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Lecture title: Oncogenic DNA Viruses

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Summary: Oncogenic DNA Viruses

Although retroviruses are the most important oncogenic viruses in animals, certain DNA viruses are also significant, including papillomaviruses, polyomaviruses, herpesviruses, and potentially others (Table

DNA tumor viruses interact with cells in one of two ways:
(1) productive infection, in which the virus completes its replication cycle, resulting in cell lysis,
or (2) non-productive infection, in which the virus transforms the cell without completing its replication cycle. During such non-productive infection, the viral genome or a truncated version of it is integrated into the cellular DNA; alternatively, the complete genome persists as an autonomously replicating plasmid (episome). The genome continues to express early gene functions. The molecular basis of oncogenesis by DNA viruses is best understood for polyomaviruses, papillomaviruses, and

adenoviruses, all of which contain genes that behave as oncogenes, including tumor suppressor genes. These oncogenes appear to act by mechanisms similar to those described for retrovirus oncogenes: they act primarily in the nucleus, where they alter patterns of gene expression and regulation of cell growth. In every case the relevant genes encode early proteins having a dual role in virus replication and cell transformation. With a few possible exceptions, the oncogenes of DNA viruses have no homologue or direct ancestors (c-onc genes) among cellular genes of the host.

The protein products of DNA virus oncogenes are multifunctional, with particular functions that mimic functions of normal cellular proteins related to particular domains of the folded protein molecule. They interact with host-cell proteins at the plasma membrane or within the cytoplasm or nucleus

Oncogenic Polyomaviruses and Adenoviruses

During the 1960s and 1970s, two members of the family Polyomaviridae, murine polyomavirus and simian virus 40 (SV40), as well as certain human adenoviruses (types 12, 18, and 31) were shown to induce malignant neoplasms following their inoculation into baby hamsters and other rodents. With the exception of murine polyomavirus, none of these viruses induces cancer under natural conditions in its natural host, rather they transform cultured cells of certain other species and provide

experimental models for analysis of the molecular events in cell transformation. Polyomavirus- or adenovirus-transformed cells do not produce virus. Viral DNA is integrated at several sites in the chromosomes of the cell. Most of the integrated viral genomes are complete in the case of the polyomaviruses, but defective in the case of the adenoviruses. Only certain early viral genes are transcribed, albeit at an unusually high rate. By analogy with retrovirus genes, they are now called oncogenes. Their products, demonstrable by immunofluorescence, used to be known as tumor (T) antigens. A great deal is now known about the role of these proteins in transformation. Virus can be rescued from polyomavirustransformed cells—that is, virus can be induced to replicate, by irra¬diation, treatment with certain mutagenic chemicals, or co-cultivation with certain types of permissive cells. This cannot be done with adenovirus-transformed cells, as the integrated adenovirus DNA contains substantial deletions. It should be stressed that the integration of viral DNA does not necessarily lead to transformation. Many or most episodes of integration of polyomavirus or adenovirus DNA have no recognized biological consequence. Transformation by these viruses in experimental systems is a rare event, requiring that the viral transforming genes be integrated in the location and orientation needed for their expression. Even then, many transformed cells revert (abortive transformation). Furthermore, cells

displaying the characteristics of transformation do not necessarily produce neoplasms.

Oncogenic Papillomaviruses

Papillomaviruses produce papillomas (warts) on the skin and mucous membranes of most animal species. These benign neoplasms are hyperplastic epithelial outgrowths that generally regress spontaneously. Occasionally, however, they may progress to malignancy, which in part is a property of specific virus strains. Virusinduced papillomas occur in many species, and papillomaviruses are also the cause of sarcoids in horses, some human oropharyngeal carcinomas, and cervical carcinoma in women, and are associated with some squamous cell carcinomas in cats and dogs. In benign warts, the papillomavirus DNA is episomal, meaning it is not integrated into the host-cell DNA and persists as an autonomously replicating episome, whereas in papillomavirus-induced cancers the viral DNA is integrated into that of the host. Thus, integration probably is necessary for malignant transformation, as the pattern of integration is clonal within cancers: each cancer cell carries at least one, and often many incomplete copies of the viral genome. The site of virus integration is random, and there is no consistent association with cellular proto-oncogenes. For some papillomaviruses, integration disrupts one of the early genes, E2, which is a viral repressor. Other viral genes may also be deleted, but the viral oncogenes (e.g., E6 and E7) remain intact, are expressed efficiently, and cause the malignant

transformation. The proteins expressed by the viral oncogenes interact with cellular growth regulating proteins produced by proto-oncogenes and tumor suppressors such as p53 to block apoptosis and promote cellular proliferation. Another relevant example is bovine papillomavirus type 1 E5 oncoprotein, which alters the activity of cell membrane proteins involved in regulating cellular proliferation—for example, platelet derived growth factor receptor

Oncogenic Hepadnaviruses

Mammalian, but not avian, hepadnaviruses are associated strongly with naturally occurring hepatocellular carcinomas in their natural hosts. Woodchucks that are chronically infected with woodchuck hepatitis virus almost inevitably develop hepatocellular carcinoma, even in the absence of other carcinogenic factors. Oncogenesis induced by mammalian hepadnaviruses is a multifactorial process, and there are differences in the cellular mechanisms responsible for carcinogenesis associated with different viruses. Whereas ground squirrel and woodchuck hepatitis viruses activate cellular oncogenes, the mode of action of human hepatitis B virus is uncertain, as it apparently has no consistent site of integration or oncogene association. The hepatocellular regeneration accompanying cirrhosis of the liver also promotes the development of neoplasia in hepatitis virus-infected humans, but there is no cirrhosis in the animal models. The likelihood of

hepadnavirus-associated carcinoma is greatest in animals (and humans) infected at birth.

Oncogenic Herpesviruses

Oncogenic Alphaherpesviruses Marek's disease virus of chickens transforms T lymphocytes, causing them to proliferate to produce a generalized polyclonal T lymphocyte neoplasm. The disease is preventable by vaccination with live-attenuated virus vaccines that lack the retrovirus v-onc genes that are present in Marek's disease virus

Oncogenic Gammaherpesviruses

Herpesviruses of the subfamily Gammaherpesvirinae are lymphotropic and the etiologic agents of lymphomas and carcinomas in hosts ranging from amphibians to primates, including humans. Epstein–Barr virus (human herpesvirus 4) in otherwise healthy young human adults causes infectious mononucleosis (glandular fever), in which there is B lymphocyte proliferation that resolves. The mechanism by which the virus goes on to produce malignancy in some individuals has been best studied in Burkitt's lymphoma, a malignant B cell lymphoma that occurs in children in East Africa and less frequently in children in other parts of the world. The Epstein–Barr viral genomic DNA is present in multiple copies of episomal DNA in each cell of most African Burkitt's lymphomas. Lymphoma cells

express viral nuclear antigen, but do not produce virus. These cells also contain a characteristic 8 : 14 chromosomal translocation. Burkitt's lymphoma may develop as a consequence of c-myc deregulation resulting from this translocation, which in turn causes an arrest of normal cellular maturation and differentiation processes. Some Burkitt's lymphomas also have mutations in the cellular tumor suppressor gene, p53. The subfamily Gammaherpesvirinae includes several other viruses that cause lymphomas in heterologous primate hosts (e.g., herpesvirus siamiri), human herpesvirus 8, associated with Kaposi sarcoma mostly in humans with AIDS, and bovine malignant catarrhal fever virus, an acute fatal lymphoproliferative disease of cattle and certain wild ruminants (see Chapter 9). These viruses are lymphotropic and contain numerous unspliced genes that appear to have been captured from the host during virus replication, over considerable evolutionary time. These captured genes typically encode proteins that

(1) regulate cell growth,

(2) are immunosuppressive,

or (3) are enzymes involved in nucleic acid metabolism—they include genes encoding cytokine or cytokine receptor homologues, regulatory proteins such as cyclins that control the cell cycle, and proteins such as bcl2 that can block apoptosis. The function of these various virusencoded proteins is consistent with the lymphotropic transforming

properties of these viruses. Thus these herpesviruses seem to have evolved/acquired different strategies to overcome cell cycle arrest, apoptosis, and activation of cellular immunity, all to favor virus replication and survival, all also causing lymphocyte proliferation and transformation. Certain members of the family Alloherpesviridae are associated with neoplasia in their respective hosts, including renal adenocarcinomas of frogs and epithelial tumors of salmonid fish

Oncogenic Poxviruses

Although some poxviruses are regularly associated with the development of benign tumor-like lesions , there is no evidence that these ever become malignant, nor is there evidence that poxvirus DNA is ever integrated into cellular DNA. A very early viral protein produced in poxvirus-infected cells displays homology with epidermal growth factor and is probably responsible for the epithelial hyperplasia characteristic of many poxvirus infections. For some poxviruses (e.g., fowlpox, orf, and rabbit fibroma viruses), epithelial hyperplasia is a dominant clinical manifestation and may be a consequence of a more potent form of the poxvirus epidermal growth factor homologue.