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Major Histocompatibility (B) Complex Control of the Growth Pattern of \( v\)-src DNA-Induced Primary Tumors

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Observations that the major histocompatibility (B) complex is a determinant of the growth pattern of Rous sarcoma virus (RSV)-induced tumors raised the question as to whether control is exerted at the level of a \( v\)-src-determined, i.e., transformation-specific, function. To investigate this point, the tumor size scores and tumor profile indices of \( v\)-src-induced tumors were compared in two lines of chickens congenic for B complex genotypes. The finding that the growth patterns of tumors, induced by \( v\)-src DNA inoculation at 6 weeks posthatch, differ in these two lines establishes that the B complex exerts control over tumor growth at the level of a \( v\)-src-determined function. The potential importance of this control, in terms of the naturally occurring case of an avian sarcoma virus infection, is suggested by the observation that the patterns of tumor growth in a given congenic line are similar whether the tumors are induced by \( v\)-src DNA or by RSV.

Early findings that the pattern of growth of Rous sarcoma virus (RSV)-induced tumors is under host genetic control have prompted several studies aimed at identifying the relevant genetic elements. These elements are now known to include genes of the major histocompatibility (B) complex (MHC) (1, 2). Given the involvement of MHC-encoded elements in immune function (3), it is reasonable to infer that host immune responsiveness is implicated, via the recognition of a virus-encoded or virus-induced target antigenicity, in the phenomenon of B complex control of RSV-induced sarcoma growth.

However, an issue left unresolved by these studies is whether control is exerted at the level of a \( v\)-src-mediated, i.e., transformation-specific, function: for example (to accord with the presumption of an immune-based control), the expression of a tumor-specific antigenicity. The problem in using results based on RGV-induced tumor formation to resolve whether B complex control is at least partially exerted via \( v\)-src is that the expansion of an RSV-induced tumor proceeds not only by tumor cell proliferation, a process mediated by \( v\)-src, but also by infection-mediated recruitment of new tumor cells, a process in which the viral replication-specific genes play a dominant role. Either or both of these two processes could provide an underpinning for a mechanism of B complex control, especially as env, one of the viral replication-specific genes, encodes a structure that is itself highly antigenic. Nevertheless, despite this ambiguity, a hypothetical basis for invoking B complex control at the level of \( v\)-src is suggested by two earlier observations: (i) lines (noncongeneric) that differ at the B complex show different patterns of \( v\)-src DNA-induced tumor growth (4); (ii) \( v\)-src DNA-induced tumor growth is associated with a characteristic immunogenicity (5).

The present study was undertaken to determine whether the B complex exerts control over the growth pattern of tumors induced at the wingweb site of inoculation of DNA fragments possessing \( v\)-src but lacking viral replication-specific genes. Analysis was based on the use of the pVSRC-C1 construct (4) as a tumorigenic agent; the insert to this construct contains \( v\)-src as the only coding region. Tumor growth was compared in two chicken lines developed at the University of New Hampshire and congenic for B complex alleles. The genetic background of these lines derived from Single Comb White Leghorn line 61, an inbred line whose major histocompatibility (B) complex genotype is \( B2/B2\), which was originally developed at the USDA Avian Disease and Oncology Laboratory (East Lansing, Michigan). Line 15, (\( B5/B5\)) also from the USDA Avian Disease and Oncology Laboratory was crossed with line 61 to produce F1 progeny (heterozygous \( B2/B5\)), and these progeny were then backcrossed to line 61. Heterozygous progeny in each generation were detected by blood typing with a panel of specific alloantisera (6). After 10 backcross generations, heterozygous chickens were mated inter se to produce \( B2/B2\) and \( B5/B5\) homozygotes with >99% background gene uniformity. These two lines are designated lines 6.6-2 (\( B2/B2\)) and 6.15-5 (\( B5/B5\)) according to the nomenclature previ-
A complex exerts control over the pattern of growth of tumors that are induced by inoculation at 6 weeks posthatch of v-src DNA lacking viral replication-specific sequences. This conclusion is evidenced by the significant difference in the tumor size scores (Fig. 2B) and TPI (Fig. 3B) for 6.6-2 vs 6.15-6 chickens.

At present, the mechanism underlying B complex control of v-src DNA-induced tumor growth is not known. Our working hypothesis is that control is exerted via the strength of the immune response generated to a transformation-specific antigen. However, the absence of a B complex-dependent difference in v-src DNA-induced tumor growth in chickens inoculated at 1 day of age (Fig. 1B) requires that this hypothesis be modified by a subsidiary assumption; namely, that the tumor expansion in chickens inoculated at 1 day of age is due to the generally reduced immunocompetence of chickens during the first few weeks posthatch (8). One approach to future testing of the proposed role of a transformation-specific immunity would be to ascertain if the transfer of lymphocytes from a tumor-bearing 6.6-2 chicken, which had been

viously described (7). Earlier studies had shown that the patterns of RSV-induced tumor growth (wingweb inoculation at 6 weeks posthatch) differ for the progeny from the inter se matings of $B^2/B^5$ chickens derived from the $6, \times 15$, cross, such that the $B^6/B^6$ progeny showed regressive, and the $B^6/B^5$ progeny progressive, sarcoma growth (7).

The tumor size scores (as defined in the legend to Fig. 1) are shown in Figs. 1 and 2 for eight groups of chickens. These groups were assigned on the basis of (i) congenic line (6.6-2 or 6.15-6), (ii) age of inoculation (1 day or 6 weeks posthatch), and (iii) tumorigenic agent (the Rous-associated virus type 1 [RAV-1] pseudotype of the Bryan high-titer strain of RSV or pVSR- C1, the latter inoculated after restriction with HindIII and EcoRI (4) to free the v-src(+) insert from the cloning vector). The tumor profile indices (TPI, defined in the legend to Fig. 3) for chickens inoculated at 6 weeks posthatch are shown in Fig. 3. The major conclusion to emerge is that the B complex exerts control over the pattern of growth of tumors that are induced by inoculation at 6 weeks posthatch of v-src DNA lacking viral replication-specific sequences. This conclusion is evidenced by the significant difference in the tumor size scores (Fig. 2B) and TPI (Fig. 3B) for 6.6-2 vs 6.15-6 chickens.

At present, the mechanism underlying B complex control of v-src DNA-induced tumor growth is not known. Our working hypothesis is that control is exerted via the strength of the immune response generated to a transformation-specific antigen. However, the absence of a B complex-dependent difference in v-src DNA-induced tumor growth in chickens inoculated at 1 day of age (Fig. 1B) requires that this hypothesis be modified by a subsidiary assumption; namely, that the tumor expansion in chickens inoculated at 1 day of age is due to the generally reduced immunocompetence of chickens during the first few weeks posthatch (8). One approach to future testing of the proposed role of a transformation-specific immunity would be to ascertain if the transfer of lymphocytes from a tumor-bearing 6.6-2 chicken, which had been
inoculated with v-src DNA at 6 weeks of age, would confer protection against tumor growth on a 6.6-2 recipient that had been inoculated with v-src DNA at 1 day of age.

A second point emerges from the data in Figs. 1 and 2, with respect to chickens of the same line that are inoculated at the same age: a comparison of tumors induced either by pVSRC-C1 or by RSV demonstrated that the overall pattern of tumor growth is similar (as indicated by the respective shapes of the curves of the tumor size scores), even though the sizes of the tumors vary. While this similarity may be fortuitous, these results are consistent with the possibility that a v-src-determined function (hypothesically, the expression of transformation-specific antigen) is a critical focus of B complex control of RSV-induced tumor growth. This possibility, while presently speculative, can be rationalized by supposing that for certain B complex genotypes, the two opposing effects on tumor growth of the viral replication-specific genes, i.e., infection-mediated recruitment versus a tumor cell-associated target antigenicity of viral protein, may be at least partially offsetting.

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