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Mechanism of Leukemogenesis Induced by Mink Cell Focus-Forming Murine Leukemia Viruses

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The Friend or Moloney mink cell focus-forming (MCF) virus encodes a recombinant-type envelope glycoprotein, gp70, that is closely related to the membrane glycoprotein, gp55, of Friend spleen focus-forming virus (SFFV). We have shown previously that gp55 has the ability to activate cell growth by binding to the cellular receptor for erythropoietin. Here we show that gp70 encoded by either the Friend or Moloney MCF virus also binds to the erythropoietin receptor and that coexpression of the receptor and gp70 in an interleukin-3 (IL-3)-dependent cell line can activate IL-3-independent growth. Furthermore, when the cDNA for the human IL-2 receptor β chain, which is related by sequence to the erythropoietin receptor, was introduced into this cell line, it became growth factor independent after infection either with SFFV or with one of the two MCF viruses but not with an ecotropic virus. Based on these observations, we propose a mechanism for the early stage of leukemogenesis induced by the MCF-type murine leukemia viruses.

There is a class of murine leukemia viruses (MuLVs) that have a characteristic envelope glycoprotein (gp70) that allows infection of cells from many species. They transform mink cells and are called mink cell focus-forming (MCF) viruses (29). Many murine-tropic viruses convert to MCF viruses in animals by recombination in the *env* region with endogeneous MCF virus-type sequences (7, 9, 21, 23, 49, 56). Particularly relevant to the present work is that the spleen focus-forming viruses (SFFVs) encode a glycoprotein, gp55 that is a truncated form of MCF gp70 (2, 5, 15, 65).

Various MCF viruses have been isolated from a variety of spontaneous and virus or non-virus-induced leukemias and lymphomas, including spontaneous lymphomas of AKR (16, 29) or HRS/J (27) mice; ecotropic Friend MuLV-, Rauscher MuLV (R-MuLV)-, or Moloney MuLV-induced leukemias or lymphomas (14, 22, 51, 59, 61, 62); X-ray induced lymphomas (28); and graft-versus-host-induced reticulum cell neoplasms (3). Some of the MCF viruses are potent leukemogens, and they cause tissue-specific neoplasms when injected into susceptible newborn mice (14, 32, 61). Others can accelerate the leukemogenic process in mice with high incidence of spontaneous leukemias (16). The mechanism of leukemogenesis induced by the various MCF viruses is not known.

Previous studies of several cloned MCF virus genomes revealed extensive sequence identities in their amino-terminal *env* regions (1, 8, 34, 35, 63). Recombinations between the nonleukemogenic amphotropic virus 4070 and leukemogenic Friend MCF (F-MCF) virus have shown that, in addition to the long terminal repeat (LTR) sequences, the *env* gene of F-MCF virus is required for leukemogenicity (48). Further studies have established that the tissue specificities of many virus-induced diseases are determined by sequence elements in the LTRs of the viral genomes (11, 12, 25, 33, 40, 63).

Friend SFFV causes an acute erythroleukemia in adult mice (24, 41, 58). SFFV gp55 encoded by the recombinant-type *env* gene (57) is directly involved in leukemogenesis (37, 38, 43, 52). Sequence analyses of the *env* genes from several different SFFVs have indicated that they all contain a 5′-terminal region highly homologous to the MCF virus *env* sequences and that they may actually be derived from the MCF virus *env* gene through a major deletion and some point mutations (2, 5, 15, 65). There is evidence that SFFV gp55 binds to the cellular receptor for MCF viruses and that this binding interferes with MCF virus superinfection (13, 38).

We have shown previously that SFFV gp55 binds to the cellular receptor for erythropoietin (Epo-R) and that this interaction can activate cell growth (39). This provides a plausible explanation for how the viral protein may cause a prolonged proliferation of the infected erythroid cells, which may eventually lead to the activation of an additional cellular oncogene(s) (47) and to the development of leukemia. Because Epo-R appears to belong to a family of growth factor receptors (4, 18, 19), including the recently cloned human interleukin-2 (IL-2) receptor β chain (IL-2Rβ) (31), it is possible that the recombinant-type viral glycoproteins interact with various members of this receptor family which are expressed during certain stages of hematopoiesis in various target cells, causing a prolonged proliferation of these cells in the preleukemic stage.

Here we show that the gp70 encoded by either the F-MCF or Moloney MCF (M-MCF) virus, like the SFFV gp55, binds to Epo-R and that this interaction can activate growth factor-independent proliferation of an IL-3-dependent lymphoid cell line. Furthermore, when coexpressed with IL-2Rβ, these glycoproteins can also activate cell growth. We propose a general model for leukemogenesis induced by the MCF virus-type MuLVs involving growth factor receptor-mediated proliferation.

MATERIALS AND METHODS

Cell culture and virus infection. Mouse NIH 3T3 fibroblast cells were maintained in Dulbecco's modified Eagle medium supplemented with 10% calf serum, and IL-3-dependent pro-B lymphoid Ba/F3 cells (44) were grown in RPMI plus 10% fetal bovine serum and 10% WEHI-3 supernatant as a source of IL-3. For virus infection, about 5×10^5 to 2×10^6

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cells were mixed with 2 to 5 ml of various supernatants collected from virus-producing fibroblasts immediately before infection. Polybrene (8 μg/ml; Sigma) was added to facilitate the infection. After 4 h of incubation at 37°C, fresh medium containing IL-3 was added, and the cultures were kept for 48 h before they were switched to medium without any added growth factors or with IL-2 (2 U/ml; Boehringer Mannheim), Epo (0.5 U/ml; Amgen), or IL-3 as control. After 1 week of incubation at 37°C, the infected cells were cloned by limiting dilution. R-MuLV was produced from the Rwt NIH 3T3 line (38), and Friend SFFV was produced from fibroblast packaging cells after they were transfected with a molecular clone (42) of the Lilly-Steeves polycythemia strain.

Plasmid construction and DNA transfection. The plasmid pIL-2Rβ30, which contains cDNA or human IL-2Rβ (31), was a gift from T. Taniguchi. A DNA fragment encompassing the coding sequence for IL-2Rβ was engineered to be compatible with *Bam*HI-*Eco*RI sites and was cloned into retroviral vector pSFF (6) through these sites. The resulting plasmid, pSF-I2Rβ, was transfected into a mixture of psi-cre and psi-crip packaging cells (20) by calcium precipitation (26), and virus containing the IL-2Rβ cDNA sequence was obtained from the culture supernatant after 2 weeks of cocultivation according to the previously described method (6). The molecular clone of either F-MCF virus (plasmid pFr-MCF1310) (1) or M-MCF virus (plasmid pMo-MCF-I) (8) was transfected into NIH 3T3 cells, and the corresponding virus was obtained from the culture supernatant 2 weeks later.

IP. The general method of immunoprecipitation (IP) was described previously (53). For double IP, the [^{35}S]methionine (50 μC/ml; New England Nuclear)-labeled cells were lysed with IP buffer (20 mM Tris [pH 7.4], 0.1% sodium dodecyl sulfate [SDS], 1% Triton X-100, 0.5% sodium deoxycholate, 0.5 M NaCl, 1 mM EDTA), and the protein extracts were precleared of cell debris by ultracentrifugation (Beckman TL-100; 90,000 rpm for 10 min). After the first IP with an anti R-MuLV gp70 antiserum (National Cancer Institute) which cross-reacts with both SFFV gp55 and MCF virus gp70, the IP pellets were resuspended in 0.05 ml of loading buffer (60 mM Tris [pH 6.8], 2% SDS, 10% glycerol, 1% 2-mercaptoethanol) and heated at 100°C for 10 min. After a brief microcentrifugation, the supernatants were diluted 1:20 with IP buffer and subjected to a second IP using an anti Epo-R antiserum (39). Anti-IL-2Rβ IP was carried out with the anti-human IL-2Rβ monoclonal antibody Mik-β1 (31), generously provided by M. Tsudo. Protein samples from the IP pellets were analyzed by electrophoresis through 12.5% SDS-polyacrylamide gels.

RESULTS

MCF virus envelope glycoproteins bind to Epo-R. To determine whether the MCF virus envelope glycoproteins could bind to Epo-R, we infected the cell line ER-1, a fibroblast subclone that expresses a high level of Epo-R (39), with either F-MCF or M-MCF virus. IP with anti-gp70 showed a high level of gp70 expression after infection (Fig. 1A, lanes 1 and 2, for F-MCF virus- or M-MCF virus-infected ER-1 cells, respectively), and the identities of the polytropic gp70s in these cells were confirmed by additional IP with an MCF virus-specific monoclonal antibody (64; data not shown). The uninfected ER-1 cells contained ecotropic gp70 (Fig. 1, lane 3; also see reference 39).

Because of the excess of MCF virus gp70 in the IP with

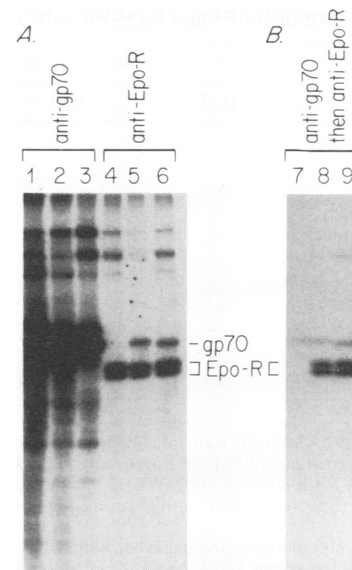

FIG. 1. SDS-polyacrylamide gel electrophoresis of [^{35}S]methionine-labeled proteins after IP. (A) Lanes 1 to 3, Single IPs by a goat anti-R-MuLV gp70 antiserum which cross-reacts with both MCF virus gp70 and SFFV gp55 (38); lanes 4 to 6, single IPs with antiserum against the NH_2-terminal (APSPSLPDPKFESKC) peptide of the Epo-R protein (39). (B) Lanes 7 to 9, Double IPs first by anti-gp70 antiserum and then by anti-Epo-R. Labeled proteins were extracted from 5×10^5 ER-1 fibroblast cells without virus infection (lanes 3, 4, and 7) or with either F-MCF virus (lanes 1, 6, and 9) or M-MCF virus (lanes 2, 5, and 8) infection.

anti-gp70 and the close comigration of gp70 and Epo-R, it was difficult to examine the possible coprecipitation of the two proteins in this experiment. However, when the anti-Epo-R antiserum which did not cross-react with the MCF virus gp70 (data not shown) was used, it clearly showed that both M-MCF virus gp70 (Fig. 1, lane 5) and F-MCF virus gp70 (lane 6) could be coprecipitated with Epo-R, whereas the ecotropic gp70 could not (lane 4; also see reference 39), indicating that in MCF virus-infected ER-1 cells, some MCF virus gp70 was tightly bound to Epo-R. The identities of the two MCF virus gp70s were confirmed by the fact that the M-MCF virus gp70 normally migrates slightly more slowly than the F-MCF virus gp70 (compare lane 5 with lane 6; data not shown).

To further confirm this finding, we first immunoprecipitated the proteins from either uninfected or MCF virus-infected ER-1 cells with anti-gp70 and then dissociated the proteins that precipitated and subjected them to a second IP with anti-Epo-R. Only Epo-R protein from ER-1 cells infected with either of the MCF viruses could be recovered from the final precipitates (Fig. 1B, lanes 8 and 9). For uninfected ER-1 cells, no Epo-R could be detected in the final precipitate (lane 7), presumably because the Epo-R remained in the supernatant during the first IP with anti-gp70. This result, along with that presented above, shows that the recombinant-type gp70 encoded by either F-MCF or M-MCF virus, like SFFV gp55 (39), interacts strongly with Epo-R.

Binding of Epo-R by MCF virus gp70s can activate cell growth. To examine whether the interaction of MCF virus gp70 and Epo-R had a growth-promoting activity, we isolated a subclone from IL-3-dependent lymphoid Ba/F3 cells

TABLE 1. Growth of Ba/F3 and Ba/F-ER cells after infection[a]

Cell line and source of infection	Growth in medium supplemented with[b]:		
	IL-3	Epo	Nothing
Ba/F3			
Mock	+	−	−
R-MuLV	+	−	−
F-MCF virus	+	−	−
M-MCF virus	+	−	−
Ba/F-ER			
Mock	+	+	−
R-MuLV	+	+	−
SFFV	+	+	+
F-MCF virus	+	+	+
M-MCF virus	+	+	+

[a] About 5×10^5 to 2×10^6 cells were infected with various viruses that were harvested from supernatants of NIH 3T3-producing cells. After infection, the cells were kept for 48 h in IL-3 (10% WEHI-3 supernatant) before being switched to either Epo (0.5 U/ml) or regular medium without any added growth factors.

[b] +, rapidly growing cells became established within 1 week of infection; −, no viable cells were left within 3 to 4 days after infection, and no cell growth occurred even after up to 1 month of incubation.

(44) after these cells had been infected with an Epo-R cDNA-containing virus (39). This subclone, called Ba/F-ER, was Epo (or IL-3) dependent for growth. When Ba/F-ER cells were infected with either F-MCF or M-MCF virus, about 0.05 to 0.1% of the cells could grow in the absence of any added growth factors, while either the mock-infected or the ecotropic R-MuLV-infected Ba/F-ER cells still required IL-3 or Epo (Table 1). The low infectability of Ba/F3 cells by retroviruses was reported previously (44), and we found that a similar percentage (about 0.1%) of these cells could be infected by either MCF virus or R-MuLV (data not shown). The growth factor independence was observed only when both Epo-R and one of the recombinant-type glycoproteins were expressed in these cells: the parental Ba/F3 cells could not be converted to growth factor independence after infection by either of the MCF viruses (Table 1) or by SFFV, as shown previously (39). These results clearly indicate that binding of Epo-R by the MCF gp70, like the interaction between Epo-R and SFFV gp55, can activate cell growth. This was further confirmed by the finding that when growth factor-independent Ba/F-ER cells were cloned after infection with MCF viruses, all of the individual clones expressed a high level of MCF gp70 (Fig. 2). Interestingly, many of these clones also expressed an SFFV gp55-like protein (lanes 2 to 7 and 9). This suggests that there may be a strong selection for the expression of these truncated proteins during growth factor-deprived growth of these cells (see Discussion). Nevertheless, the fact that there were clones that expressed MCF gp70 alone (lanes 1, 8, and 10) indicated that the interaction of MCF gp70 with Epo-R was sufficient to activate cell growth.

Coexpression of IL-2Rβ and recombinant-type glycoproteins can also activate cell growth. It has been shown that Epo-R and IL-2Rβ share limited amino acid sequence identities (18) and that they may belong to a family of growth factor receptors (4, 19). Human IL-2Rβ is homologous to that of mouse (31, 36), and its cDNA when introduced into Ba/F3 cells could convert these cells to IL-2 dependence (30). To see if IL-2Rβ had the ability to substitute for Epo-R during growth factor-independent proliferation of virus-infected Ba/F3 cells, we cloned human IL-2Rβ cDNA into the retroviral vector pSFF (6) and introduced it into a mixture of psi-cre and psi-crip packaging cells (20). After 2 weeks of cocultivation, a high level of human IL-2Rβ was expressed in these cells (Fig. 3, lane 2), and virus harvested from the supernatant contained IL-2Rβ cDNA sequences and was infectious to mouse NIH 3T3 fibroblasts (data not shown).

When this virus was used to infect Ba/F3 cells, we obtained several clones that depended on either IL-2 or IL-3 for their growth (data not shown) and expressed human IL-2Rβ (Fig. 3, lanes 3 and 4). One of these clones, Ba/F-I2, was infected with various viruses and subsequently grown in medium without any added growth factors. As shown in Table 2, only those infected with SFFV, F-MCF virus, or M-MCF virus could grow in the absence of growth factors. The mock- or R-MuLV-infected cells retained absolute IL-2 (or IL-3) dependence. When factor-independent Ba/F-I2 cells infected with various recombinant-type viruses were cloned, a high level of viral glycoprotein expression was seen in all of the individual clones (Fig. 4, lanes 2 and 3, SFFV-infected clones; lanes 4 and 5, F-MCF virus-infected clones; lanes 6 to 9, M-MCF virus-infected clones), while in mock-infected Ba/F-I2 cells, no such glycoprotein expres-

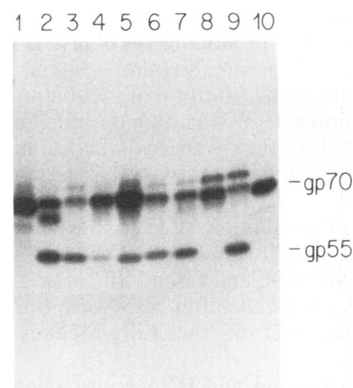

FIG. 2. Electrophoretic separation of labeled proteins after anti-gp70 IP. Ba/F-ER clones were infected with F-MCF virus (lanes 1 to 3) or M-MCF virus (lanes 4 to 10).

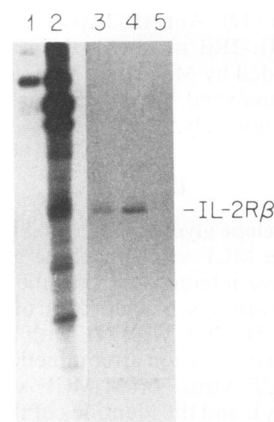

FIG. 3. Electrophoretic separation of labeled proteins after IP with anti-IL-2Rβ. Lane 1, NIH 3T3 cells; lane 2, psi-cre–psi-crip packaging cells after transfection with pSF-I2Rβ; lanes 3 and 4, two IL-2-dependent clones of Ba/F3 cells after infection by the IL-2Rβ cDNA-containing virus; lane 5, uninfected Ba/F3 cells.

TABLE 2. Growth of Ba/F-I 2 cells after infection[a]

Source of infection	Growth in medium supplemented with:		
	IL-3	IL-2	Nothing
Mock	+	+	–
R-MuLV	+	+	–
SFFV	+	+	+[b]
F-MCF virus	+	+	+[b]
M-MCF virus	+	+	+[b]

[a] See Table 1, footnote *a*.
[b] The growth of these cells depended on cell density (see text).

sion was seen (lane 10). These results indicated that all three recombinant-type glycoproteins had the ability to interact with IL-2Rβ and activate factor-independent growth of Ba/F3 cells.

Factor-independent growth of virus-infected Ba/F-I2 cells is density dependent. In the process of growing SFFV- or MCF virus-infected Ba/F-I2 cells, we noticed that there were cell density requirements for the growth of these cells. This was confirmed by limiting-dilution analysis, as shown in Table 3. The growth of SFFV-infected Ba/F-I2 cells showed a density requirement of about 10^3 cells per ml to initiate positive growth in the absence of growth factors, while cells infected with either of the MCF viruses required more than 10^5 cells per ml to initiate positive growth. In contrast, SFFV- or MCF virus-infected Ba/F-ER cells grew with equal efficiency in the presence or absence of IL-3 (Table 3). These results indicated that unlike virus-infected Ba/F-ER cells, infected Ba/F-I2 cells had a requirement for close cell contact during factor-independent growth. This was further confirmed by the observations that these cells formed clusters in culture dishes and that constant dilutions caused extensive cell death (data not shown).

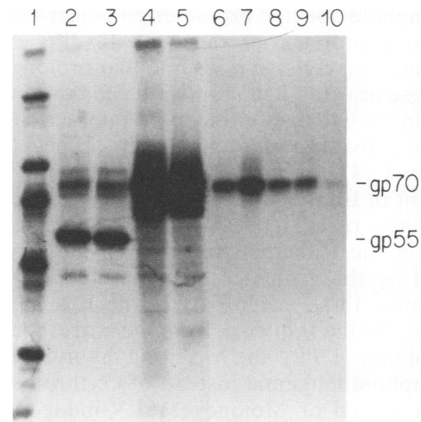

FIG. 4. Electrophoretic separation of labeled proteins after IP with anti-gp70. The proteins were extracted from Ba/F-I2 clones infected with SFFV (lanes 2 and 3), F-MCF virus (lanes 4 and 5), or M-MCF virus (lanes 6 to 9). Lane 10, Uninfected Ba/F-I2 cells; lane 1, labeled protein molecular weight markers.

DISCUSSION

Previously we showed that SFFV gp55 binds to Epo-R and that the mitogenic effect of this binding can be demonstrated by the ability to promote growth factor-independent proliferation of lymphoid Ba/F3 cells (39). We now extend this finding to MCF virus envelope glycoproteins by showing that MCF gp70s have a similar activity. Furthermore, when coexpressed with IL-2Rβ, both SFFV and MCF glycoproteins can activate proliferation of Ba/F3 cells in the absence of growth factors. Together, these results provide evidence for a common mechanism by which MCF-type MuLVs can induce neoplasms because of their propensity to interact with growth factor receptors.

We propose that in the preleukemic stage in infected animals, there is a prolonged proliferation of infected hematopoietic cells due to the interaction between recombinant-type viral glycoproteins and one member of the Epo-R–IL-2Rβ growth factor receptor family that is expressed in the specific target cells. The tissue specificity of this preleukemic proliferation depends not only on the type of the infected cells in which the viral promoter-enhancer is active, but also on the availability of a growth factor receptor that is expressed during the normal development of those cells. For example, the LTRs of both the SFFV and F-MCF virus genomes contain erythroid-specific promoter-enhancer elements (12, 54), and their glycoproteins interact with Epo-R expressed in infected erythroid precursor cells. On the other hand, the thymotropic MCFviruses, such as M-MCF virus,

TABLE 3. Limiting-dilution analysis of infected cells

Cell line and source of infection	No. of wells with positive growth[a]/total no. of wells							
	In RPMI at dilution of:						In RPMI + IL-3 at dilution of:	
	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}	10^{-6}	10^{-5}	10^{-6}
BA/F-I2								
Mock	0/36	0/36	0/36	0/36	ND[b]	ND	12/24	1/24
SFFV	36/36	36/36	24/36	2/36	ND	ND	15/24	1/24
F-MCF virus	17/36	1/36	0/36	0/36	ND	ND	9/24	2/24
M-MCF virus	18/36	1/36	0/36	0/36	ND	ND	10/24	2/24
Ba/F-ER								
SFFV	ND	ND	ND	ND	31/36	8/36	33/36	4/36
F-MCF virus	ND	ND	ND	ND	24/36	3/36	22/36	4/36
M-MCF virus	ND	ND	ND	ND	20/36	5/36	20/36	3/36

[a] Various infected cell cultures growing at about 10^6/ml were diluted and put into the 96-well culture dishes at 0.1 ml per well. Two to three weeks later, wells having viable, actively dividing cells were scored as having positive growth.
[b] ND, Not done.

contain lymphoid-specific promoter-enhancer elements (10), and their glycoproteins interact with IL-2Rβ expressed in infected lymphoid cells. We assume that prolonged proliferation of these infected hematopoietic cells as a result of this glycoprotein-growth factor receptor interaction eventually leads to the activation of an additional cellular oncogene(s) such as Spi-1 (47) or c-*myc* (17, 55, 60) and thus to the development of frank leukemia.

Several lines of evidence have suggested that the tissue specificity of the leukemias induced by various MuLVs is determined by the sequence elements in the LTRs of the viral genomes. First, when part of the F-MCF virus LTR was replaced by the sequence from the corresponding region of the Moloney LTR, the resulting hybrid virus caused mainly lymphoid leukemia instead of erythroleukemia (33). Second, in Friend or Moloney MuLV-induced leukemias, which are believed to be due to the eventual appearance of MCF viruses in the infected animals (59, 62), the tissue specificity of the disease was also determined by the LTR sequence (11, 12, 40). These findings indicate that the recombinant-type viral glycoproteins themselves do not determine tissue specificity. This is consistent with our findings that M-MCF and F-MCF virus gp70s have a similar biological effect when coexpressed with either Epo-R or IL-2Rβ in Ba/F3 cells.

SFFV gp55 seemed to have a stronger effect than MCF virus gp70s in promoting the proliferation of Ba/F-I2 cells, because SFFV-infected cells had a lower density requirement for initiating positive growth in the limiting-dilution analysis (Table 3). It is known that SFFV-induced erythroleukemia is more severe and that it occurs within a relatively short period (about 2 weeks) in adult mice (24), while F-MCF virus-induced erythroleukemia is milder and occurs several months after infection and only in newborn animals (32). The difference in biological activity of these viruses in vivo, therefore, may be a direct reflection of the differences between the effects of gp55 and gp70 in Ba/F-I2 cells.

The nature of the gp55-like proteins seen in the MCF virus-infected Ba/F-ER clones (Fig. 2) is not known. Because both of our F-MCF and M-MCF virus stocks were obtained from mouse fibroblast cells after the cells had been transfected with the corresponding molecular clones (1, 8) and because the sizes of some of these proteins as judged by their migration on SDS-polyacrylamide gels vary (Fig. 2, compare lanes 6 and 7, for example; data not shown), it is unlikely that these proteins are a consequence of contaminating SFFV genomes. It is possible that these proteins are actually from defective viral genomes that are generated either through deletions of the MCF virus *env* gene or through recombination of the MCF virus genome with some endogenous sequences. In any case, it seems that there is a strong selection for the expression of these proteins during factor-independent growth of Ba/F-ER cells. It will be of interest to see if these potentially defective viruses resemble SFFV and represent evolution from an MCF virus to SFFV.

It is possible that the putative cellular receptor which the MCF viruses use to penetrate the target cell belongs to the same receptor family as Epo-R–IL-2Rβ, although the MCF virus receptor must have an entirely different tissue distribution because it is expressed in mouse fibroblasts. The virus may actually use Epo-R–IL-2Rβ to penetrate various target cells in infected animals. It was reported that the Rauscher MCF virus isolate, which could not infect mouse NIH 3T3 fibroblasts in vitro, was fully leukemogenic when injected into animals (63), implying that it used a different receptor to penetrate target cells in vivo. The fact that there are viruses that belong to the same interference group as MCF viruses in fibroblasts yet fail to cause cytopathic foci on mink cell monolayers (50) also seems to indicate that the MCF viruses may use a variety of different receptors for their penetration of target cells.

It is surprising that IL-2Rβ, which shares only minimal sequence identities with Epo-R, can substitute for Epo-R in promoting cell growth when coexpressed with viral glycoproteins. Although we have so far failed to show a direct binding of IL-2Rβ by the viral glycoproteins in a double-IP assay, there may still be a direct interaction between the two proteins which is not as strong as that between the glycoproteins and Epo-R and which is disrupted under the conditions of our IP assay. Indeed, the observation that the growth of virus-infected Ba/F-I2 cells has a density requirement might suggest that a weak interaction between IL-2Rβ and the glycoproteins is facilitated by close cell-cell contact.

Of all the members in the Epo-R–IL-2Rβ family, including the receptors for human growth hormone, rabbit prolactin, granulocyte-macrophage colony stimulating factor, IL-3, IL-4, IL-6, and IL-7 (4, 19), Epo-R is most closely related to IL-2Rβ (18). It is unlikely that the recombinant-type viral glycoproteins can interact with all members of this receptor family. The receptor for IL-3 in Ba/F3 cells, for example, is probably not bound by the viral glycoproteins because infection with either MCF viruses (Table 1) or SFFV (39) does not convert Ba/F3 cells to growth factor independence.

A receptor-mediated model was previously proposed for virus-induced leukemogenesis (45, 46). Here we suggest that the model was fundamentally correct except that it is a hormone receptor, rather than an antigen receptor, that mediates the leukemogenic process.

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