male	-

Table 3 Incidence and ratio of tumor absence in a control group and a test group of STS mice.

Tumor induction method	Tumor absences	Tumor presences	Total
Pristane only (Control group)	10 (100%)	0 (0%)	10 (100%)
Pristane+*v-abl/myc* (Test group)	6 (60%)	4 (40%)	10 (100%)
Total	16	4	20

The incidence of tumor absence in a control was 100% while the incidence in a test group was 60% (Table 3). The relative risk of tumor resistance in a control group compared to a test group is 1.67, 95% CI = 1.005-2.765.

Discussion

Tumor susceptibility can vary in different mouse strains. This results in wide ranges of tumor susceptibility between inbred strains of mice. Tumors induced by the same method in two different mouse strains can differ in tumor number, size, prevalence and latency period, and these strain differences are frequently organ specific (Demant, 2003). To find individual or strain susceptible genes, crosses between susceptible and resistant strains are generated and then induced in each strain by the same method. The individual animals from such crosses were genotyped for a number of microsatellite or single nucleotide polymorphism markers (SNP), and the correlation between the tumor susceptibility phenotype and the presence of a microsatellite or SNP allele allowed susceptibility loci to be mapped to chromosome locations (Demant, 2005).

In our experiments, we planned to intercross the STS and T38HxBALB/c mouse strains and use their hybrid mice for a plasmacytomagenesis study assuming STS mice were resistant to PCT development. T38HxBALB/c is evidently susceptible to pristane + *v-abl/myc* -mediated PCT induction. To date, there was no report of PCT induction in STS mice. The other tumor induction experiments which have been performed in STS mice were a mammary gland tumor induction (Okumoto, et al., 1989, pp. 135-139), radiation-induced lymphoma (Okumoto, & Mori, et al, 1995) and FI (fractionated whole-body irradiation)-induced thymic lymphomagenesis (Kamisaku, et al., 2000, pp. 1105-1111). STS mice were predicted to be completely resistant to PCT induction. Surprisingly, at the average latency period of 90 days post viral infection, 40% of STS mice developed ascites and oil granulomas, which are the characteristics of peritoneal PCT. No tumors developed in pristane only-induced STS mice. These results indicate that STS mouse is not completely resistant to pristane + *v-abl/myc* plasmocytomagenesis but it modifies the PCT-tumorigenesis in a specific way, compared to BALB/c mice. This opens way to look for specific genes responsible for this effect. One might consider this a genetic screen of PCT susceptibility in the CcS strains, each of which contains a different small subset of STS genes on 88% of BALB/c background. By keeping the PCT-inducing stimulus weaker than usual, this might detect polymorphic effects of STS-resistance genes, which need not include only the notorious candidates. Nevertheless, adjusting more sample size, follow-up period and gender distribution also have to be considered.

The relationship between gender and hematopoietic tumor susceptibility in STS mouse progeny was not well-documented. Some studies used only female recombinant STS mice for tumor induction as they claimed to exclude sex difference in lymphomagenesis (Mori, Okumoto, & Yamate, 2000, pp. 367-372; Okumoto, & Nishikawa, et al., 1990). Some other studies used both mouse genders including Okumoto and colleagues whose male and female F1 hybrid CcS (BALB/cHeA x STS/A) mice were treated for radiation-induced lymphomas. The results showed a high level of tumor susceptibility but lymphoma incidences between male and female F1 mice were not much different (63% and 64% respectively)(Okumoto, et al., 1995). In another study which the CcS/Dem backcross mice (CcS-17xCcS-2)xCcS-2 were exposed to whole-body irradiation, the incidence of hematopoietic

neoplasm in females (42.39%) was slightly higher than males (41.13%) (Piskorowska, et al., 2011) corresponded to our PCT incidence in pristine+*v-abl/myc* treated STS group (female 30%, male 10%). The expanded sample size and well designed subsequent experiment need to be tested before concluding about PCT susceptibility and STS sex distribution.

The neoplastic transformation of plasma cells in fast-onset PCT results from a collaboration of *c-myc* overexpression and *v-abl* activity. The *v-abl/myc* transforming virus enters into the pristane-conditioned peritoneum, A-MuLV introduces *v-abl*, which encodes an active cytoplasmic and nuclear protein tyrosine kinase that has been implicated in processes of cell differentiation, cell division, cell adhesion, and stress response into pre B cells (Potter, & Wiener, 1992). This causes pre B cells to enter the process of B cell differentiation and ultimately they are activated by antigens and become plasma cells. Subsequently, the neoplastic phenotype from the transformation effect of *c-myc* and *v-abl* is presented. Previous work in our lab has shown the cooperative effects of these two oncogenes by the very high incidence of peritoneal PCT in pristane plus *v-abl/myc* induced PCTs in BALB/c congenics (Wiener, et al., 2010, pp. 847-858). All mice developed peritoneal PCTs in a short latency period (45 days) which indicated that the virus-infected pre B cells were chosen to express their neoplastic phenotype after B-cell maturation and differentiation. In contrast, STS mice induced in a same way developed a mixed tumor composed of lymphoma and PCT with a longer latency period (90 days). These findings are compatible with a multigenic control of susceptibility to pristane and *v-abl/myc* induced tumorigenesis since the incidence of plasmacytomas and/or lymphomas noticeably differs among strain of mice. In the case that relevant genes or susceptibility loci controlling tumor latency were repressed in STS strain, the biological relevance of these factors might affect on the susceptibility phenotypes (tumor latency or tumor number) (Quan, et al., 2012, pp. 631-643). These could be successfully dissected using the CcS recombinant congenic strains, as was the case with radiation-induced lymphomas, colon tumors and ErbB2-induced mammary tumors (Szymanska, et al., 1999, pp. 674-678).

Conclusion

The STS strain, which is resistant to many types of tumor inductions including radiation-induced lymphomagenesis and mammary tumorigenesis, is not fully resistant to pristane plus *v-abl/myc* PCT induction. Forty percent of the mice developed mixed lymphoma and PCT with a longer latency period compared to the susceptible strain. However, pristane only cannot induce plasmacytomagenesis in STS mice. *c-Myc* and *v-abl* together overcome this resistance phenotype.

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