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Summary: *Oncogenic virus*

The revolution in molecular cell biology has provided remarkable insights into the mechanisms of regulation of cell growth and differentiation, and these insights have, in turn, advanced understanding of the mechanisms underpinning failures of regulatory processes that are expressed

as neoplasia.

The genetic changes that are ultimately responsible for neoplasia may be caused by chemical or physical agents or viruses, but all involve certain common cellular pathways. Interestingly, while there are a substantial number of both RNA and DNA viruses that are oncogenic in animals, only a relatively few viruses have been definitively linked to human cancer.

The discoveries of the viral etiology of avian leukemia by Ellerman and Bang and of avian sarcoma by Rous, in 1908 and 1911 respectively, were long regarded as curiosities unlikely to be of any fundamental significance. However, study of these avian viruses and related retro¬viruses of mice has increased our overall understanding of neoplasia greatly, and since the 1950s there has been a steady stream of

discoveries clearly incriminating other viruses in a variety of benign and malignant neoplasms of numerous species of mammals, birds, amphibians, reptiles, and fish.

Many avian retroviruses are major pathogens of poultry, and other retroviruses produce neoplasms in domestic animals. Similarly, several different DNA viruses have been determined to be responsible for cancers in humans and animals. Any discussion of virus-induced neoplasia requires that a few commonly used terms are defined: a neoplasm is a new growth (syn. tumor); neoplasia is the process that leads to the formation of neoplasms (syn. carcinogenesis); oncology is the study of neoplasia and neoplasms; a benign neoplasm is a growth produced by abnormal cell proliferation that remains localized and does not invade adjacent tissue; in contrast, a malignant neoplasm (syn. cancer) is locally invasive and may also be spread to other parts of the body (metastasis). Carcinomas are cancers of epithelial cell origin, whereas sarcomas are cancers that arise from cells of mesenchymal origin. Solid neoplasms of lymphocytes are designated lymphosarcoma or malignant lymphoma (syn. lymphoma), whereas leukemias are cancers of hemopoietic origin characterized by circulation of cancerous cells.

Neoplasms arise as a consequence of the dysregulated growth of cells derived from a single, genetically altered progenitor cell. Thus, although neoplasms are often composed of several cell types, they are considered

to originate from a monoclonal outgrowth of a single cell. It recently has been proposed that neoplasms arise from cells with properties and function similar to those of the stem cells that are present in normal tissue. Specifically, many normal tissues contain a small population of resident, long-lived stem cells that are tissue progenitors; these cells can divide to produce either terminally differentiated, relatively shortlived cells with limited replicative ability, or additional long-lived stem cells. As cancers are immortal and have unlimited ability to replicate, it is assumed that they, too, must contain stem cells that arise either from normal tissue stem cells or from differentiated cells that assume stem cell-like properties

The Cellular Basis of Neoplasia

Neoplasia is the result of non-lethal genetic injury, as may be acquired by chemical or physical damage, or from viral infections. Some cancers, however, arise randomly through the accumulation of spontaneous genetic mutations. A neoplasm results from the clonal expansion of a single cell that has suffered genetic damage, typically in one of four types of normal regulatory genes:

(1) proto-oncogenes, which are cellular genes that regulate growth and differentiation;

(2) tumor suppressor genes that inhibit growth, typically by regulating the cell cycle;

(3) genes that regulate apoptosis (programmed cell death;

(4) genes that mediate DNA repair.

Carcinogenesis involves a multi-step progression resulting from the cumulative effects of multiple mutations. Once developed, neoplasms are:

(1) self-sufficient, in that they have the capacity to proliferate without external stimuli; for example, as the result of unregulated oncogene activation;

(2) insensitive to normal regulatory signal that would limit their growth, such as transforming growth factor- and the cyclin-dependent kinases that normally regulate orderly progression of cells through the various phases of the cell cycle;

(3) resistant to apoptosis because of either the activation of anti-apoptotic molecules or the inhibition of mediators of apoptosis ;

(4) limitless potential for replication. Cancers also may have the ability to invade and spread to distant tissues (metastasis), and neoplasms typically promote the proliferation of new blood vessels that support their growth. Neoplasia, regardless of cause, is the result of unregulated cellular proliferation. In the normal sequence of events during cellular proliferation, a growth factor binds to its specific cellular receptor,

leading to signal transduction that ultimately results in nuclear transcription, which in turn leads to the cell entering and progressing through the cell cycle until it divides. Proto-oncogenes are normal cellular genes that encode proteins that function in normal cellular growth and differentiation; they include

(1) growth factors;

(2) growth factor receptors;

(3) intracellular signal transducers;

(4) nuclear transcription factors;

(5) cellcycle control proteins.

Oncogenes are derived by mutation of their normal cellular proto-oncogene counterparts, and the expression of oncogenes results in production of oncoproteins that mediate autonomous (unregulated) growth of neoplastic cells. The development of cancer (malignant neoplasia) is a protracted, multi-step process that reflects the accumulation of multiple mutations. A potentially neoplastic clone of cells must bypass apoptosis (programmed death), circumvent the need for growth signals from other cells, escape from immunologic surveillance, organize its own blood supply, and possibly metastasize. Thus, tumors other than those induced by rapidly transforming retroviruses like Rous sarcoma virus generally do not arise as the result of a single event, but by a series of steps leading to progressively

greater loss of regulation of cell division. Oncogenic DNA and RNA viruses have been identified in both animals and humans, including retroviruses, papillomaviruses, herpesviruses, and several other DNA viruses. Cells transformed by non-defective retroviruses also express the full range of viral proteins, and new virions bud from their membranes. In contrast, transformation by DNA viruses usually occurs in cells undergoing non-productive infection in which viral DNA is integrated into the cellular DNA of the transformed cells or, in the case of papillomaviruses and herpesviruses, in which the viral DNA remains episomal. Certain virus-specific antigens are demonstrable in transformed cells. Some tumor-associated antigens are expressed on the plasma membrane where, in vivo, they constitute potential targets for immunologic attack.

Oncogenic RNA Viruses

Retrovirus Pathogenesis

Retroviruses are a significant cause of neoplasia in many species of animals, including cattle, cats, non-human primates, mice, and chickens, among others. Their pathogenesis is linked to their propensity to integrate randomly within the genome of host cells, thereby being infectious mutagens. The consequences of such integration are largely innocuous and clinically silent, and only seldom result in oncogenesis. As described in Chapter 14, retroviruses can be biologically divided into exogenous (horizontally transmissible) agents, or endogenous, in which

case they are integrated within the host genome. Retroviruses can be either replication-competent or replication-defective. Rarely, a replication-competent retrovirus will integrate into the genome of host germ cells. A complete DNA copy of the viral genome (known as the provirus) may thereafter be transmitted in the germ line DNA from parent to progeny (i.e., via ova or sperm) and, over the course of evolution, may be perpetuated in every individual of an animal species. Such retroviruses are said to be endogenous. As long as endogenous retroviruses remain replicationcompetent, they may also be horizontally transmissible like their exogenous relatives. Over the course of time, multiple endogenous retroviruses become integrated throughout the genome, either through new exposures, or more commonly when provirus genomes are replicated during cell division, they can then be integrated elsewhere in the genome as retrotransposons. As millennia pass, many of these “retroelements” become replication-defective but their DNA continues to have the potential to reintegrate as retrotransposons, and their partial genes may continue to encode proteins. These reintegration events, when involving functioning host genes, may result in spontaneous mutations
within the germ line of the species. This process is known as insertional mutagenesis. It is not necessarily in the best interest of the host to carry potentially deleterious viral mutagens within its genome, so the host evolves to lack somatic cell receptors for its endogenous viruses, or the

host may mutate, truncate, methylate, or even evict proviral sequences over time. In essence, endogenous retroviruses and their hosts are in a constant state of co-evolution. Some anciently acquired endogenous retroviruses have actually become vital to host physiology.

During pregnancy of mammals (except monotremes), endogenous retro-elements are expressed to high levels during embryo implantation and placental development, inducing immunosuppressive and cell fusion (syncytium formation) effects that are vital to mammalian placental and fetal development. Syncytin1 is one such gene product that is an endogenous retroelement env-derived fusigenic glycoprotein that is critical in syncytial trophoblast formation. It is a highly conserved and essential gene among placental animals.

Endogenous proviruses, like other host genes, are expressed differentially in different tissues, at different ages, and under the control of various stimuli, including hormones and immune states. When a dividing cell is co-expressing two or more proviruses, proviral genomes may recombine to form new retroviral variants with novel ability to infect somatic cells through alternate receptors. This has been illustrated in lymphoma-prone inbred mouse strains, with each mouse strain having different constellations of proviral integrations that recombine to become replicationcompetent infectious viruses that can target vulnerable tissues through novel receptor–ligand interactions. Although this has been extensively studied, the consequences of proviral

recombination and induction of neoplasia by viral recombinants is largely an artificial phenomenon that is unique to the inbred mouse.

Retrovirus-Induced Neoplasia

Oncogenic retroviruses are classified as chronic transforming or acute transforming retroviruses. These two major types of transforming retroviruses induce neoplasia in significantly different ways.

Chronic Transforming Retroviruses

Chronic transforming retroviruses induce neoplasia through random integrations into the genome of somatic cells. They exert their effect as "cis-activating" retroviruses that transform cells by becoming integrated in the host-cell DNA close to a cell growth regulating gene, and thus usurping normal cellular regulation of this gene. These cell growth regulating host genes are termed "oncogenes," or cellular oncogenes (c-onc). Despite the terminology implying that they are oncogenic, c-onc genes are host genes that encode important cell signaling products that regulate normal cell proliferation and quiescence.

The presence of an integrated provirus, with its strong promoter and enhancer elements, upstream from a c-onc gene may amplify the expression of the c-onc gene greatly. This is the likely mechanism whereby the weakly oncogenic endogenous avian leukosis viruses produce neoplasia. When avian leukosis viruses cause malignant neoplasia, the viral genome has generally been integrated at a particular

location, immediately upstream from a host c-onc gene. Integrated avian leukosis provirus increases the synthesis of the normal c-myc oncogene product 30- to 100-fold. Experimentally, only the viral long-terminal repeats (LTR) need be integrated to cause this effect; furthermore, by this mechanism c-myc may also be expressed in cells in which it is not normally expressed or is normally expressed at much lower levels. Not all chronic transforming retroviruses require insertional mutagenesis in regions of c-onc genes to be oncogenic. Both exogenous and endogenous mouse mammary tumor viruses carry an extra viral gene sequence that encodes a super-antigen (Sag) that stimulates proliferation of lymphocytes. Expression of Sag stimulates massive B cell proliferation and mouse mammary tumor virus replication in the dividing B cells, with subsequent homing of virus-expressing lymphocytes to mammary tissue. Both lymphomas and mammary tumors may ensue, but oncogenesis does not require alteration of host oncogenes. The exogenous ovine retroviruses that cause nasal carcinomas and pulmonary adenocarcinomas (Jaagsiekte) infect epithelial target cells, and transformation is related to expression of the viral env gene. Bovine leukemia virus is an exogenous retrovirus that causes chronic leukosis and B cell lymphoma. The virus encodes tax, rex, R3, and G4 genes in the 3 · end of its viral genome. The tax gene functions as a transactivator of host genes. Bovine leukemia virus is

closely related to human T lymphotrophic virus 1 (HTLV-1), which has a similar viral genome. In contrast to cis-activating retroviruses, these viruses are examples of “trans-activating” retroviruses.

Acute Transforming Retroviruses

Acute transforming retroviruses are directly oncogenic by carrying an additional viral oncogene, v-onc, and are classified as “transducing” retroviruses. The retroviral v-onc originates from a host c-onc gene, and the transforming activity of the v-onc is accentuated by mutation. Given the high error rate of reverse transcription, v-onc gene homologs of c-onc genes will always carry mutations and the strongly promoted production of the viral oncoprotein will readily exceed that of the normal cellular oncoprotein. The result can be uncontrolled cell growth. Because c-onc genes are the precursors of v-onc genes, c-onc genes are also called “protooncogenes.” Wherever acute transforming retroviruse integrate in the host genome, it is the v-onc that is directly responsible for the rapid malignant change that occurs in cells infected with these viruses. Over 60 different v-onc genes have been identified, and retroviruses have been instrumental in identifying their cellular homologues. The v-onc is usually incorporated into the viral RNA in place of part of one or more normal viral genes. Because such viruses have lost some of their viral genetic sequences, they are usually incapable of replication, and are therefore termed “defective” retroviruses. Defective retroviruses circumvent their defective

replicative ability by utilizing nondefective “helper” retroviruses for formation of infectious virions. An exception is Rous sarcoma virus, in that its genome contains a viral oncogene (v-src) in addition to its full complement of functioning viral genes (gag, pol, and env); thus Rous sarcoma virus is both replication-competent and an acute transforming virus. Rous sarcoma virus is one of the most rapidly acting carcinogens known, transforming cultured cells in a day or so and causing neoplasia and death in chickens in as little as 2weeks after infection. Although retrovirus v-onc genes often preclude virus replication, v-onc genes have been acquired over time by retroviruses, most likely because they cause cellular proliferation. As most retroviruses replicate during cell division, this favors virus growth and perpetuation in nature. Defective retroviruses carrying a v-onc gene are always found in the company of a replication-competent helper virus that supplies missing functions, such as an environmentally stable envelope. The advantage to both viruses is presumably that when they are together they can infect more cells and produce more progeny of both viruses. The various v-onc genes and the proteins they encode are assigned to major classes: growth factors (such as v-sis); growth factor receptors and hormone receptors (such as v-erbB); intracellular signal transducers (such as v-ras); and nuclear transcription factors (such as v-jun). The oncoprotein products of the various retroviral v-onc genes act in many different ways to affect cell growth, division, differentiation, and homeostasis

* v-onc genes usually contain only that part of their corresponding c-onc gene that is transcribed into messenger RNA—in most instances they lack the introns that are so characteristic of eukaryotic genes

* v-onc genes are separated from the cellular context that normally controls gene expression, including the normal promoters and other sequences that regulate c-onc gene expression

*v-onc genes are under the control of the viral LTRs, which not only are strong promoters but also are influenced by cellular regulatory factors. For some retrovirus v-onc genes, such as myc and mos, the presence of viral LTRs is all that is needed for tumor induction

*v-onc genes may undergo mutations (deletions and rearrangements) that alter the structure of their protein products; such changes can interfere with normal protein– protein interactions, leading to escape from normal regulation

* v-onc genes may be joined to other viral genes in such a way that their functions are modified. For example, in Abelson murine leukemia virus the v-abl gene is expressed as a fusion protein with a gag protein; this arrangement directs the fusion protein to the plasma membrane where the Abl protein functions. In feline leukemia virus, the v-onc gene fms is also expressed as a fusion protein with a gag protein, thus allowing the insertion of the Fms oncoprotein in the plasma membrane.

Many acute transforming retroviruses induce solid tumors in addition to hemopoietic tumors. These viruses are termed “sarcoma” viruses. In addition to many avian leukosis virus-derived sarcoma viruses that have incorporated various v-onc genes, several acute transforming defective sarcoma viruses have been isolated from sarcomas of cats naturally infected with exogenous feline leukemia virus, a woolly monkey infected with a simian retrovirus, and several sarcoma viruses have been isolated from laboratory rodents infected with both exogenous and endogenous retroviruses. Acute transforming defective retroviruses are significant as oncogens in individual animals, but are not naturally transmissible agents