The Virus-Cell Gene Balance Model of Cancerogenesis

zur Hausen, H.

Institut für Virologie, Zentrum für Hygiene, Universität Freiburg, Hermann-Herder-Str. 11, 7800 Freiburg, Federal Republic of Germany

In recent years it became increasingly clear that infection of the human host by a number of viruses results in a probably life-long persistence of these agents within specific cells (reviewed e.g. zur Hausen, 1977a). Reactivation of persisting genomes is a well-known phenomenon in individuals infected by herpes group viruses (herpes simplex virus, varicella zoster virus) where neural cells have been identified as site of virus persistence. Infection with Epstein-Barr virus, the causative agent of infectious mononucleosis, leads to viral genome persistence in certain B-lymphocytes. They can be isolated and are readily propagated in tissue culture even years or decades after primary infection (reviewed by zur Hausen, 1975). Transmission of cytomegalovirus infections by blood transfusions has been frequently recorded, even from donors who acquired the virus several years earlier.

Besides herpes group viruses, however, it became more and more obvious that a number of additional agents may persist continuously within the human host. Adeno-viruses seem to be able to persist for long periods within adenoids and specific cells of the tonsils (reviewed by Green, 1970), hepatitis B virus seems to be a candidate for extremely long periods of persistence (Zuckerman, 1975) and the 2 human polyoma-like viruses, BK and JC, apparently remain latent for life-time. Reactivation of the latter appears to be mediated by immunosuppression and may result in excretion of large quantities of viral particles in the urine of affected patients. The papilloma- or wart viruses represent additional candidates for longtime persistence (zur Hausen, 1977b).

The observations cited above permit the statement that every individual, increasing with life-time, is exposed correspondingly to viral infections which result in an increasing "burden" of persisting genomes within certain cells. Although it is presently impossible to predict the actual percentage of cells being affected by viral genome persistence at a given age, it is probably justified to assume a substantial number in every cell compartment of human adults. This can be considered as an epigenetic potential which may remain genetically silent in most instances.

It is a remarkable feature of a substantial number of these persisting agents that many of them are oncogenic when inoculated into non-natural hosts:

Human BK and JC viruses induce malignant tumors after infection into newborn rodents. Brain tumors have been induced in owl monkeys after inoculation of JC virus (London et al., 1978).

Epstein-Barr virus induces malignant lymphomas and lymphoproliferative disease in cottontop marmosets (Shope et al., 1973, Epstein et al., 1973, Wenner et al., 1975).

Certain serotypes of human adenoviruses exert oncogenic potential after inoculation into newborn rodents.

Herpes simplex and cytomegaloviruses are considered as potential tumor viruses, since both of them seem to mediate malignant transformation of rodent cells in vitro (Duff and Rapp, 1971; Albrecht and Rapp, 1973).

It would be easy to prolong this series by including persisting animal viruses, like SV40, polyoma virus, the herpesviruses saimiri, ateles, papio and bovine papillomaviruses. All of these agents represent more or less harmless pathogens within their natural hosts but are effective oncogens in certain heterologous species.

Since tissue culture studies reveal that most of these viruses are able to transform specific cells of their native hosts in vitro, thus exhibiting their proliferation-stimulating capacity also in certain natural host cells, we have to postulate an in vivo mechanism which shields the host against the oncogenic potential of his usually ubiquitous tumor viruses. Such mechanism seems to be mandatory in evolution in order to prevent extinction of the host and guarantee optimal spreading for the viruses.

This protective control could be visualized by immunosurveillance (Burnet, 1970) or by intercellular or intracellular interference factors (zur Hausen, 1977a). Although immunosurveillance appears to play some role in the regulation of viral particle synthesis as evidenced by BK and (or) JC virus excretion in immunosuppressed patients, the rare occurrence of progressive multifocal leucencephalopathy (PML) due to JC virus replication within the brain of such patients and frequent zoster eruptions in patients with Hodgkin's disease, there exists little evidence for a role of immunosurveillance in the prevention of oncogenic properties of persisting natural tumor viruses. Experimental data do not support a role of the immune system in the suppression of oncogenic expression of such agents. Moreover, the efficient induction of tumors by such agents in immunocompetent heterologous species lends little support for this model.

An attractive alternative is the postulation of an intra- or intercellular regulatory system which controls the expression of viral "oncogens" (zur Hausen, 1977a). Cellular interference factor(s) (CIF) interfer with synthesis or function of virus-specified gene products which mediate and maintain the transformed phenotype of a cell. The essential features of such model are outlined in Fig. 1. A viral transforming factor (VTF) is controlled by a cellular set of regulatory genes which mediate this control by a cellular interference factor (CIF). The intracellular control would represent a direct interaction, intercellular control could be mediated by an indirect interaction requiring the existence of a diploid set of "response" genes in the respective target cells. They would need activation by factors of different cell compartments in order to respond with CIF synthesis.

According to this model carcinogenesis depends on the presence of an "effector" mediating the synthesis of a transforming protein and the failure of

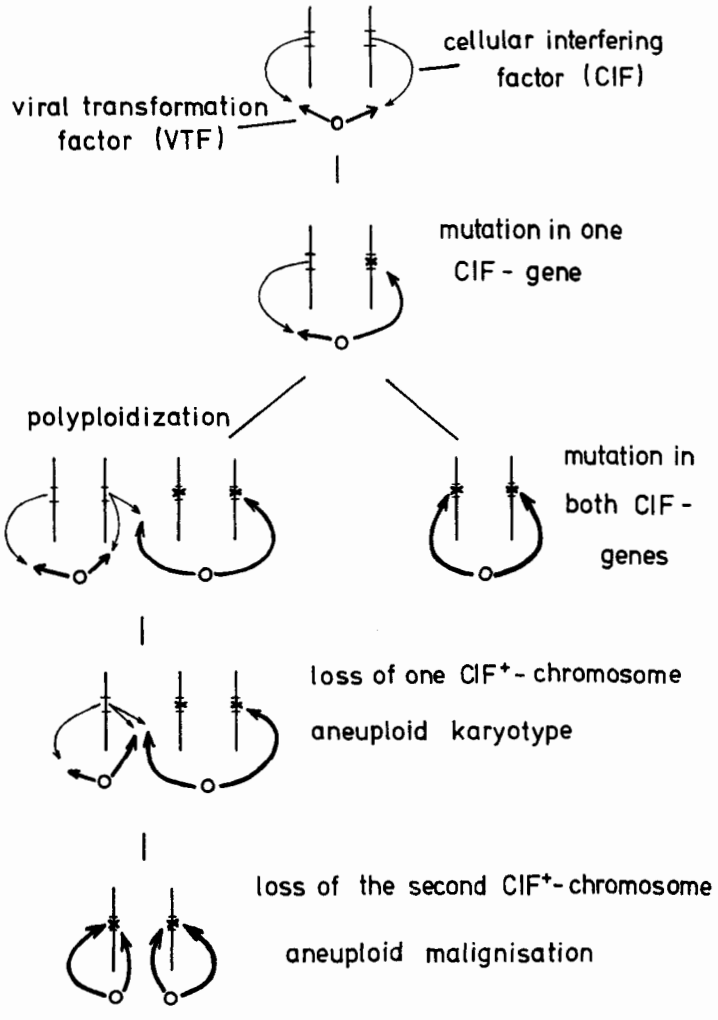

Fig. 1

the controlling CIF alleles. The postulation of a balanced control by CIF of the effector gene(s) (zur Hausen, 1977a) predicts an enhanced growth potential of effector-positive cells carrying a mutation in one CIF gene of the allelic set. This would result in the outgrowth of monoclonal, phenotypically normal cells and could explain observations by Fialkow (see this volume) in patients with chronic myelogenous leukemia and erythrocythemia vera, revealing not only monoclonality in the respective tumor cells but also in normal cells derived from the same stemline.

Mutations in both sets of CIF genes of an effector-containing cell should be an extremely rare event if we consider the spontaneous mutation rate for a specific gene (Spandidos and Siminovitch, 1978; Barret and Ts'o, 1978). They would result in immediate "malignisation" of a diploid tumor cell. Such events, however, would be somewhat facilitated by selective growth advantage of cells carrying a mutation in one CIF allele or by specific integration of viral DNA into these genes or specific mutagenisation due to viral or other agents (zur Hausen, 1967).

Polyploidization should enhance the progression to malignancy in some subsequent steps. Polyploid cells show an increased tendency to loss of individual chromosomes and it should be statistically predictable how many cell divisions are required before the loss of both functioning alleles results in an aneuploid tumor cell.

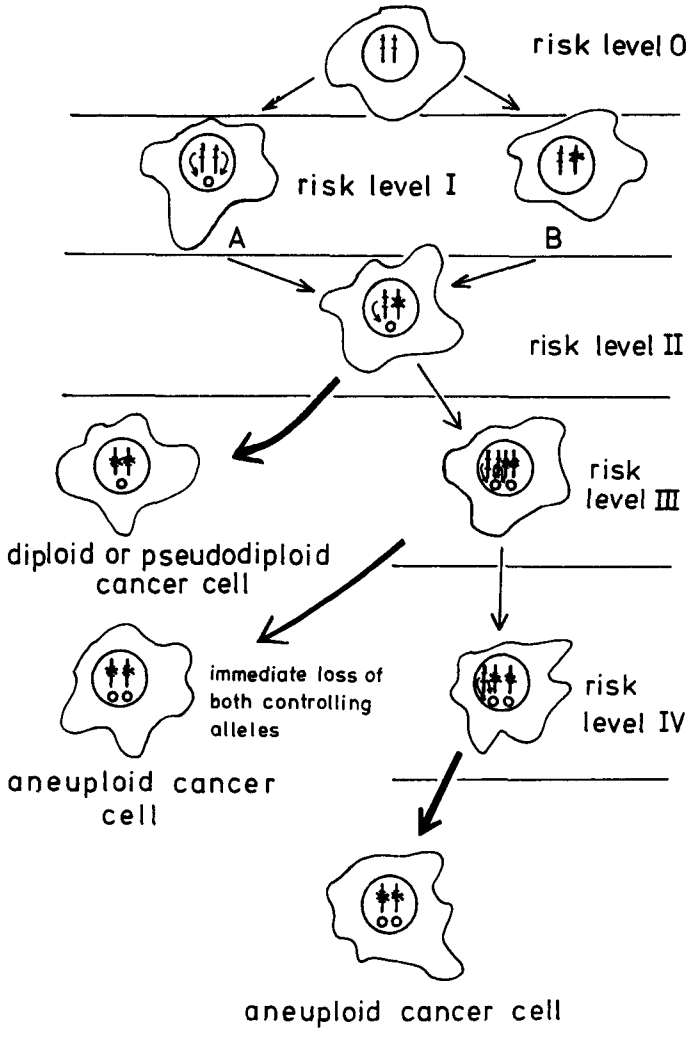

Fig. 2

The model permits the staging of risk levels for malignisation of individual cells. This is attempted in Fig. 2. An effector-free normal cell would be at risk level 0. It is questionable whether such cells exist in reality since genes of endogenous (vertically transmitted) viruses and possibly also genes of cellular origin may possess effector properties. It is possible, however, that the difficulties in transforming human cells in tissue culture by chemical and physical carcinogens (initiators) when compared to rodent cells, may result from the lack of effectors or their reduced number in comparison to e.g. mouse cells.

The model of carcinogenesis described here conveniently explains some of the prevalent features of cancer cells:

the monoclonality,

the stepwise tumor progression, going along with long latency periods,

the prevalent aneuploid karyotype often associated with specific chromosomal aberrations and the commonly observed recessive character of malignancy by intraspecies fusion of malignant with normal cells (Stanbridge and Wilkinson, 1978).

Tumor initiators would act by irreversibly mutagenizing CIF genes. This is in line with the mutagenic potential of the vast majority of chemical carcinogens and of X- and UV-irradiation.

The role of tumor promoters which appear to be non-mutagenic would fit into the scheme according to recent observations (zur Hausen et al., 1978a and b): At least promoters of the diterpene type are effective inducers of persisting genomes of herpesviruses and probably also of some other types of viruses. Their role could thus be envisaged in a transient amplification of effector molecules which would increase the target cell pool for malignant transformation. In addition, an intracellular effector amplification in a CIF-balanced system could shift the balance towards proliferation.

The reconciliation of a model with most well established observations in cancerogenesis does not prove its correctness. It would fulfill, however, its purpose by stimulating experiments which prove or disprove its substance, if this provides further insight in the complex development of human cancer and in effective means of its control.

References

1. Albrecht, T., Rapp, F.: Malignant transformation of hamster embryo fibroblasts following exposure to ultraviolet-irradiated human cytomegalovirus. Virology **55,** 53–61 (1973)
2. Barrett, J. C., Ts'o, P. O.: Relationship between somatic mutation and neoplastic transformation. Proc. Natl. Acad. Sci. USA **75,** 3297–3301 (1978)
3. Burnet, F. M.: The concept of immunological surveillance. Prog. Exp. Tumor Res. **13,** 1–28 (1970)
4. Duff, R., Rapp, F.: Properties of hamster embryo fibroblasts transformed in vitro after exposure to ultraviolet-irradiated herpes simplex virus types. J. Virol. **8,** 469–477 (1971)
5. Epstein, M. A., Hunt, R. D., Rabin, H.: Pilot experiments with EBV in owl monkey (Aotus trivirgatus). I. Reticuloproliferative disease in an inoculated animal. Int. J. Cancer **12,** 309–318 (1973)
6. Green, H.: Oncogenic viruses. Ann. Rev. Biochem. **39,** 701–756 (1970)
7. London, W. T., Houff, S. A., Madden, D. L., Fucillo, D. A., Gravell, M., Wallen, W. C., Palmer, A. E., Sever, J. L., Padgett, B. L., Walker, D. L., Zu Rhein, G. M., Ohashi, T.: Brain tumors in owl monkeys inoculated with a human polyomavirus (JC virus). Science **201,** 1246–1249 (1978)
8. Shope, T., Dechairo, D., Miller, G.: Malignant lymphoma in cottontop marmosets following inoculation of Epstein-Barr virus. Proc. Natl. Acad. Sci. USA **70,** 2487–2491 (1973)
9. Spandidos, D. A., Simonovitch, L.: The relationship between transformation and somatic mutation in human and Chinese hamster cells. Cell **13,** 651–662 (1978).
10. Stanbridge, E. J., Wilkinson, J.: Analysis of malignancy in human cells: Malignant and transformed phenotypes are under separate genetic control. Proc. Natl. Acad. Sci. USA **75,** 1466 to 1469 (1978)
11. Werner, J., Wolf, H., Apodaca, J., zur Hausen, H.: Lymphoproliferative disease in a cottontop marmoset after inoculation with infectious mononucleosis-derived Epstein-Barr virus. Int. J. Cancer **15,** 1000–1008 (1975)
12. Zuckerman, H. J.: Human viral hepatitis. Amsterdam: North Holland Publ. Comp. 1975
13. zur Hausen, H.: Induction of specific chromosomal aberrations by adenovirus type 12 in human embryonic kidney cells. J. Virol. **1,** 1174–1185 (1967)
14. zur Hausen, H.: Oncogenic herpesviruses. Biophys. Biochem. Acta **417,** 25–53 (1975)
15. zur Hausen, H.: Cell-virus gene balance hypothesis of carcinogenesis. Behring Inst. Mitt. **61,** 23–30 (1977a)
16. zur Hausen, H.: Human papilloma viruses and their possible role in squamous cell carcinomas. Current Top. Microbiol. Immunol. **78,** 1–30 (1977b)
17. zur Hausen, H., O'Neill, F. J., Freese, U. K., Hecker, E.: Persisting oncogenic herpesvirus induced by the tumor promoter TPA. Nature **272,** 373–375 (1978)
18. zur Hausen, H., Bornkamm, G. W., Schmidt, R., Hecker, E.: Tumor initiators and promoters in the induction of Epstein-Barr virus. Proc. Natl. Acad. Sci. USA **76,** 782–785 (1979)