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## Immune Responses of Rats to Antigens of Moloney Leukemia Virus

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IMMUNE RESPONSES OF RATS TO ANTIGENS OF MOLONEY LEUKEMIA VIRUS

Rats represent an attractive model for immunogenetic studies, since their major histocompatibility locus (RT1) resembles in structure the major histocompatibility locus of humans (HLA) (Gill, 1978), and since the immune responses to retroviruses that are associated with disease processes in humans resemble more closely the responses seen in rats than those seen in mice (Panem and Reynolds, 1979; Jones et al., 1978).

Brown Norway (BN) rats exhibit high antibody responses and high susceptibility to tumor induction by Moloney sarcoma virus, whereas Lewis (LEW) rats exhibit low responses and low susceptibility (Veit et al., 1977). In previous studies, control of these responses was shown to be influenced by genes linked to RT1, but an influence of other genes was also indicated (Jones et al., 1978; Veit et al., 1977). The present studies provide additional evidence that genes linked to RT1, if necessary, are not sufficient for high antibody responses when this locus is bred onto the background of a low responder strain.

The rat strains used in these studies, the sources and some of their properties are summarized in Table 1. Additional details of most strains were described by Festing and Staats (1973). Approximately equal numbers of males and females were used at three to six months of age.

Purified Moloney leukemia virus (MuLV) was obtained from the Resources Branch of the National Cancer Institute. A vaccine was prepared by treating the virus with 1:2000 formalin for 24 hrs at 4°C. Rats were immunized with vaccine by two subcutaneous and one intravenous injection at weekly intervals, and serum samples were collected one week after the last injection. Rat Moloney sarcoma tumor cells (MST) have been previously described (Jones et al., 1974). Rats were injected subcutaneously with  $5 \times 10^6$  MST cells, and serum samples were collected 22 days later.

The p15, p30 and gp70 polypeptides of MuLV were prepared and labeled with  $^{125}\text{I}$  as described (Jones et al., 1978), and radioimmunoassays for antibody conducted as described (Jones et al., 1977). Briefly, 0.3 to 0.5 ng  $^{125}\text{I}$  labeled antigen was incubated with 5 $\mu\text{l}$  rat serum, and rat immunoglobulin with bound antigen was precipitated with an excess of goat anti-rat gamma globulin. Values were corrected for specificity by tests with normal rat serum from the strain being tested.

Table 2 shows that when immunized with oncogenic virus (MuLV) or with tumor cells (MST), BN rats exhibit high antibody responses and LEW low responses. LEW-1n congenics with RT1n of BN bred on a LEW background exhibited responses similar to LEW. TO rats, which differ genetically from all of the other three strains, exhibited responses similar to BN to p30 and responses lower than BN to gp70. This shows that higher responders to p30 are not automatically higher responders to other viral polypeptides. Table 3 shows that the phenomenon observed with LEW low responses, LEW-1n congenics with RT1n of BN bred on a LEW background exhibited responses similar to LEW. To rats, which differ congenics carrying the RT1f of AS2 on a LEW background were low or non-responders to p15. LEW-1f were also low responders to gp70 when immunized with MuLV (% precipitation  $3.8 \pm 2.6$ ), and LEW rats were low responders to p15, p30 and gp70 in all tests when immunized with MuLV.

The responses of BN and LEW rats to several antigens have been compared (Gunther, 1978), and in most cases LEW are high responders and BN are low responders. Responses to MuLV are an exception, since BN are high and LEW are low. The results with LEW-1n show that such responses are influenced by genes that are not linked to the major histocompatibility locus of rats, RT1. Although immune responses of several animal species including humans are controlled by immune response (Irr) genes linked to the major histocompatibility locus (Benacerraf and McDevitt, 1972), the present report and other studies (Doig and Chesebro, 1979) demonstrate that other genetic loci are important. While it is clear that the major histocompatibility loci (H-2, RT1, HLA) are significant, we must not become overly fascinated by these genetic regions to the extent that we tend to ignore other genetic influences which are equally significant in immune responses and in disease susceptibility. The so-called "major influences" have been explored primarily because they are the easiest to measure, but the so-called "minor influences" should also be examined.

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Table 1. Properties of inbred and congenic rat strains.

Strain	RTI <sup>b</sup>	Source <sup>c</sup>	Responder Status <sup>d</sup>	Tumor Susceptibility <sup>e</sup>
Lewis (LEW)	l	UA	Low	Res
Brown Norway (BN)	n	UA	High	Sus
Tokyo (TO)	t	HU	Med	Res
AS2 (AS2)	f	MP	Med	N.D.
LEW-RTIn (BN) (LEW-1n) <sup>a</sup>	n	MP	Low	Res
LEW-RTIf (AS2) (LEW-1f) <sup>a</sup>	f	MP	Low	N.D.

<sup>a</sup>Congenic: LEW-1n, RTIn of BN bred onto LEW background; LEW-1f, RTIf of AS2 bred into LEW background.

<sup>b</sup>Allele of rat major histocompatibility locus.

<sup>c</sup>Sources: UA, University Arkansas Medical Sciences, Little Rock; HU, Hokkaido University, Sapporo, Japan; MP, Max-Planck Institute, Freiburg, West Germany.

<sup>d</sup>Antibody responses to MuLV antigens: High, high responders to all viral polypeptides; Low, low responders to all viral polypeptides; Med, high responses to some polypeptides but low responses to others.

<sup>e</sup>Susceptibility to tumor growth when inoculated with sarcoma virus or MST tumor cells: Res, resistant; Sus, susceptible; N.D., not determined.

Table 2. Antibody responses of rats to antigens of MuLV.<sup>a</sup>

Strain	RTI	Response to: <sup>b</sup>	
		MuLV vaccine (p30)	MST cells (gp70)
LEW	l	4.4 ± 0.8	29.4 ± 8.0
BN	n	37.8 ± 12.2	70.3 ± 3.1
LEW-1n	n	5.5 ± 1.3	43.2 ± 6.9
TO	t	24.4 ± 7.9	41.5 ± 7.3

Percent of input (0.3-0.5 ng) <sup>125</sup>I-p30 precipitated by 5 μl serum, average of five animals ± std error.

<sup>b</sup>Each group was immunized with three injections of 100 μg MuLV and bled seven days after the last injection, or with one injection of 5 × 10<sup>6</sup> viable MST cells and bled 22 days later.

Table 3. Antibody responses of AS2 and LEW-1f rats to antigens of MuLV.<sup>a</sup>

Strain	RTI	Antigen and % precipitation <sup>b</sup>	
		p30	p15
AS2	f	0.9 ± 0.5	26.4 ± 8.1
LEW-1f	f	7.2 ± 2.4	1.5 ± 1.5

<sup>a</sup>Each animal received three injections of 100 μg MuLV.

<sup>b</sup>Percent of input (0.3-0.5 ng) <sup>125</sup>I-p15 or <sup>125</sup>I-p30 precipitated by 5 μl serum, average of five animals ± std error.

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