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Generation of Recombinant Murine Leukemia Viruses De Novo: An Alternative Model for Leukemogenesis

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A. Summary

Evidence for the viral etiology of murine lymphoma is very complex. Although ecotropic viruses were considered in the past to be the causative agents, envelope gene recombinant (RM) types of murine leukemia virus (MuLV) seem to be the best candidates at present. The following factors are relevant in the murine model: Pure ecotropic MuLV causes disease but induces RM-MuLV de novo in every case. RM-MuLV can cause disease in pure form. However, the mere presence of RM-MuLV may not be sufficient to cause disease in some cases. Ecotropic MuLV is needed under natural conditions for inducing T-cell blastogenesis, donating its coat to recombinant MuLV, and to become a partial parent for RM-MuLV. Early elimination of ecotropic MuLV can prevent disease. In a number of virus-free mouse lymphomas, the only indicator of virus involvement was on RM-MuLV glycoprotein on cell surface. Based on the above, a signal hypothesis model is proposed which attempts to integrate the above observations.

B. Introduction

Murine lymphoma has been one of the earliest and most explored models in both viral and physical carcinogenesis. Despite enormous amounts of data on the role of many classes of viruses, genes, and genetically pure mouse strains, no clear-cut views of a common mechanism of etiology had been formulated. At present, there are several candidate classes of murine leukemia viruses (MuLV) which could be involved in causality. These include ecotropic (E) agents which grow only in mouse or rat cells, xenotropic agents (X) which are endogenous to mouse DNA but grow only in nonmouse cells, and viruses which have a polytropic host range. The last group includes wild mouse amphotropic C-type viruses and viruses which appear to be envelope (*env*) gene recombinants (RM) of E and X nucleotide sequences. The *env* gene product of RM-MuLV is a permuted glycoprotein, gp70, molecule identifiable by various biological and physical parameters. It is only the latter type of viruses which seems to be critically involved in leukemogenesis [6, 14]. At least some RM-MuLV could induce leukemia and fulfill the postulates of causality [7]. On the other hand, the role of these viruses in disease is very complex, and generally they are not detectable in E-MuLV stocks because they are masked with the ecotropic *env* gp70 coat [8]. However, a very simple question had not been answered: Could pure E-MuLV cause leukemia by itself or is generation of RM-MuLV required in every case? The data below unambiguously answer this question and are fitted into an alternative model for leukemogenesis.

C. Composition of MuLV Stocks

When standard leukemogenic strains of MuLV are tested for the presence of RM-MuLV or X-MuLV, they are almost always negative. However, when tested for the genomic content of individual infectious units, stocks of Moloney (M), Friend, Graf-

Procedure (Time and number of tests)	Virus assays FIU/ml in[a]	
	Mouse indicator cells	Cat indicator cells
A. Direct assays of virus from SC-1 cells (3 yrs, ten tests)	5×10^6	0
B. Passage of virus through virus-free thymoma cells – Swiss and C57BL (2 yrs, 12 tests)	4×10^4	0
C. Passage of virus through mouse S+L– cells: by assay of pseudotype host range (2 yrs, six tests)	7×10^5	0
D. Assay of property of individual infectious units (65 tested)	65/65 positive	0/65 positive

[a] Indicator cells were S+L– FG/10 mouse or clone 81 cat cells for leukemia viruses and normal mouse 3T3FL cells and normal feline fibroblast cells for the assay of MSV pseudotype viruses in C

Table 1. Genetic purity and stability of ecotropic Moloney MuLV passed in tissue culture

fi, and Gross MuLVs all contained RM-MuLV between 1%–10% of total viruses [10]. The strain 1869 of M-MuLV was cloned by single focus isolation and end-point limiting dilution techniques (M-1869). The genetic purity and the ecotropic stability of this virus were ascertained by various procedures. As seen in Table 1, this virus grew to high titers in normal mouse fibroblast cells, and in 3 years of passage never generated any virus with an extended host range on direct testing in mink or cat sarcoma-positive, leukemia-negative (S+L–)cells. Virus was also passed through several types of virus-free mouse thymic lymphoma cells in culture. In several years of testing in E-MuLV nucleotide sequence- free Swiss lymphoma cells (NIXT line) or in the C57B1 RL-12 lymphoma line, no recombinant virus was generated. Extensive unmasking experiments were performed by checking whether RM-MuLV was contained in an ecotropic MuLV coat because of serum oncornavirus inactivation factor (OIF) selection pressure [21]. This was done most simply by passing cloned M-1869 through mouse S+L– cells and checking whether any MSV progeny virus was detected which could form foci in cat or mink cells [7]. No RM-MuLV was detected at a sensitivity level of $\leqq 10^{-6}$. Finally, individual infectious units of M-1869 were tested for their genomic content by infecting microtiter wells containing mouse S+L– cells at an effective e.o.p. of 0.2. The progeny of all 65 single infectious unit positive wells was strictly ecotropic MuLV, indicating that RM-MuLV was not induced in tissue culture and that mixed "diploid" genomes were not detected. Accordingly, this M-1869 stock was considered to be free of associated RM- or X-MuLVs.

D. De Novo Induction of Recombinant MuLV in Vivo

The cloned pure ecotropic M-1869 was inoculated into newborn Balb/c mice. After an inoculum of 2×10^5 FIU of M-1869 per mouse, the animals rapidly became viremic and leukemia developed in ~90% of the animals in 3–5 months. The disease was compatible with the previously described Moloney syndrome [5]. Table 2 presents data on virus status on 32 individually tested Balb/c mice in various stages of their disease. High titers of virus were seen in the plasma within a week after inoculation. The animals continued to be viremic, but no free or masked X- or RM-MuLV was detected until ~60 days of age, when about half of the animals had very low amounts

Table 2. Generation of RM-MuLV in vivo after ecotropic M-MuLV inoculation

Balb/c mice age in days (condition)	Mice[a] tested	MuLV titer (FIU/ml)			% RM-MuLV[b] of total virus (number of mice +)
		Direct in mouse S+L−	Direct in cat S+L−	Masked RM-MuLV	
7–30 (viremic)	14	$\geqq 10^6$	0	0	0 (0)
30–60 (viremic)	4	1.3×10^6	0	2.9×10^2	0.02% (2)
60–90 (preleukemic)	4	9.8×10^5	0	4.3×10^3	0.44% (4)
75–150 (leukemic)	10	9.4×10^5	0	2.7×10^4	2.9% (10)

[a] Pooled organ extracts from each mouse were tested individually. In some cases, the thymus, spleen, or liver were tested separately

[b] Average values of all individuals. In the leukemic population RM-MuLV as percent of total virus varied from 0.33% to 6.8%

of masked RM-MuLV in their plasma. During the preleukemic phase, all the animals had detectable masked RM-MuLV (0.5% of all ICCs). During the early frank leukemic phase, the E M-1869 virus titer remained 10^6 FIU/ml, but no free RM-MuLV was detected. These animals had a high level of circulating OIF in their plasma. However, about on average 2.9% of all virus was masked RM-MuLV. In *every* case of leukemia, new RM-MuLV was detected. The presence of this virus was coincidental with disease, and had to arise de novo.

To test these phenomena more precisely, infectious cell center (ICC) experiments were carried out. Lymphoid cells in thy-

Table 3. Infectious cell centers by lymphoid cells from organs of M-MuLV 1869 inoculated Balb/c mice

Days after infection	Organ	Percent of infectious cell centers[a]	
		Ecotropic: on mouse S+L− cells	Recombinant: on cat S+L− cells
10	Thymus	0.8	$<10^{-6}$[b]
	Spleen	5	$<10^{-6}$
20	Thymus	11	$<10^{-6}$
	Spleen	3	$<10^{-6}$
30	Thymus	22	$<10^{-6}$
	Spleen	9	$<10^{-6}$
40	Thymus	15	0.005
	Spleen	9	$<10^{-6}$
57	Thymus	21	0.3
	Spleen	7	$<10^{-6}$
150	Thymus	10	0.04
	Spleen	8	0.01

[a] From 10^3 to 10^6 twice-washed lymphoid cells from freshly harvested organs were added to mouse or cat S+L− cells. Foci of infections were counted 6 and 12 days later in mouse or cat S+L− cells respectively

[b] Lower level of sensitivity: no foci detected at 10^6 cells/dish

muses and spleens were tested by using dilutions of washed cells (10^6–10^3 per dish of mouse or cat S+L– cells) and determining the proportion of cells yielding virus in either test system. Table 3 shows virus growth in cells of thymuses or spleens. Very rapid growth of virus occurs during the first week of life in the cells of both organs. Between 10% and 25% of all lymphoid cells could act as ICCs for ecotropic MuLV, which is 10–1000 fold higher than in the endogenous AKR disease development [12]. The high ecotropic MuLV titers persist throughout life and into the leukemic phase. When the aliquots of the same cells were tested in cat S+L– cells to determine whether they produced RM- or X-MuLV, no RM-MuLV producing cells were apparent until about day 40. After that, essentially all animals were positive for RM-MuLV regardless of time of testing. Virus-positive cells were present essentially only in the cells of the thymus and not in the spleen or the liver. RM-MuLV positive cells were detected in other organs only during late stages of disease. The rather strict appearance of RM-MuLV only in the thymus underscores the fact that recombination generating RM-MuLV probably took place only in the thymic environment.

E. Properties of the Induced RM-MuLVs

It is generally known that individual RM-MuLVs, derived even from a single type of MuLV, exhibit a remarkable variety of changes in their *env* gene coded gp70 product [4, 13, 23]. Additionally, RM-MuLVs derived from Moloney stocks had Moloney-specific p12 and p15 peptides [9]. It was of interest to test the nature of newly derived RM-MuLVs from the relatively

Table 4. Envelope characteristics of selected RM-MuLVs derived from Moloney ecotropic MuLV

Property measured	Virus isolate					
	RM-M_{HIX}	RM-Mp_1	RM-M_{57}	RM-M_{PB9}	RM-AKR_{Tul}	*Eco*869
Growth in mouse S+L– cells	$\geqq 10^5$[a]	$\geqq 10^5$	10^2	10^3	$\geqq 10^4$	1×10^6
Growth in mouse fibroblasts (SC-1)	$\geqq 10^5$	$\geqq 10^5$	10^3	$\geqq 10^4$	NT	6×10^6
Growth in cat S+L– cells						
Type of focus	Syncytial	Syncytial	Syncytial	Syncytial	Round cells	0
In cat or mink cells	$\geqq 10^5$	$\geqq 10^5$	$\geqq 10^2$	$\geqq 10^4$	$\geqq 10^4$	0
Interference pattern[b]	RM-type	RM-type	RM-type	RM-type	RM-type	Ecotropic type
Neutralization with[c]						
Anti M gp70 MAb	+	+	+	+	–	+
Anti xenotropic gp70 serum	–	–	–	–	–	–
Anti AKR gp70	–	–	–	–	+	–
Sensitivity to OIF[d] (normal mouse serum)	+	+	+	+	+	–

[a] Focus-inducing units/ml; NT, not tested

[b] Interference patterns can be of three types: The ecotropic type tested by using free ecotropic F-MuLV (2 μg/dish) gp70 on mouse cells which reduces the number of ecotropic MuLV FIU by ≧90% [15]; The RM-type, in which a preinfection of either a mouse or nonmouse cell induces complete interference with any other RM-MuLV, the xenotropic type in which a preinfection of a nonmouse cell with xenotropic MuLV prevents growth of both RM-MuLV, and xenotropic MuLV. RM-AKR_{Tul} was isolated from the plasma of an uninoculated leukemic AKR mouse [10]

[c] Monoclonal antibody (MAb) 1D11 against ecotropic Moloney MuLV gp70 produced in tissue culture neutralizes only ecotropic Moloney MuLV but not Friend, Rauscher, Graffi, or AKR MuLVs [2]

[d] Normal STU mouse serum used at 1 : 100 dilution, which neutralized about 99% of virus

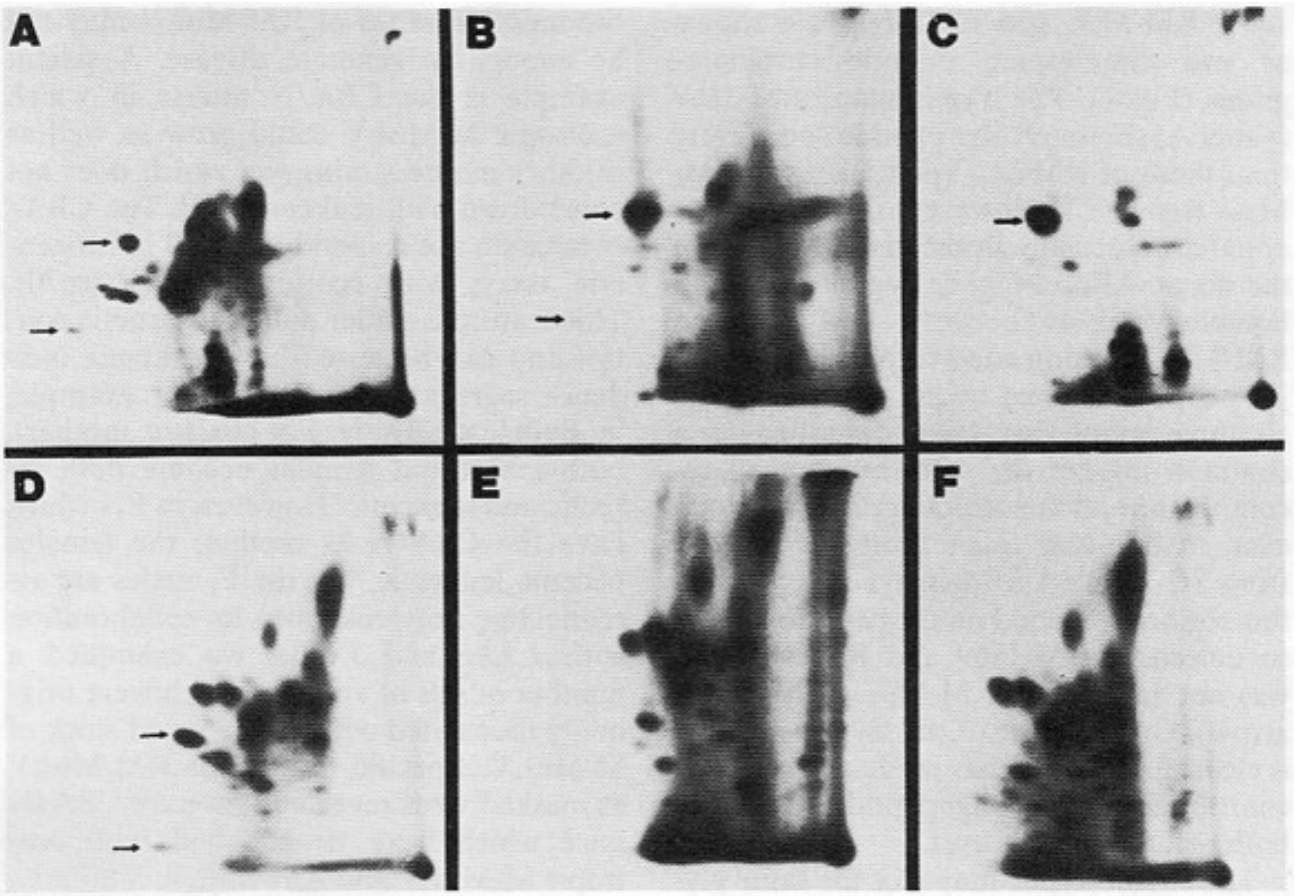

Fig. 1. Comparison of tryptic (*panels A–C*) and chymotryptic (*panels D–F*) peptides of gp70 polypeptides isolated from 1869-MuLV (*panels A, D*), RM_{57}-MuLV (*panels B, E*), RM_{PB9}-MuLV (*panels C, F*) cell culture fluids. The *arrows* denote specific peptides discussed in the text. The origin is at the *lower right* in each panel with the first dimension electrophoresis to the *left side* and second dimension ascending chromatography to the *top* in each panel. Technical aspects of iodination and two dimensional maps have been described [4]

early stages of the infective process. Accordingly, we isolated one RM-MuLV from a healthy, viremic mouse 56 days after inoculation (RM-M_{57}), and another from an early leukemic phase (RM-M_{PB9}). Two or more cycles of single focus isolation and limiting dilution isolation in cat diploid cells were performed in each case. What became apparent was that in terms of growth, RM-M_{57} did not grow avidly in any cell tested, but had a definite predisposition for growth in mouse cells (Table 4). In contrast, RM-M_{PB9} grew substantially better, yet favored heterologous cells in which it grew to higher titers. Both of these viruses are in contrast to other standard isolates such as RM-M_{HIX} or RM-M_{PI}, which grew equally well to higher titers in both mouse and nonmouse cells. However, all of the RM-M-MuLV derivatives produce very distinct syncytial foci in cat S+L– cells in contrast to RM-MuLVs from other types.

On testing of further *env* properties of these de novo isolated viruses, it was clear that all were very susceptible to mouse serum OIF as other RM or X-MuLVs. Neither virus was susceptible to any major degree to type-specific anti AKR or anti X-MuLV gp70 specific antisera. A clear relationship was detected to the presumed parental ecotropic M-MuLV gp70 in that specific neutralization was observed with a monoclonal antibody to Moloney gp70, which neutralized only M-MuLVs. Interference patterns of the new isolates are being examined whether they also follow a unique one-way interference pattern as described [9]. It is clear that although RM-MuLV isolates share an interference group, they are not interfered with by ecotropic gp70 and that X-MuLV can penetrate the RM-MuLV preinfection barrier in heterologous species cells [10].

The tryptic and chymotryptic oligopeptides of gp70 molecules isolated from M-

1869, RM-M_{57}, and RM-M_{PB9} are shown as two dimensional peptide chromatograms (Fig. 1). The tryptic map of M-1869 (panel A) shows greater peptide complexity than those of RM-M_{57} (panel B) and RM-M_{PB9} (panel C). However, similarities are apparent especially in the central region of the maps. Also, a higher degree of overall homology exists between RM-M_{57} and RM-M_{PB9} as contrasted to M-1869. A major peptide, denoted by the upper arrow in all three maps, has been described as a common marker for most but not all recombinant and xenotropic gp70s [4]. However, in this case, pure ecotropic M-1869 from SC-1 cells also displays a peptide in this region. A second minor peptide was also detected in M-1869 and RM-M_{57} that was not detected in RM-M_{PB9} gp70 (lower arrow). On the basis of the tryptic maps, it is clear that M-1869 has made a substantial contribution to the oligopeptide content of both recombinant viruses.

The chymotryptic maps for the same glycoproteins were also compared in Fig. 1. A striking degree of homology exists between the three glycoproteins, most noted between RM-M_{57} and RM-M_{PB9}. RM-M_{57} gp70 does contain a series of unique peptides of low electrophoretic mobility. The M-1869 contains two peptides unique to itself (arrows in panel D). The peptides in the lower right region of the maps of the presumed recombinant gp70s appear to contain the P32 group described as pathognomonic for RM-MuLVs [22].

F. Factors Required in Murine Viral Leukemogenesis

At this time, two other sets of phenomena besides the de novo induction of RM-MuLV seem to be operative in murine leukemogenesis which complicate the picture. The first factor is that the presence of an ecotropic virus during the first few days of life is mandatory. The best evidence for this is the fact that either in the spontaneous AKR or in the genetic M-MuLV disease, treatment with broadly neutralizing anti MuLV gp70 serum neutralized the ecotropic MuLV, and eliminated or reduced the ICCs, and prevented disease effectively [12, 24]. The second feature is that the mere presence of RM-MuLV may not be enough to generate disease. A salient example is the CBA/N mouse in which ecotropic M-MuLV could grow as well as in other mouse strains, yet which does not come down with leukemia [19]. The CBA/N mice do not respond in T-cell blastogenesis assays with ecotropic MuLV gp70s. This feature is under maternal genetic control and can be tested how leukemia incidence segregates in crosses. For example, in Balb/c×CBA/N F_1s (Balb/c mother), both males and females become both viremic and leukemic. However, in F_1s which have the CBA/N as mother, the females become leukemic, but the F_1 males are viremic but not leukemic. In collaboration with J. Lee and J. Ihle, we examined a number of sets of animals which were originally inoculated with a noncloned stock of M-MuLV. Specific testing for RM-MuLV as masked virus revealed that pure CBA/N mice which were viremic had both ecotropic M-MuLV and RM-MuLV. Similarly, in the F_1 cross with Balb/c mice, both variable sets and both sexes had similar amounts of masked RM-MuLV whether they developed leukemia or not. It is clear that at least in this genetic strain, RM-MuLV may be requisite, but of itself not sufficient for the development of leukemia. Because this strain has an inoperative system for blastogenesis after ecotropic MuLV gp70 stimulation, it may be inferred that an expanded lymphoid target cell population is also critical.

G. Role of RM-MuLV in Virus-Free Lymphomas

Despite the plethora of viral agents causing leukemia in the mouse, a classical phenomenon is the induction of a high percentage of leukemia in several strains of mice with X-rays [17]. Many of these leukemias are free of virus. Although in some cultured lymphoma lines, various MuLVs are released, many of these cultured lymphoma cell lines are free of detectable virus and viral antigens. A Swiss X-irradiation induced virus-free thymoma cell line (NIXT), and the RL-12 virus-free lymphoma were examined [11, 16]. Viral antigens were not detected with standard reagents, but in

each case antiserum against the RM-MuLV VL3 gp70 isolate stained a portion of cells in immunofluorescent assays [3]. The cells were highly resistant to infection with RM-MuLV, but not ecotropic MuLV. In both cases, a form of gp70 could be found on the cell surface and in the supernates. Based on peptide mapping, it was clear in both cases that there was a single species of gp70 on each cell. Both gp70s were of the RM-MuLV class, which was compatible with the supposition that specific interference was responsible for the RM-MuLV resistance of these two cell lines. The specific molecular origins of the RM-MuLV like gp70s are as yet unknown. However, in at least one mouse strain, a preexisting endogenous RM-MuLV class gp70 gene was described [1].

H. Signal Hypothesis Models for Viral and Virus-Free Mouse Lymphomas

The known factors required for viral leukemogenesis in the mouse are the presence of an E-MuLV, the generation of an RM-MuLV, and an expanded population of cells of the T-cell lineage. Viral gp70 is known to stimulate blastogenesis, and this response is known to be critical for and predictive of development of leukemia [18]. The central element is that within the reactive nonspecifically expanded population, a cell occurs with a specific receptor for a single type of RM-MuLV gp70. Such cells have been described. When this cell becomes infected with the matching RM-MuLV, it produces both the driving signal

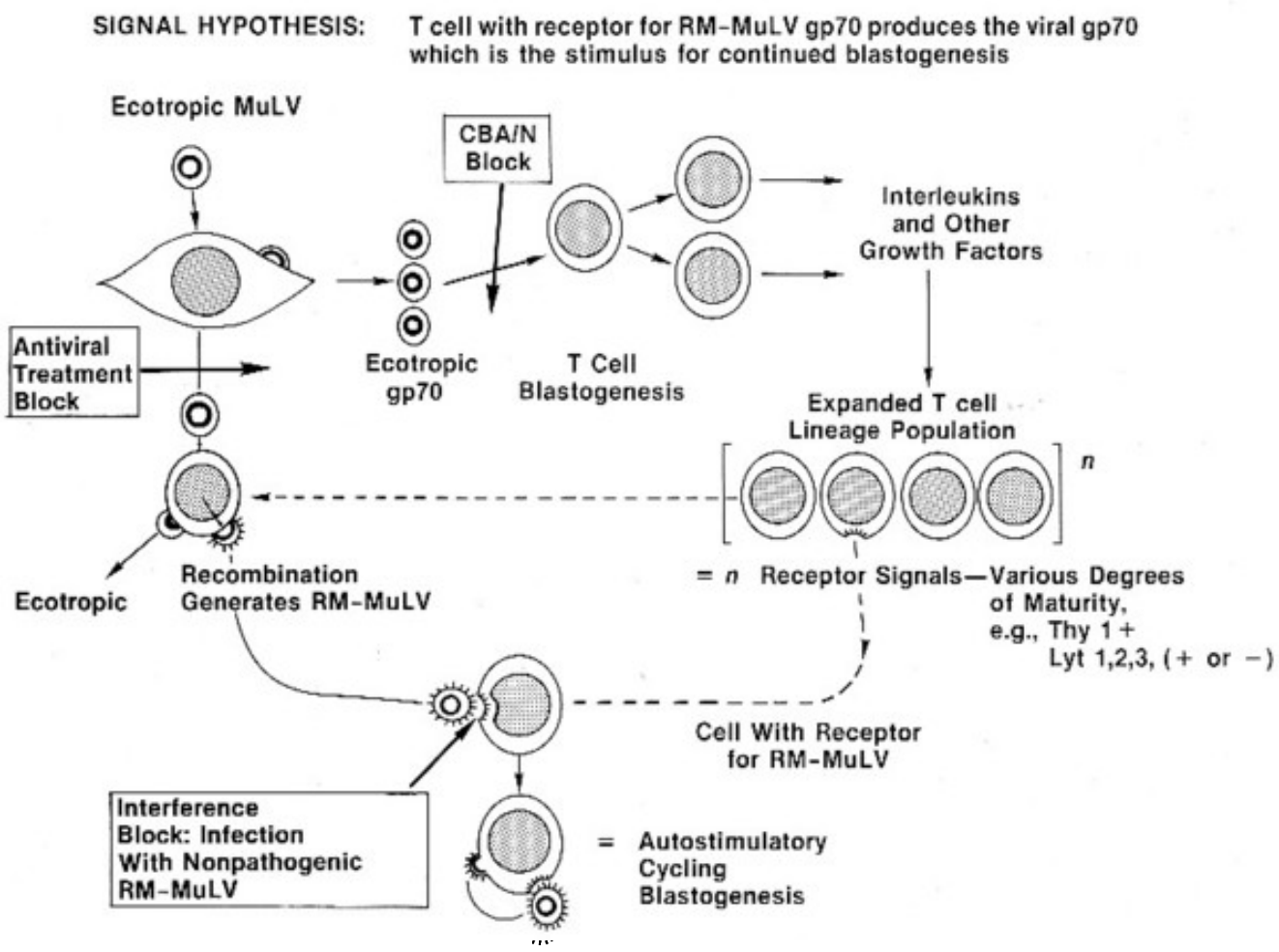

Fig. 2. A model describing multiple factors required for development of murine leukemia. Ecotropic MuLV is depicted with a smooth coat, RM-MuLV with projections. Ecotropic virus first replicates in various lymphoid organs in null cells and only later in T cells. CBA/N "block" describes the inability of lymphoid cells of that mouse strain to react in blastogenesis after exposure to ecotropic gp70, although the ability to generate new E and RM-MuLV appears not to be impaired. Interference "block" refers to the possibility that less pathogenic strains of RM-MuLV could preinfect the target cell which is then refractory to infection with the more pathogenic variant

and the receptor for it, resulting in a clonal population of autostimulated cells. This view, presented in Fig. 2, is different in principle from the Weissman model, which presupposes anergy to endogenous ecotropic MuLV gp70 [20].

The etiology of virus-free mouse lymphoma may be the more important example of the hypothesis. The ultimate requisite signal would be only an RM-MuLV gp70. Recombinational events could occur within the genome, involving whole or partial retrovirus-like gp70 sequences after chemical or physical perturbation of DNA. Whole virus need not be produced. However, if such recombination generates a surface gp70 in a cell with a receptor for it, such a cell could be capable of cycling blastogenesis resulting in an unlimited clonal expansion. The presence of loosely attached, unique, single species of an RM-MuLV like gp70 in virus-free lymphomas of several mouse strains would tend to support such a view [11].

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