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Viruses as Tumor Initiators and Tumor Promoters

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The role of specific viral genes in the induction of malignant tumors is well established in viral infections by papovaviruses and adenoviruses (e.g. review by zur Hausen 1980). In these infections viral DNA may integrate into the host cell genome, and continuous expression of a viral function is a prerequisite for the maintenance of the transformed state.

Chemical and physical carcinogens, on the other hand, introduce transient modifications in the DNA (e.g., DNA adducts, cross-links, single-stranded breaks), which subsequently result in mutational events and also in selective DNA amplification (SDA) in most systems investigated thus far (Lavi 1981; Heilbronn et al. 1985). It appears that "permanent" hereditable changes induced in initiated cells result mainly from the latter events (Heilbronn et al. 1985). No consistent exposure to the damaging event is required for the induction of malignant growth.

In recent years there has been some investigation of the question as to whether specific viral infections may lead to initiator-like effects by modifying the host cell genome similarly and by inducing cell transformation without persistence and continued expression of viral genome functions. This question was raised first when herpes simplex virus DNA, which transforms rodent cells (Duff and Rapp 1973) and has been suspected of playing a role in human cervical cancer (Rawls et al. 1968), was not detected in transformed cells and human cervical cancer biopsies (zur Hausen et al. 1974; zur Hausen 1975, Skinner 1976). Subsequently, experimental data were provided that revealed initiator-like properties of herpes simplex virus infections: The virus was shown to induce mutations within the host cell genome (Schlehofer and zur Hausen 1982) and very efficiently induced SDA in infected cells (Schlehofer et al. 1983).

At least one of the enzymes responsible for inducing these last changes was identified as herpes-specific DNA polymerase (Matz et al. 1984). This enzyme shares functional properties with host cell DNA polymerase alpha, which was recently identified as the key enzyme in SDA induced by chemical and physical carcinogens (Heilbronn et al. 1985).

Thus, herpes simplex viruses at least share properties with initiators under specific conditions they may possibly interact with host cell DNA as chemical and physical carcinogens do. It will be interesting to determine whether additional members of the herpes-virus group, such as cytomegalovirus or Epstein-Barr virus, possess similar properties.

Tumor promotion is not yet defined at the molecular level. Promoting chemicals, if applied for prolonged periods of time to initiated cells, lead to papillomatous proliferations which convert into malignant tumors. Promotors do not act as carcinogens, but they interact with carcinogen-pretreated cells, ultimately resulting in carcinomatous growth. It is tempting to speculate that

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promoters induce expression of amplified "initiated" genes.

There is one group of viruses which, upon infection of susceptible cells, shows a remarkable functional resemblance to tumor promoters: the papillomaviruses (zur Hausen et al. 1984). It appears that in the majority of specific infections with these viruses leading to malignant conversion additional interaction with chemical and physical carcinogens is required. The molecular mechanism of this interaction is presently not understood. Preliminary data suggest, however, that events favoring integration of the otherwise episomal papillomavirus DNA into the host cell genome may contribute to this process (Schwarz et al. 1985). It appears that additional changes, possibly affecting the host cell genome, are also involved.

Thus, interaction of specific types of papillomavirus infections with chemical and physical carcinogens suggests a promoter-like activity of these agents.

This is further underlined by observations revealing the effectiveness of a potent inhibitor of chemical promotion, retinoic acid, in the treatment of clinical warts and experimental papillomas (Lutzner and Blanchet-Bardon 1980; Jablonska et al. 1981; Ito 1981).

At present it is very difficult to correlate these effects with promotion at the molecular level. It is suggestive, however, that papillomaviruses represent suitable models for analysis of the process of promotion.

We can therefore conclude that viruses, in particular herpes simplex virus and specific papillomavirus types, may lead to intracellular events resembling effects exerted by chemical and physical carcinogens and tumor promoters. The availability of these agents and the accurate study of their gene organization and gene expression may render them suitable models for use in work that will expand our understanding of basic processes in carcinogenesis.

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