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Cell Surface Receptors for Endogenous Mouse Type C Viral Glycoproteins and Epidermal Growth Factor: Tissue Distribution In Vivo and Possible Participation in Specific Cell-Cell Interaction

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We have described previously the detection and tissue distribution of free cell surface receptors for ecotropic R-MuLV envelope glycoprotein and the growth factor EGF in vivo [1]. More recently, we have reported the chromosomal map position of the ecotropic viral receptor and its conservation between subspecies of the genus Mus [2]. This work has shown, for the first time, the presence of multiple, independently segregating cell surface receptor genes specific for different classes of ecotropic type C viral envelope glycoprotein. In this report we extend these findings and identify chromosome 2 as coding for the receptor used by M813, an ecotropic MuLV from a feral Asian mouse. This new receptor is probably also used by oncogenic, recombinant (MCF class) MuLV of C3H origin.

Key words: cell surface receptors, type C viral glycoproteins, growth factors

Organization of cells into tissues and the induction of specific patterns of differentiation in these tissues presumably requires cell surface components that can mediate specific intercellular adhesion [3] as well as growth stimulation and morphogenesis [4]. Endogenous and transforming type C viruses code for or induce gene products that can act as ligands for both classes of cell surface receptors; those involved in cell adhesion and others participating in mitogenesis. Thus, the viral envelope glycoprotein gp70, which can be expressed independent of complete virus production [5], specifically binds to cell surface receptors [6] and may thereby affect the social behavior of cells. There are multiple receptors for the different classes of endogenous mouse type C viruses [2]. At least one of them shows a tissue-specific distribution in vivo [1, 7], and the linkage group to which its gene has been assigned is conserved between different species of the genus Mus [2]. Sorting out of cells into tissue-specific combinations from mixtures that were derived from different species also shows that organ specificity of cell adhesion is maintained across species barriers [8]. These findings are consistent with the hypothesis that endogenous viral envelope gene products or their cellular homologues (progenitors), together with the corresponding receptors, may mediate tissue-specific cell-cell adhesion [2].

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Mammalian sarcoma viruses, on the other hand, code for or induce polypeptides, which interact with cell surface receptors that are responsible for mitogenesis and, possibly, morphogenesis. A specific example of this is sarcoma growth factor (SGF) that is produced by MSV- or FeSV-transformed cells and acts through the EGF receptor on cells [9].

During chronic infection of mouse cells with endogenous mousetropic MuLV, variants emerge that have gained the ability to induce infected cells to growth in soft agar and/or to show an altered tissue tropism for oncogenesis [10, 11]. At least some of these variants have a substitution in their envelope gene [12] resulting in the recognition of a new cell surface receptor for infection, as is shown in this report. Thus, it appears that variants of endogenous mouse type C viruses that differ in their tissue tropism for infection and others that induce infected cells to autonomous growth can be used as tools for the identification of ligands, as well as receptors, that may be important in the establishment and maintenance of differentiated cells.

MATERIALS AND METHODS

Cells

All cell lines were maintained in Eagle's minimal essential medium (MEM) with 10% heat-inactivated fetal calf serum (FCS). The origin and characteristics of the cell lines used for virus growth and virus assays have been described [13]. The C3H/10T1/2 C18 line was developed from a C3H/Heston mouse embryo. This strain has a low "spontaneous" leukemia incidence. The 10T1/2 line and chemically transformed derivative lines have previously been shown to have endogenous type C viruses that can be activated [14].

Viruses

The ecotropic viruses M813 and Moloney MuLV (from M cervicolor popaeus) were maintained in NIH3T3 cells [15]. MCF class recombinant MuLV clones Z6 and Z9 were obtained from endogenous C3H MuLV as described previously [10, 12].

Preparation of Tissues for Binding Assays With gp70 and EGF

Cells from all major mouse tissues were obtained as previously described [1]. Cell or tissue fragments were suspended at 1×10^6 cells per ml, or approximately 0.2 mg protein per ml, and washed twice with 2 ml portions of Dulbecco's modification of Eagle's medium containing 1 mg/ml of bovine serum albumin and 50 mM N,N-bis-(2-hydroxyethyl-2-aminoethanesulfonic acid (BES), pH 6.8 (binding buffer). Binding assays were performed by incubating 10 ng of radiolabeled gp71 with cells in 1 ml of binding buffer for 2 h at 22°C. At the end of this incubation, the cells were centrifuged for 10 min at 500g, the pellets were washed 3 times with binding buffer and lysed, and the bound radioactivity was determined by liquid scintillation counting as previously described [1]. The same procedure was followed when the binding of iodinated mouse EGF was determined.

Radioimmunoassay for gp71

The 71,000 mol wt glycoprotein purified from R-MuLV was iodinated to high specific activity [1]. Competition radioimmunoassays were performed by incubating goat ant-Gross MuLV antiserum (Viral Oncology Program Resources, National Cancer

Institute, Bethesda, MD) and competing antigen at 37°C for 1 h in 0.2 ml reaction mixtures containing 10 mM Tris HCl, pH 7.8, 1 mM EDTA, 0.4% Triton X-100, 0.1 M NaCl. The ^{125}I-labeled antigen (12,000 cpm) was then added and the mixture incubated for an additional hour at 37°C and 18 h at 4°C. This was followed by the addition of 50 μl of rabbit anti-goat immunoglobulin G to each reaction mixture. Incubation proceeded for 1 h at 37°C and 3 h at 4°C, after which time precipitates were pelleted by centrifugation at 1,300 g for 15 min. The supernatants were aspirated, the pellets washed twice with the above described buffer, and radioactivity in the precipitate was measured in a gamma counter.

Construction of Somatic Cell Hybrids and Isozyme Analysis

Hybrids between mouse and Chinese hamster fibroblasts were obtained as described previously [2]. Three sets of hybrids were used in this study [1] between M cervicolor and Chinese hamster E36 cells [2] and between M musculus strain C57BL/6 G IX$^+$ and E36 cells [17]. For isozyme analysis soluble extracts were prepared as described previously [2]. The following isozymes were determined: dipeptidase 1 (DIP-1,3,4,11), phosphoglucomutase-2 (PGM-2,2.7.5.1), phosphoglucomutase-1 (PGM 1,2.7.5.1), 6-phosphogluconate dehydrogenase (6 PGD, 1,1.1.44), glucosephosphate isomerase (GPI,5,3.1.9), mannosephosphate isomerase (MPI, 5.3.1.8), nucleoside phosphorylase (NP, 2.4.2.1), tripeptidase-1 (TRIP-1, 3.4.11), dipeptidase-2 (DIP-2,3.4.11), adenine phosphoribosyltransferase (APRT, 2.4.2.7), acid phospatase (ACP-1,3.1.3.2), adenylate kinase (AK-1, 2.7.4.3), dipeptidase-D (DIP-D, 3,4.11.9), and hypoxanthine phosphoribosyl transferase (HPRT, 2.4.2.8), Glyoxylase-1 (GLO-1,4.4.1.5), triosephosphate isomerase (TPI, 5.3.1.1.), galactokinase (GALK, 2.7.1.6), glutathione reductase (GR, 1.6.4.2), malic enzyme (MOD-1,1.1.1.40).

RESULTS

Tissue Distribution of Free Receptors for RLV gp70 and EGF

Table I summarizes the data obtained from the binding of ^{125}I-labeled RLV gp70 and EGF to cells freshly prepared from CBA mice at 4 weeks of age. The highest binding activity per mg protein was found in the bone marrow, followed by cells from the other major lymphoid tissues. Among the nonlymphoid tissues, brain showed the highest level of binding that cannot be explained by the presence of contaminating lymphocytes, since this organ is known to be void of lymphatic structures. Free receptors for ^{125}I-labeled EGF showed a more limited distribution. Liver was the only major organ with high levels of free receptors. Lung, kidney, and brain also bound radiolabeled EGF to a limited extent (between 0.3 and 0.5%) relative to liver.

Tissues that were negative for binding of either RLV gp70 or EGF were also low or negative in expression of endogenous viral gp70 or EGF [1]. Thus, the absence of binding activity was not due to the presence of blocked receptors.

Evidence for Multiple Receptors Specific for Different Classes of Endogenous MuLV Envelope Glycoproteins

Somatic hybrids between hamster and mouse cells were used to determine which mouse chromosomes were essential for infection of cells by different classes of MuLV. The Chinese hamster fibroblasts E36 are negative for the salvage pathway enzyme hypox-

TABLE I. Results of Binding of ^{125}I-Labeled RLV gp70 and EGF to Cells Prepared from CBA Mice at 4 Weeks*

	Tissue								
Assay	Heart	Brain	Kidney	Lung	Liver	Bone marrow	Thymus	Spleen	Small intestine
cpm of ^{125}I-EGF bound/mg protein	40	138	175	225	47,700	0	0	0	0
cpm of ^{125}I-gp71 bound/mg protein	3,100	28,900	5,000	7,750	12,500	176,000	105,000	120,700	24,400
ng EGF per mg protein	<1	<1	4.6	<1	<1	<1	<1	<1	<1
ng gp71 per mg protein	14	14	16	44	4	376	79	64	72

*Binding reactions were carried out in 1 ml of binding buffer containing either 10 ng of [^{125}I] gp 71 (49,000 cpm) or 3 ng of [^{125}I] EGF (210,000 cpm). Each assay contained approximately 0.20 mg of the tissue examined. The cellular concentrations of gp71 and EGF were determined on aliquots of the samples using a radioimmunoassay as described in Methods. The data shown are for specific binding, which is obtained by subtracting the counts per minute bound to an identical reaction mixture containing 5 μg of unlabeled gp71 (180–420 cpm). All major tissues were freed of lymphatic structures such as lymph nodes or Peyers patches before preparation for binding assays.

anthin-guanin phosphoribosyltransferase (HGPRT-) and therefore do not grow in medium containing hypoxanthin, aminopterin, and thymidine (HAT). These cells were fused with mouse spleen and thymus cells and colonies of hybrid cells selected in HAT medium. The retention of mouse chromosomes was analyzed by electrophoresis for 19 isozyme markers specific for individual chromosomes. All hybrid cells had in common the retention of the mouse X chromosome (due to HAT drug selection) and loss of chromosome 11. The other mouse chromosomes were present in variable numbers and combinations.

Ecotropic MuLV From Mus musculus Uses a Chromosome 5 Coded Receptor

Various sets of hybrids between hamster and Mus cervicolor or hamster and Mus musculus cells were thus analyzed for mouse isozymes and tested for their ability to replicate Moloney MuLV and to bind RLV-gp70. The results from such an experiment with hamster X Mus cervicolor hybrids is shown in Table II, which shows synteny between Moloney replication, RLV-gp70 binding, and retention of PGM-1. PGM-1 is a marker enzyme for chromosome 5 of the mouse [18]. Marker enzymes for other chromosomes did not show synteny [2].

When hybrid cells between hamster and Mus musculus cells were tested in a similar fashion, Moloney MuLV replication and RLV gp70 binding were again syntenic with retention of chromosome 5 and asyntenic with all other isozymes tested [2].

Ecotropic MuLV From Mus cervicolor Uses a Chromosome 2 Coded Receptor

The presence of multiple receptors for different classes of ecotropic as well as for xenotropic MuLV has been reported previously by our laboratory [2]. Here we extend these findings and show synteny between M813 replication, an ecotropic MuLV from Mus cervicolor, and adenylase kinase AK-1, a marker enzyme for chromosome 2 of Mus

TABLE II. Moloney MuLV Replication, gp70 Binding, and Chromosome 5 Marker in M cervicolor X Hamster Hybrid Cells

Hybrid clone	Replication[a]	gp70 Binding[b]	PGM-1
C36 1	–	1.89	–
2	–	1.53	–
3	–	0.95	–
4	–	1.30	–
5	+++	17.4	+
6	+++	32.0	+
7	NT	1.02	–
8	+++	24.1	+
9	+++	16.2	+
11	+++	25.3	+
13	–	0.26	–
14	–	1.46	–
15	+++	47.4	+
16	++	54.4	+
19	+++	31.9	+
20	–	2.54	–
21	+++	49.3	+

[a] NT, not tested

[b] Femtomoles bound per 10^6 cells. E36 and NIH cells bound 2.20 and 34.5 fmoles respectively.

musculus [19]. These data are summarized in Table III. RLV-gp70 binds to mouse × hamster hybrid (or mouse) cells that replicate M813 provided they retain mouse chromosome 5. Hybrids that have lost chromosome 5 still replicate M813. However, all the clones that replicate M813 retain chromosome 2. Using additional hybrid cells resulting from an independent fusion, we observed concordance between M813 replication and mouse adenylate kinase-1 (AK-1) in 59 of 62 hybrids.

Oncogenic Recombinant Viruses (MCF-class) Derived From C3H MuLV May Also Use the Chromosome 2 Coded Receptor

M813 MuLV induces lymphomas in inbred NFS/N mice after adaptation to high titered growth in culture [Rapp and Callahan, unpublished data]. Therefore, we decided to test whether oncogenic recombinant MCF-class MuLV derived from endogenous C3HMuLV as described previously [10–12] might also use a new cell surface receptor, different from that used by its ecotropic parent MuLV and possibly identical to the one used by M813. Table IV shows that the two MCF class MuLV from C3H, Z6, and Z9 do indeed use a new cell surface receptor as evidenced by the fact that RLV gp70 still binds to productively infected cells. M813 infection also does not intefere with this binding, whereas this is completely abolished upon infection with Rauscher MuLV. We therefore used Z6 and Z9 MuLV for infection of hybrid cells that had lost either chromosome 2 or chromosome 5 (Table V). Both MCF-class MuLV from C3H replicate in chromosome 2 positive, chromosome 5 negative hybrid cells but they do not infect a hybrid clone that is positive for chromosome 5 and negative for chromosome 2. M813 shows a pattern of replication that is identical to that observed with Z6 and Z9.

DISCUSSION

Tissue Distribution of Receptors for RLV gp70 and Epidermal Growth Factor, EGF

We have described here that free receptors for gp70 prepared from R-MuLV are present on cells from all major lymphoid organs of young CBA mice. Certain nonlymphoid tissues, most notably brain, also have large numbers of free gp70 cell surface receptors. The absence of detectable receptors does not result from the expression of excess endogenously produced gp71.

Cell surface receptors for EGF appear to be highly restricted in vivo. The only tissue from CBA mice with high binding activity was liver. Lung, kidney, and brain showed approximately 0.5% activity/mg protein relative to liver, and most other tissues did not bind EGF at all. Again, lack of binding was not due to expression of endogenous EGF.

It might be argued that our method for the preparation of cells for the in vitro binding experiments destroyed active receptors in some of the tissues. We attempted to control for this possibility by mixing experiments between cells from receptor-positive and receptor-negative organs. None of these experiments provided any evidence for the presence in non-binder tissues of trans-acting components with the ability to block specific binding of either gp70 or EGF (data not shown).

The high binding activity of liver cells for EGF might indicate that this tissue is the main site of action in adult mice. Our experiments did not screen all mouse tissues for binding, however, and thus it is still possible that cell types present, for example, in skin, might also have high concentrations of free receptors. The use of primary cell

TABLE III. Rauscher gp70 Binding to Cells Previously Infected With M813 Ecotropic MuLV

Mouse X hamster hybrid clone	gp70[a] binding	Chromosome 5	M813 replication	Chromosome 2
FV 1	21.0	+	+	+
NF 1	14.7	+	+	+
FV 5	13.6	+	+	+
NF 4	14.4	+	+	+
NF 5	1.1	–	+	+
NF 7	1.0	–	+	+
NF 10	0.90	–	+	+
NF 12	1.1	–	+	+
FV 11	1.3	–	–	–
FV 13	0.70	–	–	–
Control cells				
Mouse (NIH)	31.4			
Cat (FEC)	1.6			
Hamster (E36)	1.3			

[a]fmoles gp70 bound per 10^6 cells.

TABLE IV. Rauscher gp70 Binding

Culture cells	gp 70 binding
Uninfected	
NIH (mouse)	+
E36 (hamster)	–
NIH infected with MuLV	
RLV	–
Z6	+
Z9	+
M813	+

TABLE V. Replication of MuLV on Hybrid Cells Retaining Mouse Chromosomes 2 or 5

Hybrid cell	M813/NIH[a]	M813/M813[b]	M813/A10924[c]	Z6	Z9	Moloney
Retains 2 but not 5	+	+	+	+	+	–
Retains 5 but not 2	–	–	–	–	–	+

[a]M813 virus after long-term passage on NIH cells.

[b]Early freeze-down of primary culture from which M813 was originally isolated.

[c]M813 virus isolated from co-cultivation of tumor produced by injecting an NIH mouse with M813/NIH virus.

culture systems [20] for cell types that were not readily accessible to in vitro testing by the methods employed in this study should permit us to test this possibility. Our experiments also did not definitively establish whether binding of EGF to liver cells was mediated by a cell surface receptor such as has been purified from established cell lines [21] or by the presence of an EGF transport protein that might be produced in this tissue. Further characterization of the ligand–receptor complex from liver will be needed to settle this question.

Genes Controlling Receptors for Different Classes of Mouse Type C Viruses

Although the physiological significance of growth factor receptors is readily apparent, this is not so for receptors which bind type C viral glycoproteins. It may be worthwhile at this point to digress for a moment and consider some basic features of endogenous type C viruses that have a bearing on the interpretations of our findings reported here. The available data on the distribution of type C viruses in the genomes of vertebrate species allow two alternative views of their origin. Either they were deposited there as a consequence of horizontal spread of infectious viruses, or they evolved from within the vertebrate genome, only occasionally giving rise to highly infectious forms that could spread between members of a species as well as possibly infect different species. In the former case the presence in the hosts genome of multiple divergent copies would be a consequence of the eventual decay of the original infecting viral genome. If they evolved from within the genome to highly infectious forms, their progenitors might have been either sets of genes with a genetic structure analogous to that of type C viruses, such that only small changes, if any, had to occur before they could be expressed as an infectious virus. Or the precursors of type C viruses were genes that are normally not physically linked and jointly expressed. The formation of an infectious viral genome would then be a rare evolutionary artifact resulting from the assembly of genes that otherwise are used individually as building blocks for normal cells. A mechanism by which this might occur has been suggested by Temin [22].

In the first case, endogenous type C viral functions, as a rule, would not be expected to participate in normal cellular processes, except in rare instances where the host has learned to make use of them for its own ends. In the second case, component parts of the virus would have cellular homologues. But even if one were to take the view that all endogenous type C viruses are stranded, exogenous viruses, those of their gene products which had to interact specifically with cellular structures for the virus to be a successful parasite presumably had to mimic a normal host function. Thus, type C viral gene products may be used to probe into vital cell processes.

What are some of the interactions between virus and cell that would lend themselves to the identification of important cellular functions? Little is known in this regard, but 4 (poorly defined) targets seem apparent. One is the cell surface receptor, to which the viral envelope glycoprotein has to bind before entry into the cell is gained. The envelope gene also encodes a polypeptide, p15E, which appears to act as a cellular receptor for Clg, a component of complement [23]. A third receptor or receptor-binding site appears to be located within the viral gag (internal structural protein) gene [24]. In this case interaction is with an intracellular target that can restrict the course of virus infection. The host gene(s) controlling this latter function, Fv-1, has been mapped. No evidence of a possible normal function of this gene has so far been obtained. A fourth class of cellular target molecules is affected by the products of transforming genes carried by

oncogenic type C viruses. In this case it is immediately obvious that the cellular target(s) is vital for normal function, since expression of a transforming gene in the appropriate cell drastically alters its phenotype.

In this report we have described in some detail host genes controlling cell surface receptors for type C viruses. We, and others, have shown previously that a prototype ecotropic MuLV from inbred mice, RLV, uses a chromosome 5 coded receptor for infection of cells [2, 25–27].

The linkage between a gene controlling the RLV gp70 receptors and PGM-1 was retained in hybrids between Chinese hamster × Mus cervicolor cells. Thus, this receptor appears conserved between different species of the genus Mus. Here we show that replication of another ecotropic MuLV, M813, which was isolated from Mus cervicolor popaeus spleen, is associated with retention of mouse adenylate kinase-1 (AK-1). This enzyme is a marker for chromosome 2 [19]. The data specifically exclude any association between M813 replication and chromosome 5. The level at which M813 virus replication is controlled by a gene on chromosome 2 is probably the M813-specific cell surface receptor. This appears most likely, since absence of chromosome 2 does not affect replication of ecotropic MuLVs other than M813.

The specific synteny between chromosome 2 and the M813 virus receptor excludes a relationship between receptor and the major histocompatability complex. (Two hybrid clones that are negative for chromosome 17 but retain chromosome 2 are permissive for M813 replication). However, chromosome 2 does contain a minor histocompatability locus, as is also true of chromosome 5.

We have examined the question of whether use of a certain cell surface receptor for infection would correlate with the pathogenicity in vivo of a given MuLV. M813 virus does induce lymphomas upon inoculation into newborn NFS/N mice (data not shown); so does RLV and Mol MuLV, which infect cells via a chromosome 5 coded receptor. However, the latter viruses invariably generate envelope gene recombinants prior to or during induction of disease, and we therefore cannot conclude that oncogenicity is independent of receptor specificity. To test this possibility further, we determined the receptor used for infection by two such recombinant MCF class MuLV, which we had previously isolated and characterized [10, 12]. As we have shown in this report, both of these oncogenic viruses do not use the chromosome 5 coded receptor; rather, they replicate in hybrid cells that have lost this chromosome as long as they retain chromosome 2. In the course of disease development induced by these latter viruses, no variants that reverted to the use of the chromosome 5 coded receptor emerged [U. R. Rapp, unpublished data]. Thus, we can conclude that interaction with the chromosome 5 coded receptor is not necessary for malignant transformation by MuLV. Interaction between viral envelope glycoprotein and a chromosome 2 coded cell surface receptor, however, may be a critical factor in the transformation of sensitive target cells by MuLV, either because it mediates infection of such cells without being involved in the subsequent transformation process, or because binding of viral gp70 to this receptor directly effects transformation in chronic producer cells. In vitro infection of appropriate target cells with M813 or the MCF class recombinant viruses Z6 and Z9 versus treatment of such cells with viral envelope glycoprotein may allow us to distinguish between these possibilities.

We have hypothesized in a previous report [2] that binding of viral envelope glycoprotein in one cell to the corresponding receptor on the surface of the other cell could provide a basis for modulating cellular recognition and organization in normal and pathological processes [2]. The present results extend this suggestion concerning the

role of endogenous viral gp70 and its corresponding receptor in at least two ways. By defining a new gene controlling a new ecotropic receptor, it supports the concept of receptor diversity in mouse cells. The hypothesis that certain interactions between cells are mediated by viral related genes would seem to require multiple receptors, each with its own specificity. In addition, it suggests that genetic recombination, which is a mechanism of generating diversity among type C viruses, may lead to altered receptor specificity. Similar processes may generate diverse viral glycoproteins, which may accumulate in the cell membrane and thus generate new intercellular interaction mediated by specific receptors.

We have shown that mouse cells have the genetic capacity to express distinct receptors for closely related ecotropic type C viruses. Recently, it has been shown that differential expression of specific receptors for similar type C viruses can be related to leukemic transformation in certain mouse cells [28]. Preferential binding of leukemogenic viruses was demonstrated using the fluorescence-activated cell sorter [28]. Our results showing separate genetic control of receptors for two ecotropic type C viruses provide a genetic basis for such processes.

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