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Major Histocompatibility (*B*) Complex Gene Dose Effects on Rous Sarcoma Virus Tumor Growth[1]

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Abstract: Major histocompatibility (*B*) complex (MHC) gene dose effects on Rous sarcoma outcome were examined using chickens aneuploid for the MHC-bearing chromosome. Six-week-old chickens were inoculated with subgroup A Rous sarcoma virus (RSV). Tumors were scored for size six times over a 10-wk period followed by assignment of a tumor profile index (TPI), which indicated the degree of tumor growth. In Experiment 1, matings between Line FCT-15 trisomic (*B*15*B*15*B*15) sires and dams produced disomic (*B*15*B*15), trisomic (*B*15*B*15*B*15), and tetrasomic (*B*15*B*15*B*15*B*15) progeny. The progressive tumor growth engendered by *B*15 did not differ significantly among the three B complex doses. In experiment 2, matings between UNH 193 (B19B19B19) trisomic parents produced progeny having 2, 3, and four *B*19 haplotype doses. Most Line 193 chickens regressed their tumors. However, disomic Line UNH 193 chickens had a significantly lower TPI than trisomic but not tetrasomic chickens. In experiment 3, Line UNH 193 was crossed with Line 6.15-5 (*B*5*B*5), a tumor progressor genotype, to produce either *B*5*B*19 or *B*5*B*19*B*19 genotypes. Mean tumor growth over time and mean TPI were significantly lower in *B*5*B*19*B*19 chickens compared with *B*5*B*19 chickens. These data indicate that B complex gene dose alterations for *B*15 did not affect Rous sarcomas but changes involving extra *B*19 doses enhanced tumor development. Furthermore, when combined with the progressive *B*5 haplotype, two doses of the tumor regressor-associated *B*19 haplotype were significantly more effective for inhibiting tumor development compared to one *B*19 dose.

Key words: Aeuploid, MHC, oncogeny, Rous sarcoma virus, trisomic

Introduction

The chicken major histocompatibility (*B*) complex (MHC) resides on a single chromosome approximately 16th in size (Bloom and Bacon, 1985; Bloom *et al*., 1987). This chromosome also contains a second group of genes, *Rfp*-*Y*, that has considerable MHC homology (Briles *et al*., 1993; Miller *et al*., 1994, 1996). The nucleolar organizer region (NOR) encoding the ribosomal RNA genes, a region of high frequency recombination, separates the (*B*) complex from *Rfp*-*Y* on microchromosome 16. Line FCT-15 chickens that possess the *B*15 haplotype, are aneuploid (trisomic and tetrasomic) for the *B* complex-bearing chromosome and represent the only viable trisomic and tetrasomic animal model (Bloom and Bacon, 1985). An important feature of this animal model is that B complex-encoded molecules are expressed in a dose-dependent manner, while ribosomal RNA gene expression is regulated in aneuploid cells to diploid levels (Muscarella *et al*., 1985; Delany *et al*., 1988). This unique model has been useful for studies of B complex dose effects on immune system development and functions as well as disease resistance.

Previous research revealed expression of MHC antigens on B lymphocytes (Delany *et al*., 1988) increased proportionally with *B* complex gene dose. Bursal lymphocyte subpopulation profiles were also altered with *B* complex dose (Delany *et al*., 1992). Aneuploid MHC doses affected primary lymphoid organ development as well as bursal and thymic lymphocyte counts (Hemendinger *et al*., 1992). In addition, class II MHC molecules on macrophages were expressed in proportion to their *B* complex chromosome dose (Qureshi *et al*., 1989; Lin *et al*., 1991, 1993). Macrophage functional analysis demonstrated that aneuploidy affected SRBC phagocytosis (Qureshi *et al*., 1989), *in vitro* antigen presentation (Lin *et al*., 1991), generation of reactive oxygen intermediates (Lin *et al*., 1992), anti-tumor activity, and nitrite production (Lin *et al*., 1993).

Particular *B* complex genotypes exert a powerful influence on susceptibility to viral, bacterial, and parasitic disease vectors (Dietert *et al*., 1991; Kaufman *et al*., 1999). Collins *et al*. (1977) and Schierman *et al*. (1977) first reported the central role of the *B* complex in determining tumor outcome after induction by the oncogenic retro virus, Rous sarcoma virus (RSV). Rous sarcomas in *B*2*B*2 and *B*5*B*5 chickens regressed and progressed, respectively (Collins *et al*., 1977). Tumor regressed in *B*6*B*13 chickens but progressed in *B*13*B*13 chickens (Schierman *et al*., 1977). Additional work by numerous investigators confirmed the MHC control of RSV tumor growth (Taylor, 2004).

Experimental evidence indicating *B* complex molecule expression consistent with gene dose as well as altered bursal and thymic development in aneuploid chickens, raised questions about MHC gene dose effects on *in vivo* immune responses. LePage *et al.*, (1996) examined the *B* complex gene dose effect on antibody titers to the T cell-dependent antigen, sheep red blood cells (SRBC). In that study, MHC gene dose did not affect peak antibody titer or day of peak titer following a 5% SRBC antigenic challenge. The aneuploid animals, trisomics and tetrasomics, had significantly more rapid rates of decline from the maximum titer compared with disomic individuals.

The current investigation's objective was to determine the effects of different *B* complex doses on the progression/regression of tumors induced by RSV. Two different trisomic lines, FCT-15 (*B*15*B*15*B*15) and UNH 193 (*B*19*B*19*B*19) produced progeny that were used to study the effects of increased B complex doses for an individual B haplotype (B15 or B19) on RSV-induced tumor progression/regression. Crosses involving Line UNH 193 (*B*19*B*19*B*19) and Line 6.15-5 (*B*5*B*5) were used to study the effects of B complex doses on RSV-induced tumors involving combinations of *B*19 tumor regressor and *B*5 tumor progressor *B* complex haplotypes.

Materials and Methods

Stock: Animals utilized in Experiment 1 were the FCT-15 trisomic line (*B*15*B*15*B*15) developed at Cornell University (Bloom and Bacon, 1985; Bloom *et al.*, 1987). These birds have three copies of the microchromosome, which bears both the major histocompatibility (*B*) complex and the nucleolus organizer region (NOR). The number of NORs, and nucleoli they produce, serves as a useful diagnostic marker for the number of MHC-bearing chromosomes in cells. Matings between trisomic sires and dams produced disomic (*B*15*B*15), trisomic (*B*15*B*15*B*15), and tetrasomic (*B*15*B*15*B*15*B*15) progeny.

Line UNH 193 trisomic chickens were derived from the FCT-15 trisomic line. A trisomic sire (*B2B*15*B*15) from a cross of FCT-15 trisomic line to inbred Line 6.6-2 (*B2B2*) (Miller *et al.*, 1996) was mated to modified Wisconsin Line 3 Ancona dams (*B*19*B*19) to produce chickens having 3 *B* complex (*B2B*15*B*19) haplotypes. Trisomic dams were then back crossed twice to *B*19*B*19 Line 3 Ancona sires until trisomic chickens were homozygous for the *B*19*B*19*B*19 genotype. These chickens were the foundation for Line UNH 193. All blood types were confirmed by hemagglutination assays using alloantisera specific for *B* complex haplotypes (Briles and Briles, 1982). Matings between Line UNH 193 trisomic sires and dams produced progeny having *B*19*B*19, *B*19*B*19*B*19 or *B*19*B*19*B*19*B*19 MHC haplotypes and these progeny were used in Experiment 2.

For Experiment 3, Line UNH 193 (*B*19*B*19*B*19) trisomic dams were mated to a Line 6.15-*5* (*B*5*B*5) sire. This second line, a known progressor of RSV-induced tumors, is one of a congenic pair described by Dix and Taylor (1996). Progeny from this mating had either *B*5*B*19 or *B*5*B*19*B*19 MHC chromosome doses.

Fertile eggs for all experiments were incubated and hatched at the University of New Hampshire Poultry Research Farm. Chicks were banded for identification and were housed in heated brooding batteries. A commercially prepared chick starter consisting of 20.0% crude protein and 2,860 kcal ME/kg, which met the essential nutrient requirements, was fed throughout the experiments. Marek's disease and Newcastle-bronchitis vaccines were administered at hatch and 10 d, respectively. After six weeks of age, chicks were transferred to isolation cages.

Determination of MHC chromosome doses: Pin feathers were collected from chicks at hatch. Feather pulp samples were prepared in 50% acetic acid and coated on microscope slides as described previously (Bloom and Bacon, 1985; Muscarella *et al.*, 1985). Nuclei were examined using phase contrast examination according to the method of Delany *et al.*, (1992). The maximum number of nucleoli found in cells of each chicken indicates the number of MHC chromosome doses (Delany *et al.*, 1992).

Virus Inoculations and Tumor Evaluation: Six-week-old chickens were inoculated in the wing-web with 20 pock forming units (pfu) of RSV [subgroup A] in all three experiments. The tumors that developed were scored for size at 2, 3, 4, 6, 8, and 10 wk postinoculation using the values 0 = no palpable tumor; 1 = small tumor up to 0.5 cm diameter; 2 = tumor >0.5 up to 1.2 cm diameter; 3 = tumor >1.2 up to ½ wingweb area; 4 = tumor >½ wingweb area, but <entire wingweb; 5 = tumor filling the entire wingweb; 6 = massive tumor extended beyond wingweb; and 7 = death during the experiment (Collins *et al.*, 1977). The six tumor size scores were used to assign a tumor profile index (TPI), which indicates the degree of tumor growth. The TPI values were 1 = complete regression by 28 days, or earlier; 2 = complete regression by 42 or 56 days; 3 = complete regression by 70 days, or a decreasing slope, or complete regression by 56 days followed by recurrence; 4 = general upward trend, or plateau or slight regression after 56 days; 5 = terminal tumor prior to 70 days (Collins *et al.*, 1977).

Statistical analysis: Mean tumor sizes for each scoring period were evaluated by least squares analysis of variance using a repeated measures split-plot design with hatch, sex and *B* complex gene dose as main effects in each experiment. The TPI values were rank

transformed and analyzed by ANOVA as described by Conover and Iman (1981). Fisher's Protected LSD at P <0.05 separated significant means. Tumor development and mortality were subjected to chi-square analysis.

Results

Tumors developed in 71 percent of the FCT-15 trisomic line progeny in Experiment 1. The tumor growth over time did not differ significantly (P > 0.05) as assessed by repeated measures ANOVA among 22 disomic (*B*15*B*15), 36 trisomic (*B*15*B*15*B*15), and 19 tetrasomic (*B*15*B*15*B*15*B*15) progeny (Fig. 1). Tumors increased in size from 2 to 4 wk post-inoculation. Subsequent tumor growth reached a plateau in all three genotypes although tetrasomic chickens had a slight increase at 8 wk post-inoculation. The TPI of the three genotypes was statistically similar and sex was not significant. Mortality rates were 50.0, 36.1 and 52.6% for disomic, trisomic, and tetrasomic chickens, respectively. Less than 23% of any B complex gene dose completely regressed their tumors.

In Experiment 2, tumors developed in 70 percent of progeny from *B*19*B*19*B*19 x *B*19*B*19*B*19 matings. None of the gene doses differed significantly in the proportion of hosts that developed tumors. The mean TPI of *B*19*B*19 chickens (n = 28) was significantly (P < 0.05) lower than the trisomic *B*19*B*19*B*19 TPI (n = 47). The TPI of *B*19*B*19*B*19*B*19 chickens (n = 13) did not differ significantly from either disomic or trisomic B complex gene doses. All three B complex gene doses had less than 18% mortality that did not differ significantly. Complete tumor regression, also not significant, ranged from 78.6% in *B*19*B*19 in disomic chickens to 59.6% in *B*19*B*19*B*19 trisomics.

Seventy percent of the disomic and trisomic progeny injected with RSV developed tumors in Experiment 3. The proportion of chickens that developed tumors did not differ between the two gene doses. The gene dose x time interaction was significant (P = 0.036) indicating that the two gene doses had different tumor growth over time (Fig. 3A). The *B*5*B*19*B*19 genotype (n = 36) had lower tumor growth than the *B*5*B*19 genotype (n = 29). Fig. 3B shows that the TPI of *B*5*B*19*B*19 chickens was significantly (P = 0.015) lower than the TPI of *B*5*B*19 birds. There was no tumor growth or TPI difference between the sexes. Compared with the disomic dose, trisomic chickens had lower mortality (19.4% vs 41.3%) as well as a higher percentage of complete tumor regression (52.8% vs 31.0%).

Discussion

Line FCT-15 chickens did not demonstrate any difference in RSV-induced tumor growth. All three B complex doses (disomic, trisomic, tetrasomic) for MHC haplotype *B*15 had progressive tumor growth. This result is consistent with previous RSV tumor growth studies of

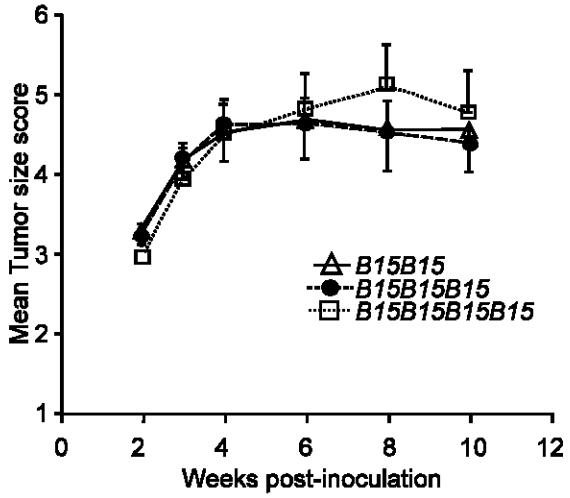

Fig. 1: Effect of major histocompatibility (*B*) complex gene dose on tumor size scores over a 10-wk experimental period in *B*15*B*15 (n = 22), *B*15*B*15*B*15 (n = 36) and *B*15*B*15*B*15*B*15 (n = 19) chicks inoculated with 20 pfu Rous sarcoma virus. Tumor growth for the three *B* genotypes does not differ significantly (P > 0.05) over time

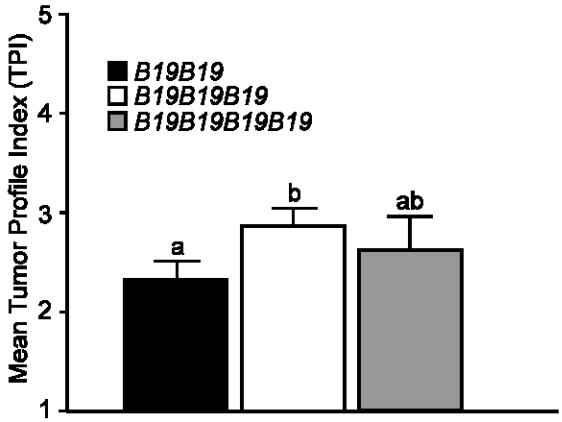

Fig. 2: Effect of major histocompatibility (*B*) complex gene dose on tumor profile indices (TPI) in *B*19*B*19 (n = 28), *B*19*B*19*B*19 (n = 47) and *B*19*B*19*B*19*B*19 (n = 13) chicks inoculated with 20 pfu Rous sarcoma virus. Bars having no common letter differ significantly (P < 0.05)

the *B*15 haplotype. Collins *et al.* (1980) compared different inbred lines for response to RSV subgroup A. Inbred *B*2*B*2 Lines 6_1 and 6_3 had a better response to tumor than did Line 100 (*B*2*B*2) and Line $15I_5$ (*B*15*B*15). Schimdt-Ruppin virus, subgroup B tumor growth in three inbred lines having different MHC types G-B1 (*B*13*B*13), G-B2 (*B*6*B*6), and G-B3 (*B*15*B*15) was tested by Cutting *et al.* (1981). Lines G-B1 and G-B3 showed 100%

progressive tumor growth whereas Line G-B2 had tumor regression. The (G-B1 x G-B3) F_1 cross of progressive lines (*B*13*B*15) produced 87.5% tumor regression indicating trans-complementation. Homozygous *B*13*B*13 or *B*15*B*15 progeny from the backcross to the parental lines (F1 x G-B1) or (F1 x G-B3) had progressive tumor growth. On the other hand, *B*13 and *B*15 were complementary as 50% of the *B*13*B*15 backcross progeny regressed tumors. The results predicted complementation between a MHC gene and a non-MHC gene.

Nordskog and Gebriel (1983) studied six genotypes from all possible combinations of *B*1, *B*12, and *B*15 haplotypes in an inbred White Leghorn Line HN. Both the *B*1 and *B*15 haplotypes were tumor progressors whereas all genotypes having *B*12 (*B*12*B*12, *B*1*B*12, and *B*12*B*15) regressed RSV subgroup A tumors. Genotypes *B*5*B*5, *B*5*B*15, and *B*15*B*15 from Line $15I_4$ all had progressive RSV subgroup B tumor growth compared with Line 63 (*B*2*B*2) (Bacon *et al.*, 1983). Greater tumor progression was also found in the *B*15*B*15 F_2 progeny of Line $15I_5$ (*B*15*B*15) x 6_3 (*B*2*B*2) inoculated with RSV subgroups A, B and C compared with the *B*2*B*2 and *B*2*B*15 genotypes (Brown *et al.*, 1984).

The B19 haplotype, that regressed tumors in the present studies was found in other previous work to be variably associated with tumor regression. For example, three homozygous genotypes from the Iowa State University S1 Leghorn line, were inoculated with RSV subgroup A. Tumor regression for chickens having *B*2*B*2, *B*19*B*19, and *B*1*B*1 genotypes was 78, 44 and 21% respectively (Gebriel *et al.*, 1979). In other studies, *B*19*B*19 chickens had TPI that were significantly greater than either *B*21*B*21 or *B*21*B*19 chickens in a test of progeny segregating for *B*19 and *B*21 (Aeed *et al.*, 1993). The higher TPI indicated more tumor progression.

Tumor progression by the *B*5 haplotype is well-documented. The F_2 progeny of the inbred lines 6_1 (*B*2*B*2) and 15_1 (*B*5*B*5) cross showed high tumor regression in *B*2*B*2 chickens and no tumor regression in the *B*5*B*5 genotype (Collins *et al.*, 1977). Viral subgroup A or B tumors had progressive tumor growth in *B*5*B*5 chickens from either inbred lines [6_3 (*B*2*B*2) x 15_1 (*B*5*B*5)] F_4 or Line $15I_4$ (Bacon *et al.*, 1981, 1983).

The *B*5 antigen cross-reacted to one or more RSV tumor antigens because Rous sarcoma progression increased in *B*2*B*2 chickens previously made tolerant to the *B*5 antigen compared with untreated *B*2*B*2 controls (Heinzelmann *et al.*, 1981a, 1981b). Taylor *et al.* (1992; 1994) confirmed that the *B*2 haplotype controlled tumor regression whereas the *B*5 haplotype controlled tumor progression using MHC congenic lines.

RSV tumor growth is affected by an immune response against antigens that are either encoded or induced by the virus (Taylor *et al.*, 1992). This immune response producing tumor regression is mediated primarily by T

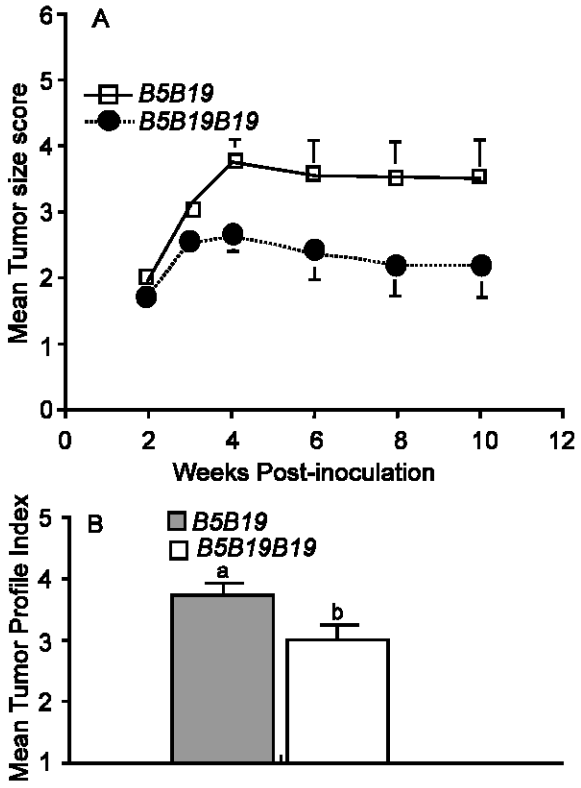

Fig. 3: Effect of major histocompatibility (*B*) complex gene dose on (A) tumor size scores over a 10-wk experimental period and (B) tumor profile indices (TPI) in *B*5*B*19 (n = 29) and *B*5*B*19*B*19 (n = 36) chicks inoculated with 20 pfu Rous sarcoma virus. Tumor growth for the two *B* genotypes differs significantly ($P < 0.05$) over time. Bars having no common letter differ significantly ($P < 0.05$).

cells (Taylor *et al.*, 2004). Thymic lymphocyte numbers were reduced in aneuploid chickens (Hemendinger *et al.*, 1992). Tumor growth did not differ among the three Line FCT-15 gene doses so the uniform progressive outcome attributable to the *B*15 haplotype outweighed possible consequences of reduced lymphocytes. The aneuploid effect was evident in Line UNH 193 because trisomic chickens had a higher TPI than did disomic chickens.

The direct effect of MHC recognition and response influenced all three experiments. Experiments 1 and 2 employed different doses of homozygous MHC haplotypes, *B*15 and *B*19. Therefore, MHC effects in those homozgotes are based upon dosage rather than the presence of dissimilar recognition capabilities. An indirect effect of altered MHC dose, such as lower thymic lymphocyte numbers, had more potential impact on tumor outcome, particularly in the regressive type. This explanation seems plausible because in the Line UNH

193 *B*19 doses, trisomic and tetrasomics had higher tumor growth than did the disomics. MHC recognition in the *B*5 and *B*19 combinations likely had greater bearing on tumor growth than did an alteration of lymphocyte numbers. It is not know if an aneuploid condition lowered lymphocyte numbers when multiple MHC haplotypes were present. Trisomic chickens (*B*5*B*19*B*19) had significantly lower tumor growth and TPI compared with *B*5*B*19 disomic chickens. This result indicated that two regressive *B*19 doses overcame the *B*5 progressor type to a greater extent than did one *B*19 dose.

Macrophage function has been evaluated in altered MHC gene doses. Phagocytic activity of unopsonized, but not opsonized SRBC was reduced in aneuploid birds (Qureshi *et al.*, 1989). Trisomic and tetrasomic Sephadex-elicited peritoneal macrophages had reduced antigen presentation (Lin *et al.*, 1991). *In vitro* anti-tumor activity and nitrite production (Lin *et al.*, 1993) were lower in the aneuploid birds. Lower *in vivo* macrophage anti-tumor activity in trisomics might have contributed to the poorer response in Line UNH 193. Potential functional deficiencies in either T or B cells have received limited study. LePage *et al.* (1996) found anti-SRBC antibody did not differ among three *B* complex doses yet aneuploid chickens did have a more rapid decline from peak antibody titer compared to disomic chickens. Analysis of lymphocyte functions from trisomic and tetrasomic chickens is an area for future investigation.

Aneuploidy for the MHC-bearing chromosome does not preclude the possibility that other genes on this chromosome may have affected the responses measured in the present study. For example, the *Rfp-Y* system contains MHC class I and MHC class II genes (Briles *et al.*, 1993; Miller *et al.*, 1994), maps to the same chromosome (Miller *et al.*, 1996) but assorts independently of the *B* complex. Rous sarcoma outcome in *B*2*B*5 birds was affected by *Rfp-Y* genotype (LePage *et al.*, 2000). The *Rfp-Y* haplotypes in Line FCT-15 and UNH 193 are unknown and may impact tumor growth. Other studies (unpublished) suggest that extreme regressor or progressor genotypes such as *B*2*B*2 or *B*5*B*5 are not affected by *Rfp-Y*. Other non-MHC background genes not found on the aneuploid chromosome, such as erythrocyte or lymphocyte alloantigens (Medarova *et al.*, 2003; Taylor 2004), may have contributed to the differential tumor growth.

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Abbreviation Key : PFU = Pock-forming Units; RSV = Rous Sarcoma Virus; TPI = Tumor Profile Index