Levels of C-type Viral p30 Antigens in Lymphoma-resistant Mice

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SUMMARY

Until relatively recently, interest has largely centered upon the causal role of oncogenic viruses especially with respect to the development of murine lymphomas. Host factors have recently come to the fore and are considered to be effective here, where we note that, in spite of relatively high levels of C-type viral antigen in the AKR × CBA F1 mouse, this hybrid remains relatively lymphoma resistant. Evidence points to an overriding host factor in this situation that is dominant with respect to tumor resistance and furthermore independent of the viral load at least as judged by levels of p30 viral antigen, an assumption confirmed by xc plaque assay.

INTRODUCTION

In contrast to the AKR mouse and in spite of being H-2k which is generally associated with susceptibility to virus-induced tumors (12), spontaneous lymphomas are uncommon in the CBA mouse (10). This has led to the suggestion of the presence of a factor(s) in the CBA mouse that is responsible for its tumor resistance (4). Although variable, the incidence of spontaneous lymphomas in AKR hybrids generally appears to parallel the level of oncogenic virus (11) linking the tumor with the virus. Here we have examined the AKR × CBA F1 mouse to see whether this apparently general rule applies in this hybrid situation.

MATERIALS AND METHODS

Sublines of CBA/H-T6 (hereafter called CBA) and AKR/J mice were used for this study. Both sublines have been maintained at the Clinical Research Centre for more than 5 years and are now designated CBA/H-T6Crc and AKR/Crc, respectively. Their derivation and incidence of tumors have been described previously (4, 5). In this experiment reciprocal crosses were investigated for the incidence of spontaneous lymphomas and for levels of murine leukemia p30 viral antigen using the indirect immunofluorescent absorption technique of Hilgers et al. (9). This assay was performed in 2 stages: (a) the primary titration of the goat anti-AKR virus p30 (National Cancer Institute) sera and (b) the subsequent titration of the same antiserum after absorption with a soluble tissue extract. In each case the reaction was determined upon fixed AKR-A lymphoma cells and demonstrated by the subsequent application of a fluorescein-labeled anti-goat serum. Viral (p30) levels were expressed as the reciprocal of the reduction in titer of the antiserum following absorption as described in detail elsewhere (9).

Xc plaque assay was performed as described by Rowe et al. (15) but on tail snippings. In practice a 1% extract was prepared with a mortar and pestle, and 0.5 ml of this extract was placed upon both NIH and BALB/c cells. Six days later the cells were irradiated and received a xc overlay (15).

The mice were examined clinically at weekly intervals and sacrificed for postmortem examination when symptoms characteristic of thymoma became apparent. At intervals during life, tail snippings were obtained for xc plaque assay. Levels of p30 were determined upon soluble extracts of thymus, spleen, and kidney from lymphomatous mice and also in a 2nd group of apparently healthy AKR × CBA hybrids together with age-matched AKR and CBA controls.

RESULTS

The results obtained from these matings show that, in 116 F1 mice, only 6 lymphomas were found and these were all in the AKR × CBA F1 cross (Chart 1). Although at this stage there is no obvious statistical difference between the 2 hybrids, if this tendency becomes more apparent then it would suggest an additional AKR maternal effect. This continues to be investigated.

As can be seen from Table 1, the levels of viral antigen in the thymus and spleen of the AKR × CBA hybrids were generally comparable or in excess of the AKR age-matched controls. p30 could not be detected in any of the 10 CBA thymuses or spleens examined.

Results in the xc plaque assay are summarized in Table 2. Clearly like findings in the AKR mouse, infective virus is present in the AKR × CBA F1 hybrid. Again as with levels of p30, no ecotropic virus could be demonstrated in the CBA controls using the xc plaque assay.

DISCUSSION

Clearly, resistance to lymphomas in the AKR × CBA hybrid occurs independently of the presence of high levels of p30 viral antigen that appear to represent at least in part infective ecotropic virus. Tumor resistance in this particular hybrid contrasts with other AKR hybrids where the incidence of lymphomas apparently parallels levels of the virus
High Levels of C-type in Lymphoma-resistant Mice

The presence of group-specific leukemia virus (p30) antigen in reciprocal AKR x CBA/H-T6 F1 crosses. S, alive; A, dead without lymphoma; Δ, dead with lymphoma.

Table 1

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* First mouse in any cross is the mother. °, not tested. † Numbers in italics were obtained on tissues obtained from mice with thymoma.

(11). Although it was conceivable that high levels of the p30 antigen are not synonymous with high levels of active oncogenic virus, this seems unlikely in view of results with the xc assay. Results in this assay record the presence of infective ecotropic virus in both reciprocal AKR x CBA crosses but not in the CBA mouse. The levels in the hybrids were extremely variable; the possible significance of this with respect to subsequent tumor development is being studied. Regrettfully, it was not possible to test for both Xc and p30 in any 1 mouse, but it is interesting to speculate on the possible significance of the very high levels of p30 and the possibility that this might not be paralleled by infectivity. In this context the real significance of the p30 levels is questioned as to what it really represents; xenotropic virus is 1 possibility that is being examined.

Findings suggest the presence of a factor in the CBA that is dominant in terms of tumor resistance and furthermore that this is active independent of high levels of p30 viral antigen and relatively high titers of infective ecotropic virus. It is not surprising that the viral load is high in the AKR x

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CBA F₁, since this is a FV-1* × Fv-1* situation permissive to replication of an n-tropic oncogenic virus (14). The reason for the relatively high levels of p30 antigen in the AKR × CBA mouse is uncertain but conceivably might be due to the lack of the corresponding antiviral antibody that characterizes the parental AKR (13).

The lack of correlation between viral load (at least p30 levels and to a lesser extent in the xC assay) and lymphoma susceptibility is in contrast to the earlier described AKR hybrids (11). This latter finding has tended to support the primary role of the virus and tumor development. From the results presented here, it is obvious that other host-determined and furthermore dominant factors apart from the virus must be considered with respect to virus-associated tumor development. It remains to define the mode of activity and location of the factor in the CBA mouse that is responsible for tumor resistance. Other evidence supporting the existence of this factor is detailed elsewhere (1, 4, 6) together with the mechanism that is possibly involved (2, 3, 6, 7).

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REFERENCES

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