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B-Lymphotropic Papovavirus (LPV) – Infections of Man?

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A. Introduction

A possibly new subgroup of papovaviruses has been isolated which appears to be characterized by its highly restricted host range which does not seem to extend beyond proliferating lymphoblasts. A virus revealing this host range derived from transformed African green monkey (AGM) lymphoblasts in described.

B. Results

I. Origin of Lymphotropic Papovaviruses

Papovavirus-like particles were observed by electron microscopy in supernatants of two Epstein-Barr virus (EBV)-transformed lymphoblastoid lines established from individual AGM. One of these lines originated from an inguinal lymph node synthesized in addition a paramyxovirus-like agent (zur Hausen and Gissmann 1979). The second line was derived from the peripheral blood of a different monkey. Cells of both lines revealed cytopathic changes. The papovavirus obtained from lymphoblasts of the peripheral blood has not yet been further characterized. Papovavirus particles were also demonstrated in a human lymphoblastoid cell line (CCRF-SB) originally derived from a leukemic child (zur Hausen and Gissmann 1979). In the following only the papovavirus found in the lymphoblasts derived from the inguinal lymphnode (LK-line) will be described.

II. Host Range

Only B-lymphoblasts obtained from AGM (Böcker et al 1980) and one EBV-negative human line BJA-B (Klein et al. 1974) were susceptible to this papovavirus. It is of interest that conversion of BJA-B cells to EBV genome carriers significantly reduced the number of cells producing AGM papovavirus. Because of its lymphotropic host range which seems to be unique among identified papovaviruses, it is tentatively designated as lymphotropic papovavirus (LPV).

III. Biochemical Characterization

The molecular weight of LPV was determined by gel electrophoresis of cleaved and uncleaved LPV DNA by using SV 40 DNA as marker. The DNA proved to be slightly smaller than SV 40 (3.2×10^6 as compared to 3.3×10^6 for SV 40 DNA (zur Hausen and Gissmann 1979; Dugaiczyk et al. 1975). The analysis of the cleavage pattern and of cross-hybridization with SV 40 DNA by the blotting technique (Southern 1975) has been reported before (zur Hausen and Gissmann 1979). The cleavage pattern of DNA from LPV differs from cleavage patterns of other characterized polyoma-like viruses. As seen in Fig. 1a LPV (left) and SV 40 (right) show completely different fragment patterns after Hae III cleavage. Figure 1b depicts LPVDNA after more than 1 year of continuous passage of the virus in human BJA-B cells. Heterogeneity seems to be due to accumulation of defective DNA molecules.

IV. Serologic Characterization

Apart from biochemical differences, the virus differs antigenetically from all characterized papovaviruses thus far. Antibodies of capsid or

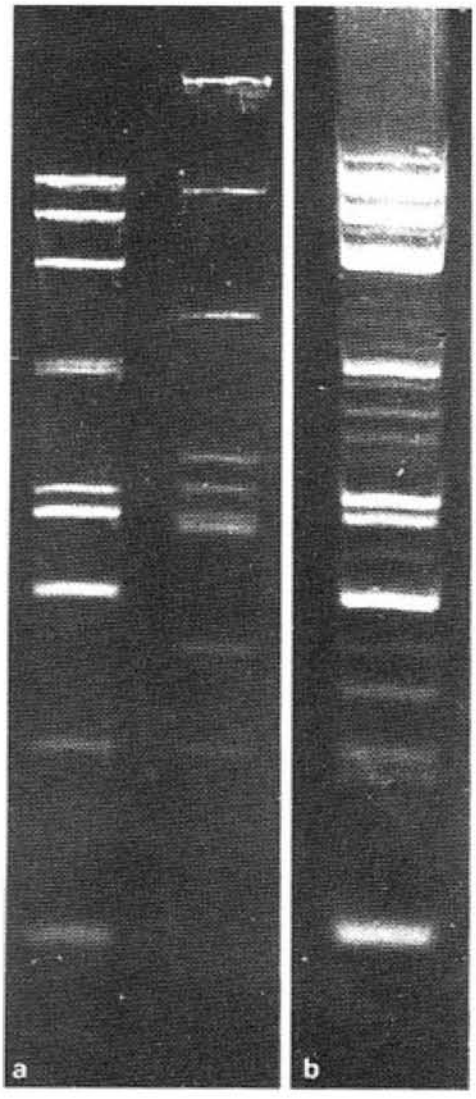

Fig. 1. a Polyacrylamide gelelectrophoresis (4%) of AGM-LPV DNA *(left)* and SV 40 DNA *(right)* after cleavage with Hae III restriction endonuclease. **b** AGM-LPV DNA after more than 1 year of continuous passage of the virus in human BJA-B cells

T antigens of SV 40 or BK virus did not crossreact with LPV in the indirect immunofluorescence test (IFT). Approximately 70% of AGM sera reacted with LPV antigens in IFT. Inoculation of four seronegative animals with LPV resulted in an antibody response within 3 days, suggesting a booster reaction. It appears, therefore, that these animals had low titers of antibodies that were not detected by IFT. The existence of human antibodies to LPV in different age groups was examined. The IFT was used to test 558 sera for antibodies, starting with a serum dilution of 1:10. Only a low number (about 10%) of sera in age groups between 0.5–29 years were found to be positive. In the decade from 30–39 years a sharp rise (to 30%) in the number of positive sera is noted, resulting in about 30% of positive sera in all age groups above 30 years (40–59, 60–79, ≥80). The titer range of positive sera varied considerably (up to 1:640) but showed no age dependence.

No disease-specific reactivity has been demonstrated thus far, although patients with symptoms involving the lymphatic system (by excluding EBV and CMV infections) showed a significantly higher percentage of reactive sera (zur Hausen et al. 1980). The percentage of positive sera in 247 patients (23.4%) tested for infectious hepatitis was about twofold higher than that observed in other groups of 221 patients (12.2%). The geometric mean titer was 1:72 in the "hepatitis group" and 1:59 in the other group. The specificity of the IFT was confirmed by immunoprecipitation (IP) studies. ^{35}S-methione-labeled cell extracts from persistently infected BJA-B-LK and from freshly infected BJA-B cells were immunoprecipitated with different sera defined by IFT (this method is described in detail by Mueller-Lantzsch et al. 1980). By this method we could prove that virus-specific antigens and not cellular antigens were involved in immunoprecipitation reactions with positive sera. AGM as well as human sera reacting in immunofluorescence with LPV antigens precipitated polypeptides of about 40 K. Neither IFT-negative sera reacted in IP with infected cells nor did IP-positive sera with uninfected cells.

From IFT-positive sera eight high-titered sera were selected for neutralization studies. They were able to neutralize completely viral infectivity as revealed by IFT.

C. Discussion

A novel member of the papovavirus group has been isolated from EBV-transformed AGM B-lymphoblasts which is characterized by its lymphotropic host range. The virus is widely spread among African green monkeys. Of human sera from adults above the age of 30, 30% reveal antibodies reacting with LP viral antigens. Sera which are highly reactive in IFT are able to neutralize LP viral infectivity. Human sera which react with LPV antigens in IFT also can precipitate viral proteins with a molecular weight of about 40 K. In analogy with SV 40 these proteins might be the major capsid proteins. (Girard et al. 1970, Hirt et al.

1971). The data suggest that an immunologically crossreacting agent also exists in man.

The existence of lymphotropic papovaviruses shows the diversity of host range within this virus group. The presence of papovavirus-like particles in a human lymphoblastoid line (CCRF-SB) may indicate that lymphotropic papovaviruses could represent a distinct subgroup of polyoma-like agents. It should be of interest to elucidate the possible role in the etiology of proliferative diseases, particularly of the lymphopoietic system.

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