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Antigenic Characterization of Type C RNA Virus Isolates of Gibbon Apes

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Type C RNA viruses initially isolated from a lymphosarcoma of a gibbon ape and from a fibrosarcoma of a woolly monkey are very closely related immunologically. However, recent studies have shown that these viruses are distinguishable in a radioimmunoassay for the 12,000-molecular-weight polypeptide (p12) of the woolly monkey virus. In the present report, an immunoassay has been developed for the p12 polypeptide of the gibbon ape type C virus. This assay is shown to further distinguish the woolly monkey and gibbon ape viruses. In type-specific assays for the p12 polypeptides of these viruses, two new type C viruses isolated from gibbons in a second colony, characterized by high incidence of hemopoietic neoplasia, are immunologically distinguishable from the original gibbon ape virus. The p12 type-specific immunoassays described in the present report may be of importance in studying the natural history of these viruses and their relationship to tumors of primates.

Type C viruses have been implicated in the etiology of cancers of several mammalian species. The isolation of type C viruses from a gibbon ape with a lymphosarcoma (21, 35) and from a woolly monkey with a fibrosarcoma (39) provided the first demonstration that such viruses existed in higher mammalian species. More recently, particle-associated DNA polymerases immunologically similar to the woolly monkey and gibbon ape reverse transcriptases were reported in human leukemias (11, 40). These findings have raised the possibility that viruses immunologically similar to the gibbon ape and woolly monkey viruses may be present in human cancers.

Studies of the natural history and epidemiology of the woolly monkey and gibbon ape viruses require assays which differentiate them. By most available immunological (14, 30, 32, 34) and biochemical (7, 29, 33) methods, the gibbon ape and woolly monkey viruses are very closely related or indistinguishable. However, in a radioimmunoprecipitation test recently developed for a 12,000-molecular-weight polypeptide (p12) of the woolly monkey virus (42), the antigenic reactivities of the woolly monkey virus and the original gibbon ape virus isolate were distinct. In the present report, using this assay and a newly developed immunoassay for the p12 polypeptide of the gibbon ape virus, the antigenic reactivities of several new type C virus isolates of gibbons were examined. The results demonstrate the existence of at least two antigenic subgroups of gibbon type C viruses, each of which is distinct from the woolly monkey virus.

MATERIALS AND METHODS

Viruses. The type C virus isolated from a gibbon ape (*Hylobates lar*) with lymphosarcoma at the University of California Medical Center, San Francisco, Calif. (21, 35) was obtained as a sucrose-gradient purified preparation through the Resources and Logistics Segment, National Cancer Institute. This virus will be referred to as the SFMC gibbon ape virus. A gibbon type C virus, isolated from an animal with granulocytic leukemia maintained in a colony at the SEATO laboratory in Bangkok, Thailand, will be designated as the SEATO gibbon ape virus (18). Type C viruses were recently isolated from two other gibbons (T. G. Kawakami, unpublished results). One animal was from the high leukemia-incidence colony at the SEATO laboratory, and the other was a household pet not traceable to either of the above laboratory colonies. Both are clinically normal at the present time. Other viruses included AKR-murine leukemia virus, Rauscher murine leukemia virus, rat leukemia virus, Rickard strain of feline leukemia virus, RD114 feline virus; type C viruses of the woolly monkey and baboon; and Mason-Pfizer monkey virus. These were obtained as sucrose gradient purified preparations either from Electro-Nucleonics Laboratories, Rockville, Md., or Pfizer, Inc., Maywood, N.J., through the Resources and Logistics Segment, National Cancer Institute.

Isolation and iodination of viral polypeptides. The woolly monkey virus major structural polypeptide (p30) was prepared by gel filtration and isoelectric focusing as previously described (17, 37). The 12,000-dalton polypeptide (p12) of the woolly monkey virus was purified by gel filtration chromatography in the presence of 6 M guanidine hydrochloride (GuHCl) as reported in detail elsewhere (42). A polypeptide antigenically related to the woolly monkey viral p12 was isolated from the gibbon ape virus by this same procedure. Briefly, the SFMC gibbon ape virus was disrupted with 6 M GuHCl, and the polypeptides were separated by gel filtration chromatography in the presence of 6 M GuHCl. After dialysis to remove GuHCl, the column fractions were tested in the woolly monkey p12 radioimmunoassay. A single major peak (95% of total activity) eluted at a position corresponding to 12,000 molecular weight. Thus, this polypeptide will be referred to as the gibbon ape viral p12. Viral polypeptides were labeled with ^{125}I by the method of Greenwood et al. (16). Each polypeptide migrated as single peak when analyzed by polyacrylamide gel electrophoresis in the presence of sodium dodecyl sulfate or by agarose gel filtration in 6 M GuHCl (42). The molecular weight designations are based on the values obtained by agarose gel filtration in 6 M GuHCl according to convention (4).

Immunological methods. Competition radioimmunoprecipitation assays for the woolly monkey virus p30 and p12 polypeptides and for the SFMC gibbon ape virus p12 polypeptide were performed according to published procedures (37, 42). These assays measure the relative abilities of unlabeled type C viral polypeptides to compete with either ^{125}I-labeled p30 or ^{125}I-labeled p12 for binding antibody to either the SFMC gibbon ape or woolly monkey type C viral polypeptides. Antisera, prepared by immunizing goats with Tween-80/ether-treated virions (42), were generously provided by R. Wilsnack, Huntingdon Research Laboratories, Baltimore, Md. The anti-gibbon ape type C virus serum was from a later bleeding of the same animal used to provide antisera in our earlier study (42). Protein was determined by the method of Lowry et al. (25). Measurement of microgram quantities of protein was performed by densitometry of samples after electrophoresis on polyacrylamide gels (43).

RESULTS

Antigenic reactivities of gibbon type C viral p30 polypeptides. The antigenic specificity of the p30 polypeptide of the SEATO gibbon ape virus was compared with that of the original SFMC gibbon ape virus isolate and also with that of the woolly monkey virus. The viruses were analyzed in a species-specific radioimmunoassay for the p30 polypeptide of the woolly monkey virus. The reactivities of the viruses were very similar with respect to the slopes of the competition curves; however, high concentrations of the SEATO gibbon virus competed slightly less effectively than the SFMC gibbon ape and woolly monkey viruses (Fig. 1A). In an heterologous interspecies radioimmunoassay for woolly monkey virus p30 (37), each virus reacted identically (Fig. 1B). This finding suggests that the small differences observed in the species-specific p30 assay were not simply due to partial denaturation or degradation of the p30 polypeptide of the SEATO gibbon ape virus. These results confirm and extend earlier studies (14, 30, 42) indicating that the p30 polypeptides of each virus are antigenically closely related.

Antigenic reactivities of gibbon viruses in the woolly monkey viral p12 radioimmunoassay. The SEATO gibbon ape virus was next tested in the type-specific radioimmunoassay for the woolly monkey viral p12. Striking differences between the reactivities of the SEATO gibbon ape virus and the woolly monkey virus were observed (Fig. 2). Although only 20% inhibition of binding was obtained with the SEATO gibbon ape virus preparation, the woolly monkey virus competed completely in the same test. The SFMC gibbon ape virus also only partially inhibited binding of labeled antigen, confirming our earlier work (42). Furthermore, the final levels of competition produced by each gibbon virus differed by about 20% and indicated a significant difference in the antigenic specificity of their respective p12

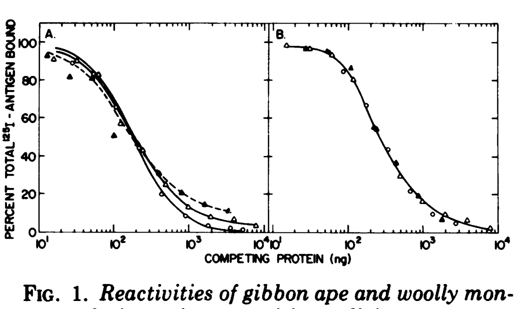

FIG. 1. *Reactivities of gibbon ape and woolly monkey type C viruses in competition radioimmunoassays for p30. Viruses were disrupted with 1% sodium dodecyl sulfate and analyzed at sufficient dilution (>1:10) so that the sodium dodecyl sulfate did not interfere with the antibody-antigen reaction. In each assay, approximately 10,000 counts/min (3 ng) of ^{125}I-labeled woolly monkey virus p30 were used. Antisera dilutions were such that approximately 50% of ^{125}I-labeled p30 was bound in the absence of competing antigen. Viruses tested included the SFMC gibbon virus, △; SEATO gibbon virus, ▲; and woolly monkey virus, ○. (A) Immunoassay using ^{125}I-labeled woolly monkey virus and an antiserum prepared against detergent-disrupted woolly monkey virus. (B) Immunoassay using ^{125}I-labeled woolly monkey virus p30 and an antiserum prepared against detergent-disrupted feline leukemia virus.*

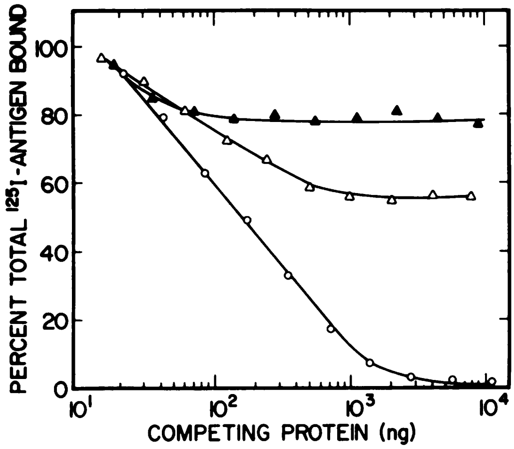

FIG. 2. *Reactivities of gibbon ape and woolly monkey type C viruses in a competition radioimmunoassay for woolly monkey virus p12. Detergent-disrupted viruses were tested in a competition immunoassay using anti-woolly monkey virus serum and ¹²⁵I-labeled woolly virus p12. Each tube contained 10,000 counts/min (2 ng) of ¹²⁵I-labeled woolly monkey virus p12 and an amount of antiserum sufficient to bind 50% of the labeled antigen in the absence of competing antigen. The symbols for the viruses tested are given in Fig. 1.*

polypeptides. The viruses were also tested in a heterologous immunoassay using ¹²⁵I-labeled woolly p12 and the anti-SFMC gibbon virus serum. As shown in Fig. 3, each virus was able to completely inhibit binding of ¹²⁵I-labeled woolly p12 in this assay. The greater slope of the competition curve for the SFMC gibbon ape virus is most likely due to a higher affinity of the antibodies for the SFMC gibbon viral p12 polypeptide. These findings demonstrate that each of the gibbon ape and woolly monkey viruses possess shared as well as unique antigenic determinants.

Competition radioimmunoassay for the SFMC gibbon viral p12. To study further the antigenic reactivities of the gibbon ape and woolly monkey viral p12 polypeptides, a radioimmunoassay for the p12 polypeptide of the SFMC gibbon ape virus was developed. In this assay (Fig. 4), the SFMC gibbon ape virus completely inhibited binding of ¹²⁵I-labeled gibbon viral p12. In contrast, only partial (65%) inhibition of binding was obtained with the highest concentrations (40 μg/ml) of woolly monkey viral proteins tested. These results are the reciprocal of those obtained in the woolly monkey p12 radioimmunoassay (Fig. 2). The SEATO gibbon ape virus preparation also reacted quite differently from the SFMC virus in this assay (Fig. 4). Like the woolly monkey virus, it only partially inhibited antibody binding of ¹²⁵I-labeled SFMC gibbon p12 (65%). The results demonstrate that prototype gibbon ape virus isolates from two gibbon colonies are distinguishable on the basis of the antigenic properties of their p12 polypeptides.

In other tests, the immunoassay for SFMC-gibbon viral p12 was shown to be highly specific for gibbon ape and woolly monkey type C viruses. No other reverse transcriptase-

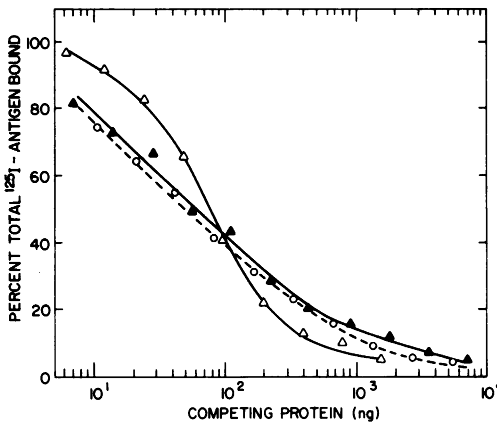

FIG. 3. *Reactivities of viruses in a heterologous radioimmunoassay for woolly monkey type C virus p12. Anti-gibbon ape virus serum was used in a competition immunoassay with ¹²⁵I-labeled woolly virus p12. As in other assays, the antiserum bound 50% of the labeled antigen in the absence of competing antigen. Symbols used are as described in Fig. 1.*

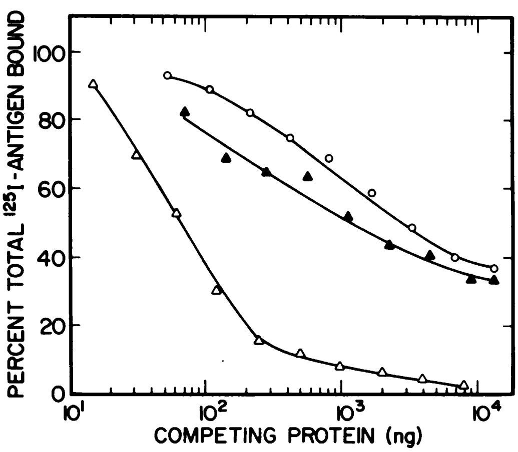

FIG. 4. *Reactivities of gibbon ape and woolly monkey type C viruses in a competition radioimmunoassay for gibbon ape virus p12. Detergent-disrupted viruses were competed with ¹²⁵I-labeled SFMC gibbon ape virus p12 (3 ng; 10,000 counts/min per tube) for binding a limiting amount of the anti-gibbon ape virus serum. The symbols are described in Fig. 1.*

containing RNA viruses tested reacted even at viral protein concentrations 10-fold in excess of that required for disrupted SFMC gibbon virus to cause 100% inhibition of binding. Those viruses tested included Rauscher and AKR strains of murine leukemia virus, feline leukemia virus, RD114, rat leukemia virus, baboon type C virus, and Mason-Pfizer monkey virus (data not shown).

Antigenic analysis of new gibbon type C viruses. Recently, a type C virus was isolated from a second gibbon of the SEATO colony. Further, another type C virus was isolated from a gibbon, kept as a pet in the United States (T. G. Kawakami, unpublished studies). The reactivities of these viruses were very similar to those of the woolly monkey, the SFMC gibbon ape, and the SEATO gibbon ape viruses in assays for the woolly monkey viral p30 polypeptide. In the viral p12 immunoassays, the reactivities of the two new gibbon ape virus isolates were indistinguishable from those of the prototype SEATO gibbon ape virus (data not shown). These results indicate that type C viruses from different animals of the SEATO gibbon colony were immunologically indistinguishable yet distinct from the original SFMC gibbon ape virus. Thus, the gibbon type C viruses constitute at least two distinct antigenic groups, each of which can be distinguished from the woolly monkey virus.

Stability of the type-specific antigenic determinants of primate type C viral p12. Previous studies of the p12 polypeptides of mouse type C viruses demonstrated that the p12 type-specific antigenic determinants are virus-specific in that the antigens are unaltered after virus growth in host cells of diverse mammalian species (38a, 41) or after prolonged growth in tissue culture (38a). Similarly, the antigenic-specificity of the woolly monkey virus p12 has been shown to be unaltered by virus growth in cells of different species (42). As shown in Fig. 5, replication of the SFMC gibbon ape virus in rat cells did not alter the reactivity of its p12 in the immunoassays described above. Further, prolonged growth of the SEATO gibbon ape virus in the original gibbon tumor cells or passage in human lymphocytes did not alter its reactivity in either homologous p12 assay (data not shown).

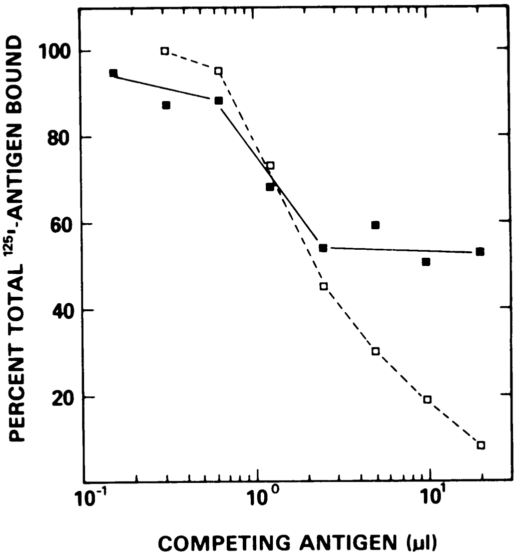

FIG. 5. *Antigenic stability of the gibbon ape type C viral p12 polypeptide. SFMC gibbon virus, grown in normal rat kidney cells (9), was tested in radioimmunoassays for woolly monkey virus p12 (■) and gibbon ape virus p12 (□). The assays were performed as described in the legends to Fig. 2 and 4.*

DISCUSSION

The present report demonstrates that type C viruses isolated from two gibbon colonies, characterized by high incidence of cancer, are distinguishable in immunoassays developed for the viral p12 polypeptide of one of the gibbon virus isolates. The evidence that at least two antigenic subgroups of gibbon ape viruses exist was further strengthened by the detection of very different reactivities of the two prototype gibbon ape viruses in an immunoassay for the p12 polypeptide of a closely related but distinguishable type C virus of the woolly monkey. In contrast, the present, as well as previous (14, 30, 32, 34), studies have detected little, if any, immunologic differences between other corresponding viral proteins of these primate-derived viruses. The present findings thus confirm the usefulness of the type C viral p12 polypeptide as a specific immunologic marker for differentiation of otherwise closely related type C viruses (38, 42).

Several lines of evidence indicate that the immunologic differences detected between the two prototype gibbon ape viruses are significant. First, the type-specific reactivity of the p12 polypeptide of each virus was shown to be unchanged after growth in cells of at least two different species. In the case of the prototype SFMC gibbon ape virus, its reactivity has been found to remain constant even after growth in tissue culture for more than two years. Finally, the present results indicate that an additional virus isolate from the SEATO gibbon colony is immunologically indistinguishable from the initial SEATO gibbon virus. All of these findings support the conclusion that the p12 antigen is virus-specific and immunologically stable, and that gibbon ape viruses of at least two antigenic subgroups exist naturally in different gibbon colonies.

By the criteria of inducibility from virus-negative cells (1, 2, 3, 10, 22, 26, 36, 44) and genetic homology of cellular DNA with virus-specific RNA (5, 27) or DNA (6, 8, 12, 13, 15, 31, 33), most mammalian type C viruses have been shown to be endogenous to the species in which they originate; however, the exact origin of the gibbon ape and woolly type C viruses remains unclear. These viruses have not as yet been shown to be inducible from gibbon ape or woolly monkey cells in culture nor has there been detectable evidence of virus-specific sequences in the cellular DNAs of these species (6, 33). There is increasing evidence, nevertheless, that these viruses may be etiologically involved in cancers that occur at high incidence in specific primate colonies. In both of the colonies from which gibbon ape viruses were obtained, there is a very high incidence of tumors (20, 21). Further, there is evidence that animals in these colonies develop neutralizing antibodies to the gibbon ape virus (20), whereas gibbons in other colonies with a much lower incidence of cancer lack detectable anti-viral antibodies (20; unpublished observations). Thus, whether or not they are endogenous, the gibbon ape and woolly monkey type C viruses may provide an important model for a viral etiology of cancer in primates through spread of the infectious agent. The ability to specifically identify antigenic subgroups of woolly and gibbon type C viruses should aid in studying the epidemiology of the diseases with which these viruses are associated.

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