Haematology and Blood Transfusion Vol. 28
Modern Trends in Human Leukemia V
Edited by Neth, Gallo, Greaves, Moore, Winkler

Papovaviruses and Human Tumors

H. zur Hausen

Papovaviruses contain the two subgroups "polyomaviruses" and "papillomaviruses" (reviewed in [20]). Members of both subgroups are clearly oncogenic, most notably the papillomaviruses, which induce papillomas within their natural hosts (see review [24]). Viruses of both subgroups can be distinguished morphologically, biochemically, and biologically. The polyomaviruses are nonenveloped, eicosaedral particles of 40 nm containing a circular double-stranded DNA molecule of about 3.3×10^6 daltons. The papillomaviruses show similar structural features. They are, however, larger in size (50–55 nm) and contain a DNA molecule of about 5.0×10^6 daltons. The structural organization of the genome is totally different in both groups: In polyomaviruses, transcription of early and late genes occurs in opposite polarity involving both strands. Papillomavirus DNA has only one transcribed strand with a long stretch of base pairs separating early and late transcripts. Polyomaviruses thus far appear to be oncogenic under experimental conditions only, mainly after injection into newborn animals. Papillomaviruses, in contrast, are the causative agents of papillomas and contribute, under certain conditions, to malignant conversion.

A. Polyomavirus Infection in Man

Two polyomavirus infections of man, BK and JC virus, were identified more than 10 years ago [2, 15]. BK virus is frequently excreted in the urine of immunosuppressed patients in high quantities without being identified as the causative agent of any human disease. JC virus was isolated from patients with progressive multifocal leukencephalopathy (PML) and appears to be the causative agent of this condition. Both viruses are oncogenic when inoculated into newborn rodents and transform hamster cells in tissue culture (reviewed in [20]). JC virus has also been shown to induce gliomas upon intracerebral inoculation into owl monkeys [12]. The occasional presence of SV40 antibodies in a small percentage of individuals (about 1%) and the identification of this virus in two cases of PML [21] may hint at the existence of human infections with this monkey virus.

Rather recently, evidence was obtained of human infections with an additional polyomavirus, the B-lymphotropic papovavirus (LPV). This virus was originally isolated from African Green Monkey (AGM) lymphoblasts [27]. Between 20% and 30% of the human adult population produce antibodies to this virus, which neutralize the AGM isolate and point to the existence of a closely related or identical agent in man. Attempts have failed thus far to demonstrate the pathogenicity of this virus or to correlate the antibody response to a specific disease pattern. Therefore, a possible role of polyomaviruses in human tumor induction remains to be elucidated.

B. Papillomavirus Infections in Man

Since 1976 [3, 5, 13], it has become apparent that several types and subtypes of papillomaviruses of man exist. So far, at least 17 distinct types of human papillomaviruses have been identified and it is predicted that additional types will follow.

Verrucae vulgares (common warts) is induced by human papillomavirus (HVP) types 1, 2, 4, and 7. The latter has only been found in butchers until now. Flat warts are caused by types 3 and 10, genital warts and laryngeal papillomas by types 6 and 11. At least seven distinct types have been isolated from patients with a rare skin disease, epidermodysplasia verruciformis (types 5, 8, 9, 12, 14, 15, and 17], and one virus isolate (type 13) originates from mucosal papillomas of the gingiva (morbus Heck).

C. Papillomaviruses and Human Cancer

More than 40 years ago, a papillomavirus infection of rabbits, the Shope papillomavirus, was identified as a potentially carcinogenic infection [16]. Additional application of chemical carcinogens at subthreshold concentrations enhances the malignant conversion and reduces significantly the latency period [17].

A few years ago, Jarrett and his colleagues [9] noted an interesting interaction between a papillomavirus infection and carcinogens in esophageal carcinomas of cattle. Papillomas caused by type 4 of bovine papillomavirus changed into squamous cell carcinomas in areas where cattle grazed on bracken, which contains a potent carcinogen.

A specific interaction between certain types of papillomavirus infections and physical and chemical carcinogens also seems to lead to certain human cancers (see review [24]); epidermodysplasia verruciformis represents a "classical" example. Generalized verrucosis is a pathognomonic feature of this condition. The papillomas are caused by distinct types of viruses. At least two types (types 5 and 8) have been identified in carcinomas arising within warts at a remarkable frequency [14], predominantly on sun-exposed sites of those patients. Skin carcinomas in these patients, therefore, seem to result from the interaction of a specific type of papillomavirus infection and the additional interaction with a physical carcinogen, namely the UV part of the sunlight.

A second example is provided by multifocal laryngeal papillomas, the majority of which seem to be caused by a predominantly genital papillomavirus (HPV-11) [6]. This condition reveals a remarkable tendency to recur after surgical removal and even iatrogenic spreading of the papillomas has been reported (reviewed in [24]). In previous decades, a number of attempts were made to treat these proliferations by x-irradiation. A high percentage of laryngeal papillomas treated under this regimen later converted into squamous cell carcinomas, even in young patients. Nonirradiated laryngeal papillomas very rarely convert into malignant tumors (see review [24]).

The most recent human condition to reveal increasing evidence for a similar interaction is human genital cancer. The epidemiology of this malignancy clearly points to an infectious event in its etiology (reviewed by [26]). Since 1968, herpes simplex viruses (HSV) have been suspected as playing a role in this condition. This was mainly based on seroepidemiologic studies pointing to a role of this virus in the etiology of genital cancer. Attempts to find HSV DNA in biopsy material derived from such tumors have largely failed, creating an obvious dilemma in linking HSV infections to genital cancer.

The failure to find HSV DNA in genital cancer biopsies stimulated the search for other viruses potentially involved in the etiology of this disease. In view of case reports on the malignant conversion of genital warts (see review [24]), human papillomaviruses appeared to be good candidates [23, 28, 29]. This led to the characterization of HPV-6 as the main agent found in genital warts (condylomata acuminata) by Gissmann and zur Hausen [4], the successful cloning of this virus in bacterial plasmids [1], and to the identification of a second agent, HPV-11, which prevails in preneoplastic dysplastic lesions of the cervix, but is also present in some condylomata acuminata [7].

The analysis of malignant genital tumors for HPV-6 or HPV-11 DNA has resulted in the following data: (1) Six of seven Buschke-Löwenstein tumors (giant condylomata acuminata or nonmetastasizing verrucous carcinomas) contained HPV- 6

or HPV-11 DNA; (2) 5 of 27 invasive carcinomas of the cervix or carcinomata in situ contained HPV-11 DNA or that of a related agent [7]. Since additional groups have reported as yet undefined papillomavirus DNAs in a few more tumors [8, 22] this clearly shows that at least a certain percentage of genital cancers (at present about 20%) contain papillomavirus DNA.

Very recently, our group cloned a third papillomavirus type directly from a cervical cancer biopsy (Dürst et al., unpublished data). This virus is very distantly related to HPV-6, HPV-11, or any of the other characterized human papillomaviruses. It will be of particular interest to test the as yet negative biopsies for the DNA of this new virus type, and such studies are presently in progress. These experiments are performed in the expectation that several distinct types of papillomaviruses cause infections of the human genital tract and a number of them may be involved in the malignant conversion of such papillomas.

We discussed previously the apparent interaction of papillomavirus infections with carcinogens (initiators) in the induction of malignant conversion. Is it possible to identify an initiator interacting with papillomavirus infections in the human genital tract? We believe this is indeed possible. This answer, at surprising first glance, refers to herpes simplex virus infections. Recently, we were able to demonstrate that HSV efficiently induces mutations within the hypoxanthin-guanine-phosphoribosyltransferase (HGPRT) locus of human rhabdomysarcoma cells [18]. More importantly, HSV was shown to share the property of inducing selective gene amplification [19] with chemical and physical carcinogens [10, 11]. This suggests that HSV may provide the initiating functions required for malignant conversion of papillomavirus "promoted" cells.

Very recent experiment (Gissmann et al. unpublished data) provide direct evidence for the amplification of papillomavirus sequences in HSV-infected cells, stressing the probability of the suggested interaction.

The available data have led to the development of a model [25] claiming that human genital cancer results from a synergistic interaction between two virus infections (papillomavirus and HSV) or one virus infection (papillomavirus) and other initiating events.

References

1. de Villiers E-M, Gissmann L, zur Hausen H (1981) J Virol 40:932
2. Gardner SD, Field AM, Coleman DV, Hulme B (1971) Lancet 1:1253
3. Gissmann L, zur Hausen H (1976) Proc Natl Acad Sci USA 73:1310
4. Gissmann L, zur Hausen H (1980) Int J Cancer 25:605
5. Gissmann L, Pfister H, zur Hausen H (1977) Virology 76:569
6. Gissmann L, Diehl V, Schultz-Coulon H, zur Hausen H (1982) J Virol 44:393
7. Gissmann L, Wolnik L, Ikenberg H, Koldovsky U, Schnürch HG, zur Hausen H (1983) Proc Natl Acad Sci USA 80:560
8. Green M, Brackman KH, Sanders PR, Loewenstein PM, Freel JH, Eisinger M, Switlyk SA (1982) Proc Natl Acad Sci USA 79:4437
9. Jarrett WHF, Murphy J, O'Neil BW, Laird HM (1978) Int J Cancer 22:323
10. Lavi S (1981) Proc Natl Acad Sci USA 78:6144
11. Lavi S, Etkin S (1981) Carcinogenesis 2:417
12. London WT, Houff SA, Madden DL, Fucillo DA, Gravel M, Wallen WC, Palmer AE, Sever JL, Padgett BL, Walker DL, Zu Rhein GM, Ohashi T (1978) Science 201:1246
13. Orth G, Favre M, Croissant O (1977) J Virol 24:108
14. Orth G, Favre M, Breitburd F, Croissant O, Jablonska S, Obalek S, Jarzabek-Chorzelska M, Rzesa G (1980) In: Essex M, Todaro G, zur Hausen H (eds) Viruses in naturally occurring cancer. Cold Spring Harbor Lab. Press, New York, Vol A, p 259
15. Padgett BL, Walker DL, Zu Rhein GM, Eckroade RJ, Dessel RH (1971) Lancet 1:1257
16. Rous P, Kidd J (1938) J Exp Med 67:399
17. Rous P, Friedwald WF (1944) J Exp Med 79:511
18. Schlehofer JR, zur Hausen H (1982) Virology 122:471
19. Schlehofer JR, Gissmann L, zur Hausen H (to be published)
20. Tooze J (ed) (1981) DNA tumor viruses. Cold Spring Harbor Lab. Press, New York
21. Weiner LP, Herndon RM, Narayan D, Johnson RT, Shah K, Rubinstein J, Preziosi TJ, Conley FK (1972) N Engl J Med 286:385

22. Zachow KR, Ostrow RS, Bender M, Watts S, Okagaki T, Pass F, Faras AJ (1982) Nature 300:771
23. zur Hausen H (1976) Cancer Res 36:794
24. zur Hausen H (1977) Curr Top Microbiol Immunol 78:1
25. zur Hausen H (1982) Lancet: II:1370
26. zur Hausen H (1983) Int Rev Exp Path (in press)
27. zur Hausen H, Gissmann L (1979) Med Microbiol Immunol 167:139
28. zur Hausen H, Meinhof W, Schreiber W, Bornkamm GW (1974) Int J Cancer 13:650
29. zur Hausen H, Gissmann L, Steiner W, Dregger I (1975) Bibl Haematologica 43:569