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# The Hamster Polyomavirus—a Brief Review of Recent Knowledge*

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**Abstract.** The hamster polyomavirus (HaPV) was first described in 1967 as a virus associated with skin epithelioma of the Syrian hamster. The tumors appear spontaneously in a hamster colony bred in Berlin-Buch (HaB). Virus particles isolated from skin epitheliomas cause lymphoma and leukemia when injected into newborn hamsters from a distinct colony bred in Potsdam, Germany (HaP). The viral genome has been totally sequenced and the overall genetic organization establishes HaPV as a member of the polyomaviruses. HaPV is a second example of an middle T (MT) antigen encoding polyomavirus and nucleotide sequence homologies designates the mouse polyomavirus (Py) as the closest relative.

Lymphomas induced by HaPV in HaP hamsters do not contain virus particles but instead accumulate different amounts of nonrandomly deleted free and/or integrated viral genomes. Transgenic mice produced by microinjection of HaPV DNA into the pronucleus of fertilized eggs of Gat: NMRI mice developed both, epitheliomas and lymphomas. Both tumor types contain extrachromosomal DNA.

HaPV DNA was found to replicate in hamster lymphoid and fibroblast cell lines. Fully reproductive cycles could be detected only in GD36 lymphoblastic leukemia cells.

HaPV carries the full transforming properties of a polyomavirus *in vitro*. Immortalization of primary rat cells is essentially carried out by the HaPV large T (LT) antigen and coexpression of HaPV MT and HaPV small T (ST) antigen is required for full transformation of rat fibroblasts. The preferential binding of HaPV MT to c-Fyn, a Src family kinase, has been proposed as a mechanism leading to lymphoid malignancies.

Heterologous expression of HaPV-VP1 allowed the formation of virus like particles (VLPs) resembling HaPV particles. The high flexibility of HaPV-VP1 for insertion of foreign peptides offers a broad range of potential applications, especially in vaccine development.

**Key words:** polyomaviruses, hamster polyomavirus, Syrian hamster, tumor virus antigens, virus transformation, Src family kinases, virus-like particles

## Introduction

The HaPV was originally described in 1967 by Graffi et al. as a virus associated with skin epithelioma of the Syrian hamster (1–4).

The tumors appear spontaneously in animals at about 3 months to more than 1 year of age in a laboratory colony bred in Berlin-Buch, Germany (HaB) (5). Virus particles identified in cell extracts prepared from skin epitheliomas cause lymphoma and leukemia when injected into newborn hamsters from a distinct and practically tumor-free colony bred in Potsdam, Germany (HaP). In contrast to the skin epithelioma, the hematopoietic tumors are virus-free but accumulate large numbers of nonrandomly deleted extrachromosomal viral DNA. Although

*Dedicated to Prof. Arnold Graffi on the occasion of his 90th birthday.

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HaPV interaction with keratinized cells may be reminiscent of the papillomavirus life cycle, the recent characterization of the viral genome classifies it as a polyomavirus. However, the HaPV tumor profile, which reflects the capacity of the virus to infect both undifferentiated keratinocytes and lymphocytes, is unique within the papovavirus family and raises interesting questions relative to the tissue restricted oncogenicity of this virus. It should be emphasized that the HaPV described in the review may not be a singular isolate: a closely related virus has been described as the etiological agent of Syrian hamster skin epithelioma in Alabama (6).

## Genome Organization

Virus particles accumulate in large amounts in skin epithelioma (1,2). The negatively stained virus particles, about 40 nm in diameter, are spherical particles with the typical icosahedral structure of polyomaviruses. Other characteristic properties such as molecular weight ($27.5 \times 10^6$), sedimentation coefficient (223S) and buoyant density (1.340 g/ml) are also within the range of murine polyomavirus (Py) and SV40 (7,8). However, the symmetry of the HaPV capsid (T = 7 laevo) differs from that of SV40 and Py, respectively (T = 7 dextro) (9).

The viral genome has been molecularly cloned from a DNA preparation purified from a pool of skin epithelioma. This cloned genome, hereafter referred to as ''wild type HaPV'' genome, has been totally sequenced (9–11). It is a double stranded circular DNA molecule of 5366 base pairs (bp), slightly larger than those of Py (5292 bp) and SV40 (5243 bp) and showing sequence homology to Py but also to the lymphotropic papovarirus LPV. No DNA sequence homology was observed between HaPV and several human and animal papillomaviruses (10,12,13). The organization of the open reading frames predicts the existence of an early and a late region transcribed on opposite strands and separated by a noncoding region displaying sequence motifs presumably involved in *cis*-regulation of transcription and replication of the viral genome. This overall genetic organization immediately establishes HaPV as a member of the polyomaviruses but, in fact, very much resembles that of Py itself (Fig. 1).

The late genome region encodes the virus capsid proteins VP1, VP2 and VP3. The major capsid protein, VP1, and the capsid proteins VP2 and VP3 are translated in different reading frames which overlap over 32 base pairs (9,11,14). The VP1-N-terminal amino acid sequence carries a Lys-Arg-Lys motif which appears to be active as a nuclear localization signal (9,11,15). The amino acid homologies of HaPV capsid proteins shared with Py varies between 65.5% (VP1), 45.4% (VP3) and 44.6% (VP2) (9). The high amino acid homology among the VP1 of HaPV and other polyomaviruses is also reflected by cross-reactivity with rabbit sera raised against SV40 and JCV-VP1 (9, unpublished results).

The putative early gene region has coding capacity for small T (ST), middle T (MT) and large T (LT) antigens.

In the noncoding sequence two consecutive near-perfect palindromic structures are located between bases 5320 and 5339 and between bases 5356 and 11. The second palindrome is highly homologous to the Py structure considered to be the origin of replication (nucleotides 5281 to 20). No TATA box is recognizable upstream of the early or late side of the putative origin of replication. However, as in Py, enhancer core elements are located on the late side of the putative origin of replication. The sequence 5304 to 5312 (A core) fits with the consensus sequence proposed for the SV40 core enhancer. The B core sequence (5183 to 5195 and 5232 to 5244) are also in good agreement with the consensus adenovirus E1A enhancer (11,16).

HaPV is a second example of a MT antigen coding polyomavirus. The similarity of organization with the Py physical map confirms early morphological and biochemical data and provides a basis for the classification as a polyomavirus despite the initial characterization as an epithelioma inducing agent.

## Natural Infection in Syrian Hamsters

Five to ten percent of 6 to 9 month-old animals of the random-bred HaB hamster colony are affected by multiple skin epithelioma (1–3). The tumors, of relative uniform aspect, occur primarily on the skin of chin, head, neck, back, and frequently also about the eyes and external ears.

Numerous nodules arising multicentrically coalesce in the cutis and subcutis to form massive layers. Histologically the tumors result from the proliferation

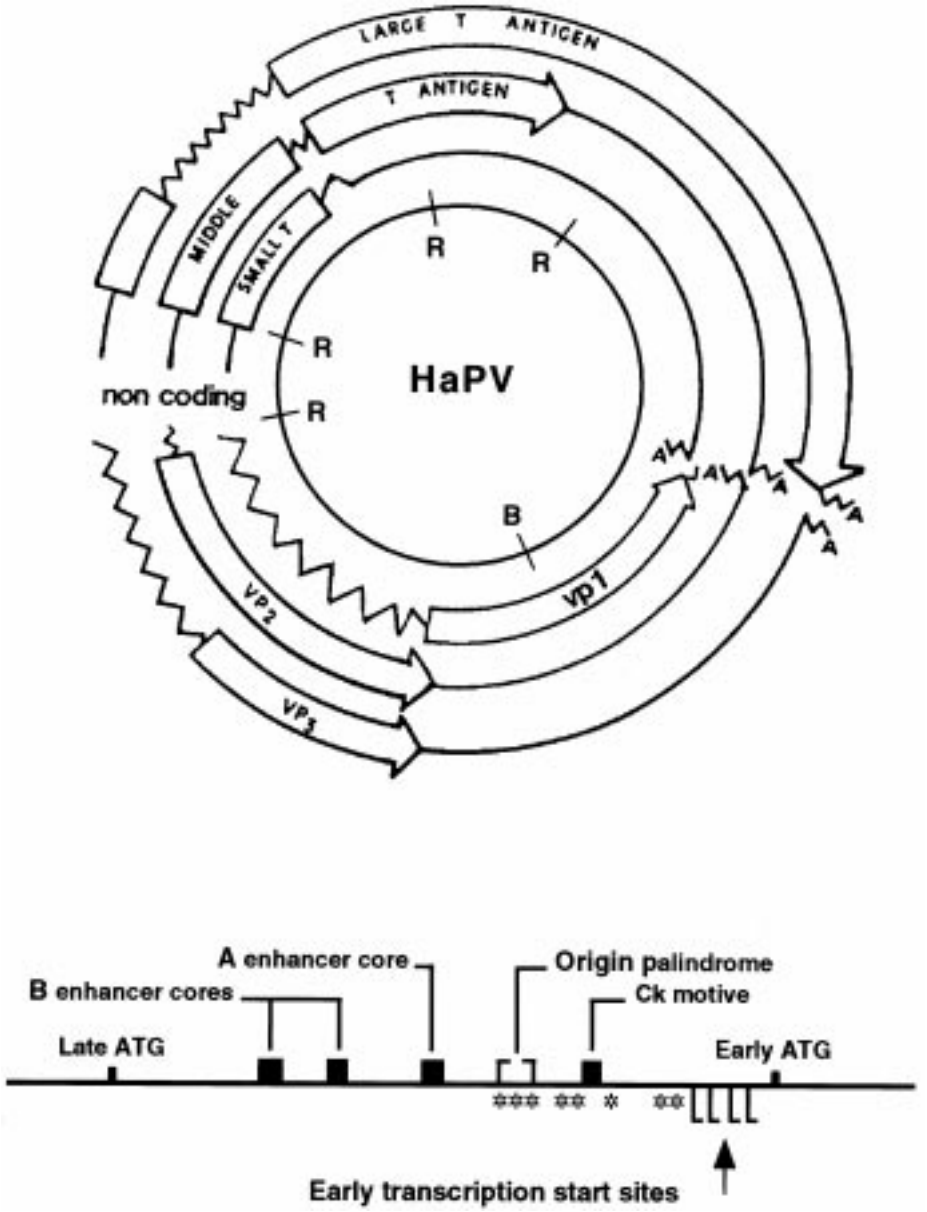


*Fig. 1.* Genetic map (top) and scheme of the noncoding region (bottom) of HaPV. *, large T-antigen binding sites; R, EcoRI restriction sites; B, BamHI restriction sites.

of hair root epithelium, which forms cyst-like masses filled with cornified material sometimes containing melanin. Virus particles are abundant in the differentiated stratum corneum but absent in the proliferating cells of the stratum basale and stratum spinosum (1–4,11,16). This tight linkage between the completion of the virus productive cycle and the terminal differentiation of the skin epithelium is strikingly reminiscent of papillomavirus infection (17). However, these two pathologies differ in regard to the nature of the respective virus target cells, i.e. the hair follicle keratinocytes for HaPV and the interfollicular epidermis keratinocytes for the papillomaviruses. A high incidence of hair follicle epitheliomas has also been reported among the multiple epithelial tumors induced by the infection

of newborn mice with the highly tumorigenic PTA strain of polyomaviruses (18).

Graffi et al. (1) first detected HaPV particles on electron micrographs of primary skin epithelioma sections. Since the spontaneous appearance of epithelioma in the HaB hamster colony more than 30 years ago, an enzootic infection has been established via massive horizontal transmission. A search for the virus reservoirs in HaB weanling animals well before the appearance of epitheliomas by *in situ* hybridization of whole body animal sections demonstrated that thymus and spleen represent the most active virus reservoirs (H. Prokoph, unpublished results). Accordingly accumulation of virus particles have been observed on electron micrographs of HaB hamster thymus (3). The absence of detectable viral genomes in total embryo tissues support the model of horizontal transmission. In contrast to primary skin epitheliomas, transplanted skin tumors have not exhibited virus particles in electron micrographs but contain viral DNA (19).

## HaPV Induces Transmissible Lymphomas

Virus particles isolated from the skin epitheliomas or DNA extracted from such virus preparations induces lymphoma and leukemia when injected into newborn hamsters from a separate, uninfected and tumor-free colony HaP. The incidence is in the range of 30–80%, and the latency is 4 to 8 weeks (3,20). In the most cases these tumors affect the liver, less frequently the thymus and the kidneys, and never the spleen (Fig. 2). In HaB hamsters the spontaneous incidence of lymphoma is low (1 to 3%) and does not increase upon inoculation of virus particles. This suggest that most HaB animals could be ''protected'' against the leukemiogenic activity of the virus via a immune response elicited to virus structural or virus induced tumor antigens or both (11,16). Indeed using recombinant HaPV proteins antibodies against the capsid proteins VP1 and VP2/3 as well as against LT, MT and ST were detected in sera of HaPV infected HaB hamsters (14,9).

A large panel of lymphomas have carefully examined for the presence of virus particles by electron microscopy; none of them showed either papovaviruses or other types of viruses. Instead, several thousands of copies of extrachromosomal deleted viral genomes (HaPV dl) on average, are accumulated in these lymphoid tumor cells (20–25). These HaPV dl molecules are characterized by nonrandom deletions which affect a common part of the noncoding region containing the two B elements in addition to a variable part of the late coding region. It appears that the accumulation of high copy levels of the nonrandomly deleted extrachromosomal genomes is the most prevalent situation. However, some deletions target exclusively the noncoding region of the viral DNA. Additionally, in two lymphomas, where extrachromosomal accumulation has not been observed, a single viral genome has been demonstrated to be integrated into cellular DNA. The absence of HaPV late mRNA in the lymphoma cells indicates that the viral genomes affected by the deletion or integrated in the cellular genome are defective (23).

Mazur et al. (22) have postulated that the two physical states of the HaPV genome are likely to be functionally equivalent: deletion and integration of the viral genome both inactivate the late coding region and the amount of viral early RNA yielded by a single integrated copy appears to be very similar to that associated with several thousands of extrachromosomal copies of the viral genome. In consequence, there might be two essential requisites for HaPV to become lymphomagenous: suppression of the late coding functions of the viral genome and expression of the viral T antigens above a threshold level (y).

The generation of deleted extrachromosomal HaPV DNA in neonatally infected HaP hamsters is first detectable during the postnatal phase of high level replication of viral DNA in haemopoietic organs (at 7 days post infection), thus clearly preceding the development of overt lymphoma (24,25). The viral replication in HaP hamsters was restricted to lymphoid cells and to blood cells in non-hematopoietic organs.

A variety of deleted HaPV DNA species is generated in lymphoid cells early after infection, but only a single species, individual for each tumor, was accumulated in the lymphomas. Thus, the spectrum of HaPV genomes narrowed when lymphomas developed (24).

The role of HaPV in the etiology of transmissible lymphoma in a hamster colony in Alabama/USA has been convincingly established by Barthold et al. (26).

Although skin epithelioma is one of the many malignancies induced by the mouse polyomavirus, transformation of lymphoid cells has never been

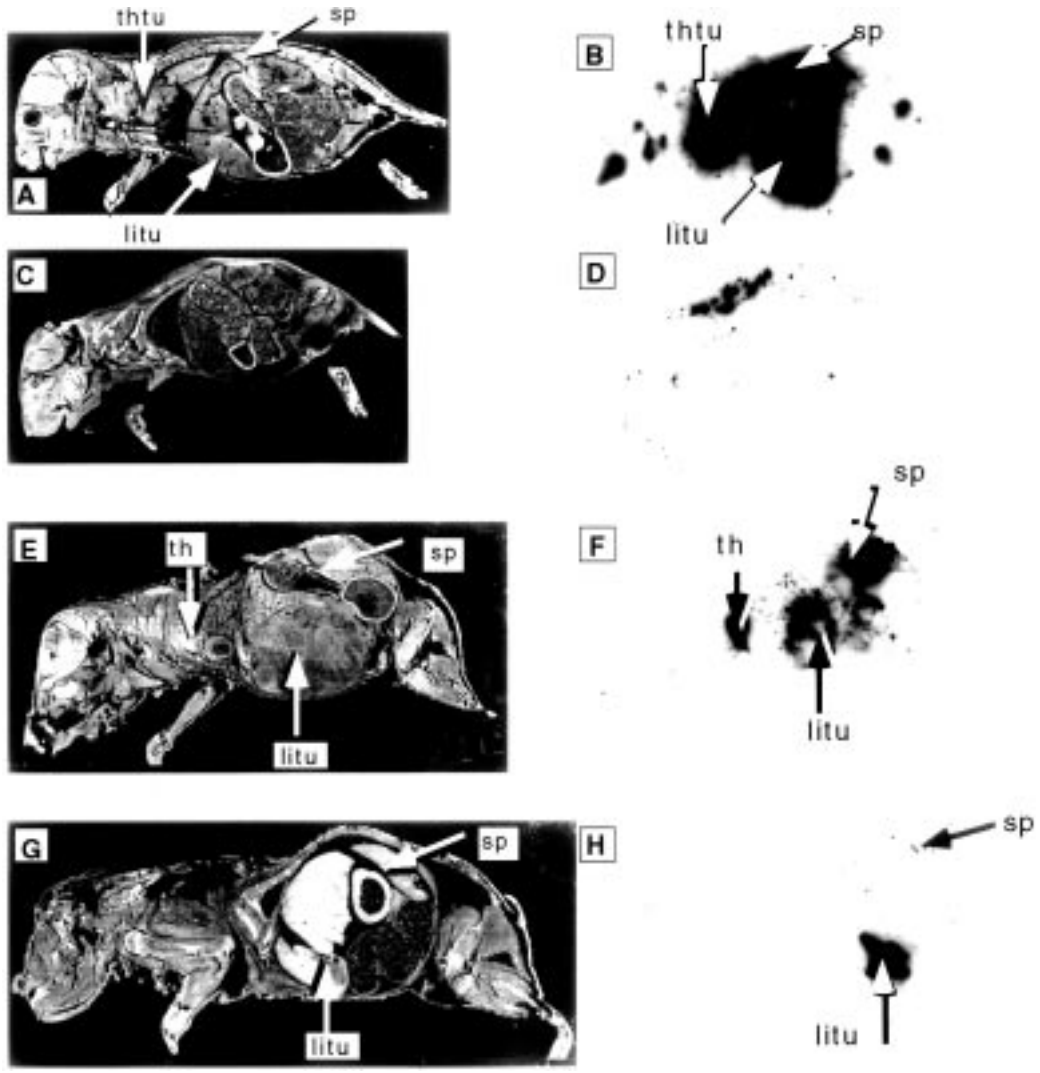


*Fig. 2.* Detection of viral DNA in HaP hamsters after infection with HaPV particles. Autoradiographs of whole body hamster sections after hybridization to a HaPV specific DNA probe (B, D, F, H). Matching reference tapes are shown in A, C, E, G, respectively. A, B: hamster at 3 weeks post infection (p.i.) with tumors in the liver and the thymus; C, D: hamster at 3 weeks p.i. without overt signs of tumor development; E, F: hamster at 4 weeks p.i. with a tumor in the liver and enlarged thymus; G, H: hamster at 5 weeks p.i. with a tumor in the liver. sp, spleen; th, thymus; litu, tumor in the liver; thtu, tumor in the thymus.

reported in animals infected with Py or in transgenic mice made with Py MT antigen.

## Transgenic Mice: a Model for HaPV Pathogenesis

Transgenic mice have been obtained by microinjection of HaPV viral supercoiled DNA into pronuclei of fertilized eggs of Gat: NMRI mice, and founder mice have been bred over three generations (27). Analysis of different tissues in all three generations have established that the HaPV transgene is present as extrachromosomal DNA and expressed preferentially in the thymus and the spleen. At the age of 18 months, four of seven founders developed skin papillomas histologically similar to that of the HaB hamster tumors.

High amounts of episomal viral genomes are accumulated in these epitheliomas without detectable virus particles. Two founder mice lines have developed lymphomas also free of virus but containing extrachromosomal viral genomes. Papillomas and lymphomas have been observed in 5- to 9-month-old F1 animals. F2 litters are affected by severe developmental and often lethal damage: These animals display almost complete thymus depletion. These lethal effects, which are less pronounced in F3 litters (15%), are not explained.

Transgenic mice in which the expression of the reporter gene *lac*Z is driven by the HaPV early promoter have shown that this promoter displays a rather specific pattern of expression restricted to hematopoietic organs (thymus and spleen, unpublished results).

## HaPV *in Vitro* Replication and Productive Cycle

Since the isolation of HaPV in 1967, no permissive host capable of supporting the full HaPV productive cycle *in vitro* has been described. Graffi et al. (3) reported that the viral infection of hamster kidney cells or newborn hamster thymus cells resulted in virus proliferation in a few cells, detectable by electron microscopy. However, no cytopathic effect of the cell layers was observed concomitantly. More recently, Barthold et al. (26) also described a similar observation of an acytopathic infection of primary total hamster embryo cells. The lack of a fully permissive host cell has hampered the detailed biological characterization of the virus for a long time. Recently a panel of cells were tested for capacity to replicate the viral genome and yield virus progeny (28). Accordingly, the hamster leukemia cell line GD36, derived from a lymphoblastic leukemia induced in the Syrian hamster by SV40 (29), was found to be permissive for a full productive cycle.

The virions produced by GD36 cells are indistinguishable from the particles isolated from the epithelioma both structurally (sizes of the capsid, restriction of the DNAs) and functionally (they induce lymphoma in the HaP hamsters). Additional experiments have shown that serial passages of transfected GD36 cells establish a persistent infection yielding virus progeny without detectable cytopathic effect.

The hamster fibroblast cell line BHK is also a competent host for viral DNA replication but does not provide a fully permissive context for virus growth (11).

By contrast with the wild-type genome, which replicates in both lymphoblastic and fibroblastic cell lines, the lymphoma-associated HaPV genomes characterized by deletions affecting the late coding region as well as a specific part of the noncoding regulatory region replicate in lymphoblastic but not in fibroblastic cell lines (21). The deletion acts in a cis-dominant manner and is the primary determinant of this host-range effect on replication. The boundaries of the regulatory region necessary for viral DNA replication in the two cell contexts have been defined. The regulatory region can be functionally divided into two domains: one domain (distal from the origin of replication) is necessary for viral genome replication in fibroblasts, and the other domain ( proximal to the origin of replication) is functional only in the lymphoblastoid cell context and contains the sequence specifically conserved in the lymphoma-associated genomes. This sequence harbors a motif recognized by a lymphoblastoid cell-specific *trans*-acting factor (30).

## HaPV Transforming Properties *in vitro*

The tumor specificity displayed by HaPV viral infection or the viral transgene *in vivo* can be bypassed *in vitro*. This can be demonstrated by the induction of unlimited proliferative capacity *in vitro* in transfected primary rat fibroblasts (immortalization) and of a spectrum of phenotypic alterations in transfected immortal rat fibroblasts such as focus formation or growth in semisolid medium (transformation) (11,31). In murine Py these biological activities are carried out by the Py early region coding for a large T antigen (Py LT), a middle T antigen (PyMT) responsible for the transformation, and a small T antigen (PyST) which specific function is still unclear (32,33). Accordingly, the HaPV early genome region carrying the coding capacities for the three T-antigens contains the genetic information necessary for immortalization of primary rat embryo fibroblasts and transformation of FIII rat cells (31,34). Attempts to assign the biological activities of the three HaPV-T

antigens to individual cDNAs have demonstrated, that immortalization of primary rat cells is essentially carried out by the HaPV LT. Although HaPV MT- and HaPV ST-antigens are not strongly required for immortalization, they stimulate proliferation and modify the phenotype of immortal cell lines (34). A parallel situation has been described for the Py mediated immortalization of primary rat cells (32,33,35).

The LT of most of polyomaviruses has been shown to bind the product of the retinoblastoma gene ( pRb) (36). Goutebrouze et al. have demonstrated that the HaPV LT can indeed complex the pRb (37). Mutation in the HaPV LT antigen ($^{134}$Glu-Lys) that obliterates this binding is strongly deleterious to the immortalization capacity of the viral genome. This mutation has no effect on transformation of F111 cells. A similar situation has been described for Py (32).

Transformation by rodent polyomaviruses is mediated primarely by MT antigen. Py MT and HaPV MT carry distinct properties for transformation of rat fibroblast F111 cells. PyMT by itself is capable of readily inducing foci upon transfection of these cells (38). By contrast, HaPV MT does not yield foci when transfected alone and coexpression with HaPV ST is required for transformation (34). The determinant for this difference may be within a region of weak homology between the two molecules (11,39). HaPV MT and PyMT are highly conserved membrane-bound proteins which do not carry intrinsic enzymatic activity but interact with and subvert the activity of a variety of cellular proteins involved in cell signalling (40,41). PyMT associates with multiple protein partners (38,39,42,43): the tyrosine kinase c-Src and, to a lesser extent, c-Fyn and c-Yes; the regulatory subunit of a phosphotidylinositol 3-kinase (PI3-K), the regulatory and the catalytic subunits of the phosphoserine and phosphothreonine phosphatase PP2A, the transforming protein Shc and the phospholipase C-$\gamma$1(PLC-$\gamma$1). The cellular protein partners for HaPV MT identified so far include PI3-K, PP2A, PLC-$\gamma$1 and among the Src family kinases exclusively the c-Fyn. Goutebrouze et al. (39) have been shown that the N-terminus of the HaPV MT carries a determinant for specific activation of c-Fyn Goutebrouze et al. (39). The preferential binding of HaPV MT to Fyn, which is an important component of the T cell receptor complex, has been proposed as a mechanism leading to lymphoid malignancies (39,41,43).

## HaPV-VP1-Derived Virus-Like Particles as Carriers for Foreign Epitopes

Non-infectious virus-like particles (VLPs) generated by the heterologous expression and spontaneous self-assembly of viral structural proteins resemble virions in their strong immunogenicity and can be used as safe and efficient vaccines (44).

According to the N-terminal amino acid (aa) sequence of HaPV-VP1 constructs were generated encoding the authentic (384 aa long) and a N-terminal extended VP1 (388 aa long), respectively, and expressed at high level in different heterologous expression systems (15, unpublished results). In all cases VLPs, similar to HaPV particles were formed (Fig. 3). The yeast expressed VP1 was shown be a highly flexible carrier molecule tolerating the insertion of short foreign sequences at several surface-exposed sites and offering a broad range of potential applications, especially in vaccine development against viruses and other pathogens (45). In addition, VP1-derived VLPs may be of interest as potential vehicles in gene transfer (46).

## Concluding Remarks

In this review we have briefly reviewed the current knowledge of HaPV biology. The different susceptibility of the hamsters from the HaB and the HaP colonies, illustrated by the strikingly different tumor pattern caused by HaPV infection raises numerous questions concerning the genetic control of the virus-host interaction. As polyomaviruses, like other viruses, are well adapted to their host cell and, due to the small size of the viral genome, easy to handle are therefore excellent tools to study the contribution and regulation of multiple signalling pathways in the course of tumorigenesis. In particular, HaPV MT and PyMT are capable of deregulating different members of the Src family kinases and this difference may account for the contrasting tumor profile induced by the two viruses. At this level both the genetic constitution of the viral genome and its host are likely to determine the pathology resulting from different virus-host interactions. The powerful techniques established, i.e. during the last years in the course of international genome projects will be of help in further elucidating these mechanisms. Of equal importance will be the study of the virus-mediated

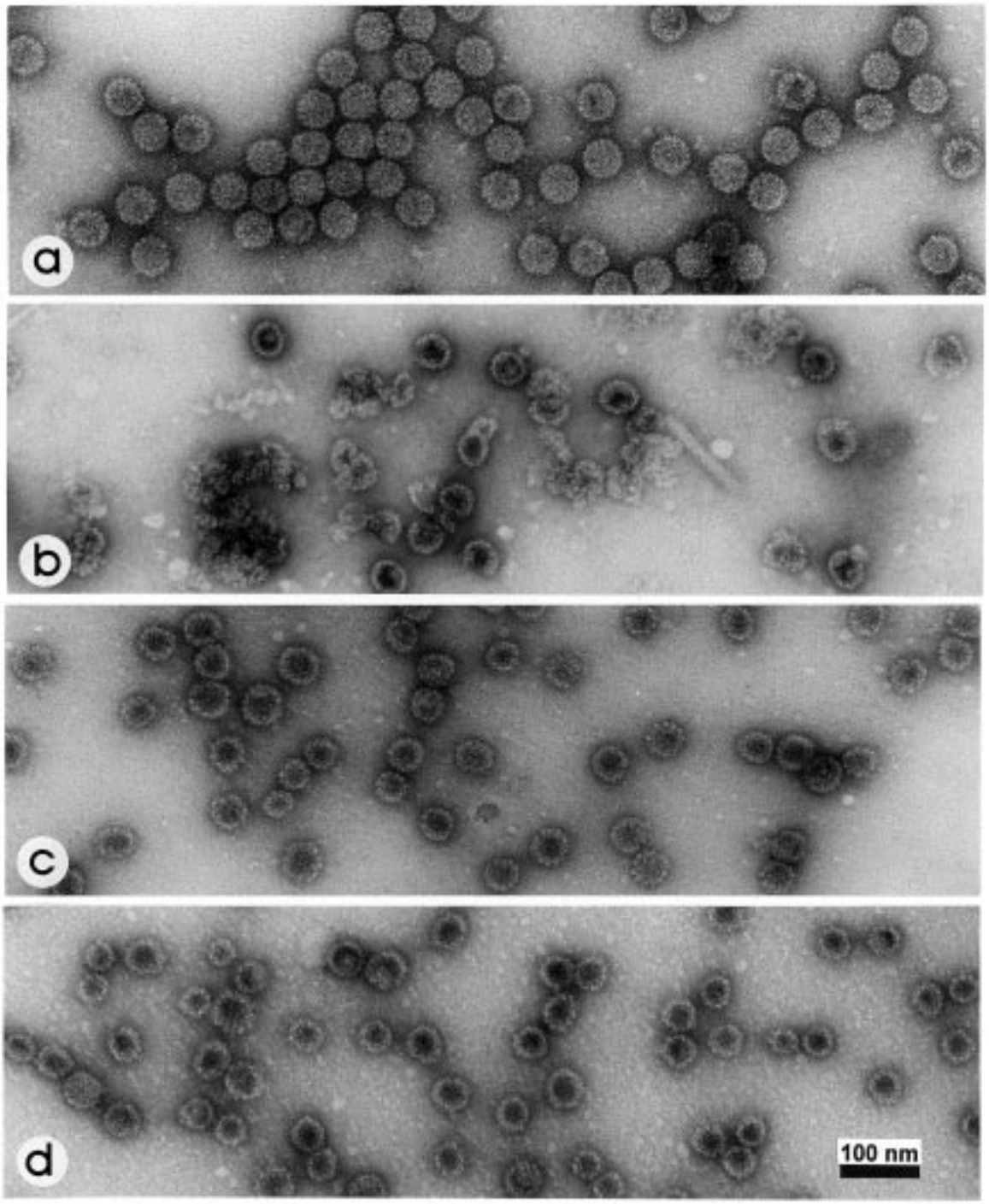


*Fig. 3*. Negative staining electron microscopy of HaPV particles (a) and HaPV-VP1 derived VLPs generated in *E. coli* (b), yeast (c) and insect cells (d). Magnification: × 125,000.

attenuation of the host's immune response. Furthermore, HaPV-VP1 derived virus-like particles prove to be promising carriers for the insertion of foreign peptides and offering a potential use in vaccine development.

Continuing the initial work of Graffi et al. the identification and characterization of many of these determinants should be a goal for future work on HaPV.

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