Decision Making in Small Animal Oncology

1
INTRODUCTION: CANCER BIOLOGY AND TERMINOLOGY

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A Definition of Tumor

- A tumor is any tissue mass or swelling and may or may not be neoplastic.
- Neoplasia is the abnormal growth of a tissue into a mass. It is usually phenotypically recognized by the fact that its cells show abnormal growth patterns and are no longer under the control of normal homeostatic growth-controlling mechanisms.
- Neoplasms can be considered as either benign or malignant tumors. Although the range of mechanisms involved in the development of tumors and the spectrum of tissues from which tumors are derived is diverse, they can be classified into three broad types:
  1. **Benign Tumors**: Broadly speaking, these tumors arise in any of the tissues of the body and grow locally. They can grow to a large size but are not invasive. Their clinical significance is their ability to cause local pressure, cause obstruction, or form a space-occupying lesion such as a benign brain tumor. Benign tumors do not metastasize.
  2. **In situ Tumors**: These are often small tumors that arise in the epithelium. Histologically, the lesion appears to contain cancer cells, but the tumor remains in the epithelial layer and does not invade the basement membrane or the supporting mesenchyme. A typical example of this is preinvasive squamous cell carcinoma affecting the nasal planum of cats.
  3. **Cancer**: This refers to a malignant tumor, which has the capacity for both local invasion and distant spread by the process of metastasis.

A Definition of Cancer

- Cancer is a disease of all vertebrate species and is well documented throughout history, with fossil records indicating dinosaurs of the Jurassic period suffered from the disease.
- The Greek physician Galen is accredited with describing human tumors of having the shape of a crab, with leglike tendrils invading deep into surrounding tissues—hence, the term cancer.

Key Point
We define cancer as any malignant growth or tumor caused by abnormal and uncontrolled cell division, able to invade tissues locally and able to spread to other parts of the body through the lymphatic system or the bloodstream. This is obviously a simplistic attempt at describing a complex disease that can utilize a myriad of biological pathways to sustain growth and proliferation.

Nomenclature

The nomenclature of tumors is based upon two concepts:
- First, tumors can be considered as either benign or malignant. For simplicity, the pathobiological differences between benign and malignant are outlined in Table 1.1.
- The second concept is concerned with the tissue or cell of origin (Tables 1.2, 1.3).

Cancer Biology

- Fundamental to our basic understanding of mammalian physiology is the concept of homeostasis.
- If we consider the body as a multicellular unit, cells within this unit form part of a specialized society that cooperates to promote survival of the organism. In terms of homeostasis, cell division, proliferation, and differentiation are strictly controlled and a balance exists between normal cell birth and the natural cell death (Argyle and Khanna, 2006).
- Cancer can be considered as a breakdown in cellular homeostasis leading to uncontrolled cell division and proliferation, which ultimately leads to a disease state.

The Pathways to Cancer

- For many years, cancer researchers have considered a stochastic model of cancer development (McCance and Roberts, 1997).

Table 1.1. The biological differences between benign and malignant tumors

Feature	Benign	Malignant
Degree of differentiation	Cells of benign tumors demonstrate a stage of development at which they have their mature morphological and functional characteristics: and are thus considered to be ***well differentiated.***	Malignant tumors demonstrate a range of differentiation from very good to very poor. A severe lack of differentiation is referred to as ***anaplasia.***
Growth rate	Benign tumors often grow slowly and have periods of dormancy when no growth is recognized.	Malignant tumors have a wide range of growth rates.
Mode of growth	The mode of growth is considered to be by ***expansion***, and tumors are usually encapsulated.	The mode of growth is initially by expansion, but eventually by ***invasion***. There is no capsule containing the tumor and the borders are ill defined. Once malignant cells have infiltrated outside their normal confines, they travel along the natural cleavage plains and interstices of tissue.
Metastatic potential	The ability for tumor cells to spread and grow in distant organs (metastasis) is **NOT** a feature of benign tumors.	Malignant tumors have varying capability to metastasize. This can be via the hematogenous, lymphatic, or trans-serosal routes.
Host consequences	The effect on the host is usually through the presence of a ***space-occupying lesion***. Consequently, this can be a minimal effect (benign lipoma in the subcutaneous tissue); or can be life threatening (benign brain tumor).	Often ***life threatening*** based on the tumor's destructive effects on tissues and vital organs, and its ability to metastasize.

Table 1.2. The nomenclature of benign tumors

Tissue or Cell of Origin	Naming
Mesenchymal	Named by the addition of the suffix ***oma*** to the cell type of origin: • Fibrous tissue = fibroma • Fat tissue = lipoma • Cartilage = chondroma
Glandular epithelium	Referred to as ***adenoma:*** • A benign tumor of the sweat gland epithelium would be a *sweat gland adenoma*.
Protective epithelium (squamous or transitional)	Referred to as ***papilloma:*** • Squamous papilloma of the skin (wart) • Transitional papilloma of the urinary bladder
Nervous tissue	Named by the addition of the suffix ***oma*** to the cell type of origin: • A benign tumor of the astrocytes would be an *astrocytoma*.

Table 1.3. The nomenclature of malignant tumors

Tissue or Cell of Origin	Naming
Mesenchymal	Named by the addition of the suffix ***sarcoma*** to the cell type of origin: • Fibrous tissue = fibrosarcoma • Fat tissue = liposarcoma • Cartilage = chondrosarcoma
Glandular epithelium	Referred to as ***adenocarcinoma:*** • A malignant tumor of the sweat gland epithelium would be a *sweat gland* or *apocrine adenocarcinoma*.
Protective epithelium (squamous or transitional)	A malignant tumor of squamous epithelium would be a *squamous cell carcinoma*. A malignant tumor of transitional epithelium would be a *transitional cell carcinoma*.
Round cell tumors	Lymphoma and other lymphoid neoplasia Plasmacytoma and multiple myeloma Histiocytoma and other histiocytic diseases Mast cell tumor Transmissible venereal tumor With the exception of the transmissible venereal tumor, round cell tumors affect cell lines of hemolymphatic origin

- In this, cancer formation is the phenotypic end result of a whole series of changes that may have taken a long period of time to develop.
- Following an initiation step produced by a cancer-forming agent on a cell, there follows a period of tumor promotion (Figure 1.1). The initiating step is a rapid step and affects the genetic material of the cell. If the cell does not repair this damage, promoting factors may progress the cell toward a malignant phenotype. In contrast to initiation, progression may be a very slow process, and may not even manifest in the lifetime of the animal.
- Over the past 4 decades, cancer research has generated a rich and complex body of information revealing that cancer is a disease involving dynamic changes in the genome. Each stage of multistep carcinogenesis reflects genetic changes in the cell with a selection advantage that drives the progression toward a highly malignant cell. The age-dependent incidence of cancer suggests a requirement for between four and seven rate-limiting, stochastic events to produce the malignant phenotype.

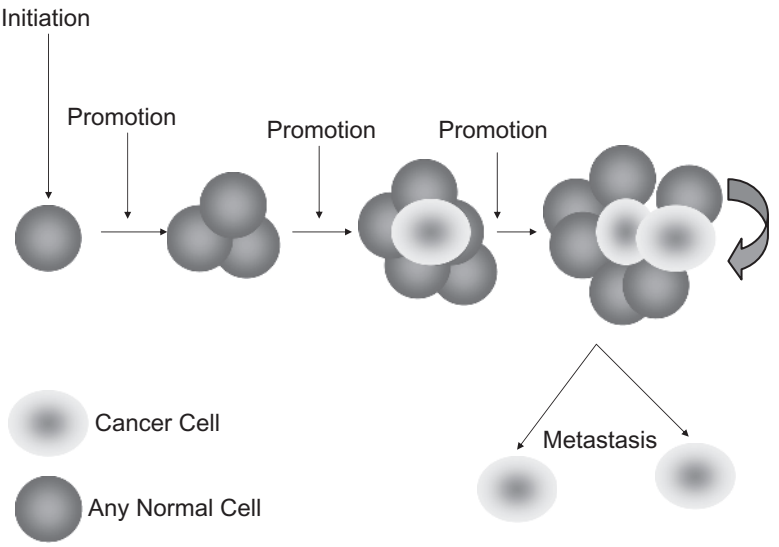

Figure 1.1. The stochastic model of carcinogenesis: Cancer formation is the phenotypic end result of a whole series of changes that may have taken a long period of time to develop. They can occur in any cell type in the body. After an initiation step produced by a cancer-forming agent on a cell is a period of tumor promotion. Each stage of multistep carcinogenesis reflects genetic changes in the cell with a selection advantage that drives the progression toward a highly malignant cell. The age-dependent incidence of cancer suggests a requirement for between four and seven rate-limiting, stochastic events to produce the malignant phenotype. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

Oncogenes

- Seminal to our understanding of cancer biology has been the discovery of the so-called "cancer genes," or oncogenes, and tumor suppressor genes.
- The term ***proto-oncogene*** is used to describe a gene that, in its native state, does not have transforming potential to form tumors but that can be altered to promote malignancy. Once altered, the gene is referred to as an *oncogene*.
- Most proto-oncogenes are key genes involved in the control of **cell growth** and **proliferation** and their roles are complex.
- For simplicity, the mode of action of proto-oncogenes in the normal cell can be divided as follows (Table 1.4, Figure 1.2):
  - Growth factors
  - Growth factor receptors
  - Protein kinases
  - Signal Transducers
  - Nuclear proteins
  - Transcription factors
- The conversion of a proto-oncogene to an oncogene is a result of **somatic events (mutations) in the genetic material of the affected cell.** The activated (mutated) allele of the oncogene **dominates** the wild-type (nonmutated) allele and results in a **dominant gain of function.**
- **The mechanisms of oncogene activation include the following (Figure 1.3):**
  - **Chromosomal translocation:** Where proto-oncogenes are translocated within the genome (i.e., from one chromosome to another), their function can be altered. In human chronic myeloid leukemia (CML) a chromosomal breakpoint produces a translocation of the c-abl oncogene on chromosome nine to a gene on chromosome twenty-two (bcr). The bcr/abl hybrid gene produces a novel transcript whose protein product has tyrosine kinase activity and can contribute to uncontrolled cellular proliferation. This tyrosine

Table 1.4. Oncogenes can be growth factors, growth factor receptors, protein kinases, signal transducers, nuclear proteins, and transcription factors

Oncogene Class	Examples
Growth factors	Platelet-derived growth factor (PDGF) Epidermal Growth Factor (EGF) Insulin Like Growth Factor-1 (ILGF-1) Vascular Endothelial Growth Factor (VEGF) Transforming Growth Factor-β (TGF-β) Interleukin-2 (IL-2)
Growth factor receptors	PDGF-Receptor (PDGF-R) EGFR-Receptor (erbB-1) ILGF-1 Receptor (ILGF-R) VEGF-Receptor (VEGFR) IL-2 receptor (IL-2R) Hepatocyte Growth Factor Receptor (met) Heregulin Receptor (neu/erbB-2) Stem Cell Factor Receptor (kit)
Protein kinases	Tyrosine Kinase, e.g.: bcr-abl, src Serine-Threonine Kinase, e.g.: raf/mil, mos
G-protein signal transducers	GTPase, e.g.: H-*ras*, K-*ras*, N-*ras*
Nuclear proteins	Transcription factors, e.g.: ets, jun, fos, myb, myc, rel

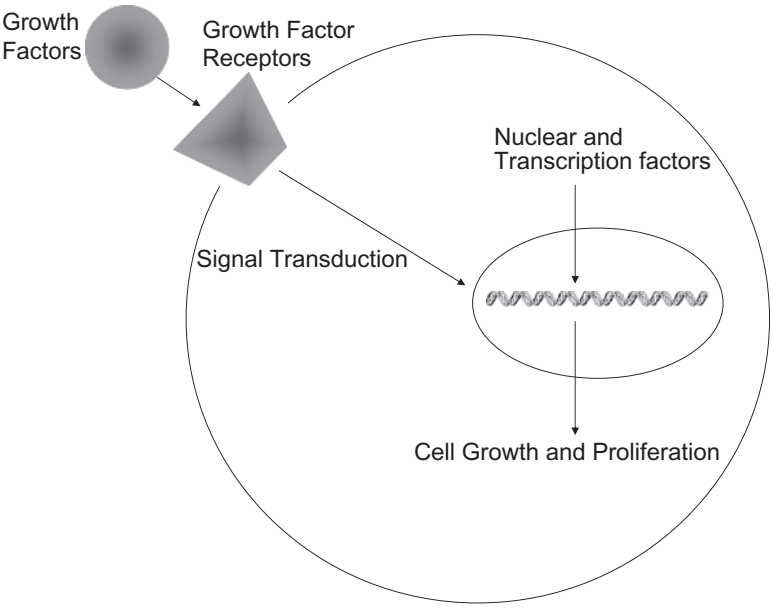

Figure 1.2. Oncogenes are normal cellular genes involved in cell growth and proliferation: Most proto-oncogenes are key genes involved in the control of cell growth and proliferation and include growth factors, growth factor receptors, protein kinases, signal transducers, nuclear proteins, and transcription factors. The conversion of a proto-oncogene to an oncogene is a result of somatic events in the genetic material of the target tissue. The activated allele of the oncogene dominates the wild-type allele and results in a dominant gain of function. The mechanisms of oncogene activation include chromosomal translocation, gene amplification, point mutations, and viral insertions. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

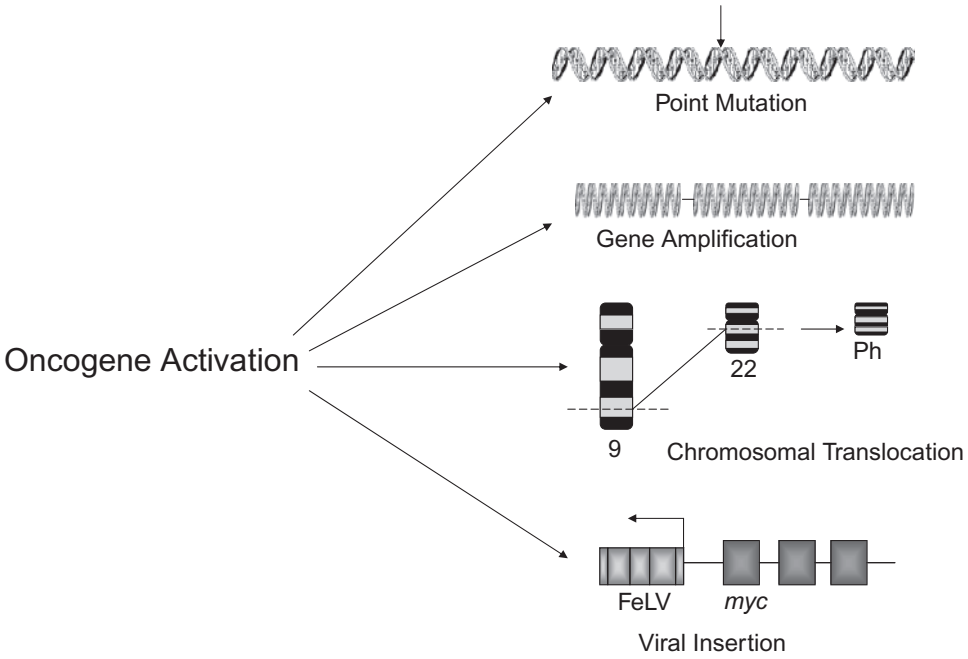

Figure 1.3. Oncogenes may become activated through point mutations, gene amplifications, chromosomal rearrangements, and viral insertions. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

kinase activity has become a major target for therapeutic intervention, with many drugs such as Imatinib (a tyrosine kinase inhibitor) in human clinical trials.

- **Gene amplification**: Amplification of oncogenes (i.e., multiple gene copies) can occur in a number of tumor types and has been demonstrated in domestic animal cancers. As an example, the MDM2 proto-oncogene has been identified in dogs and horses and has been shown to be amplified in a proportion of canine soft-tissue sarcomas.
- **Point mutations**: These are single base changes in the DNA sequence of proto-oncogenes leading to the production of abnormal proteins. For example, point mutations in the *ras* proto-oncogene are a consistent finding in a number of human tumors.
- **Viral insertions**: Studies of the tumor-causing viruses allowed for the discovery of oncogenes. The insertion of tumor-causing viral elements into the genome of a cell leads to alteration of proto-oncogene function, transforming the proto-oncogene into an oncogene. This results in the development of a tumor.

Tumor Suppressor Genes

- Changes or mutations in genes can lead to either a stimulatory or inhibitory effect on cell growth and proliferation.
- The stimulatory effects are provided by the proto-oncogenes described above. Mutations of these genes produce positive growth and proliferative signals leading to uncontrolled cellular growth.
- In contrast, tumor formation can result from a loss of inhibitory functions associated with mutation of another class of cellular genes called the *tumor suppressor genes*. In their wild-type, or non-mutated state, the role of tumor suppressor genes is to inhibit cellular proliferation and growth.
- The retinoblastoma gene (Rb) was the first gene that led to the understanding of the mechanisms of tumor suppressor genes.

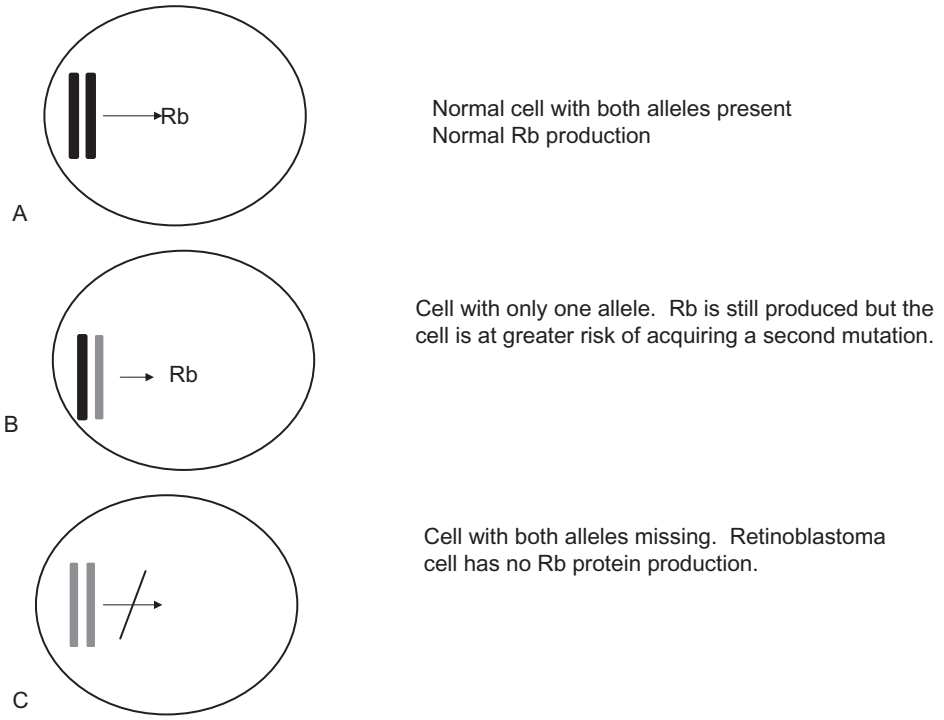

Figure 1.4. In contrast to oncogene mutations, suppressor effects are recessive. Normal cell (A). Mutation in 1 copy (B) usually has no effect but the cell is at risk. Cells with both alleles affected produce no tumor suppressor effects (C). Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

- Rb plays a central role in regulating cell cycle progression. Alteration of Rb function has been found to be a common feature of many human cancers as well as the classical retinoblastoma tumor, a childhood cancer that arises from the retina. Rb function can be abrogated by point mutations, deletions, or by complex formation with viral oncoproteins. These genetic changes lead to uncontrolled cell cycle progression and cellular proliferation.
- In a cell with one normal, nonmutated allele of a tumor suppressor gene such as Rb, that allele usually produces enough tumor suppressor product to maintain normal function of the gene and control of cellular proliferation. Mutations in tumor suppressor genes behave very differently from oncogene mutations. Whereas activating oncogene mutations in a single allele are dominant to wild-type (i.e., only one mutated allele is required for expression of the proliferating signals), tumor suppressor gene mutations are **recessive** and both alleles must be mutated for the loss of inhibitory function to be expressed.
- Mutation in one tumor suppressor gene copy usually has no effect on wild-type function of the gene, as long as a reasonable amount of wild-type protein remains as a result of the nonmutated allele (Figure 1.4).
- **P53** is a tumor suppressor gene whose product is also intimately involved in cell cycle control.
- P53 has been described as the guardian of the genome, by virtue of its ability to promote cell cycle arrest or apoptosis depending on the degree of DNA damage. Consequently, the p53 tumor suppressor gene plays an important role in cell cycle progression, regulation of gene expression, and the cellular response mechanisms to DNA damage.
- Failure by p53 to activate such cellular functions may ultimately result in abnormal uncontrolled cell growth leading to tumorigenic transformation.

- P53 is the most frequently inactivated gene in human neoplasia with functional loss commonly occurring through gene mutational events, including nonsense, missense, and splice site mutations; allelic loss; rearrangements; and deletions.

Cancer Arises Through Multiple Molecular Mechanisms

Key Points
From the preceding section we can conclude that
- Cancer is a genetic disease, involving fundamental changes in the cell at the genetic level.
- Changes in oncogenes or tumor suppressor genes may contribute to carcinogenesis.

- Cancer research has demonstrated that, despite the many potential causes of cancer and carcinogenic pathways, transformation of a normal cell into a malignant cell actually requires very few molecular, biochemical, and cellular changes.
- These changes can be considered as **the acquired capabilities of a cancer cell** that allow it to be regarded as displaying a malignant phenotype.
- These acquired capabilities appear to be common to all types of cancer.
- Consequently, we can consider that the vast array of cancer phenotypes is a manifestation of only seven alterations in cellular physiology that collectively dictate malignant growth.
- These characteristics are acquired during the process of carcinogenesis and can be considered as the following (Figure 1.5):
  - A self sufficiency in growth
  - An insensitivity to antigrowth signals
  - An ability to evade programmed cell death (apoptosis)
  - Limitless replicative potential (mainly through reactivation of telomerase)
  - An ability to sustain angiogenesis
  - An ability to invade and metastasize
  - An ability to evade host immunity

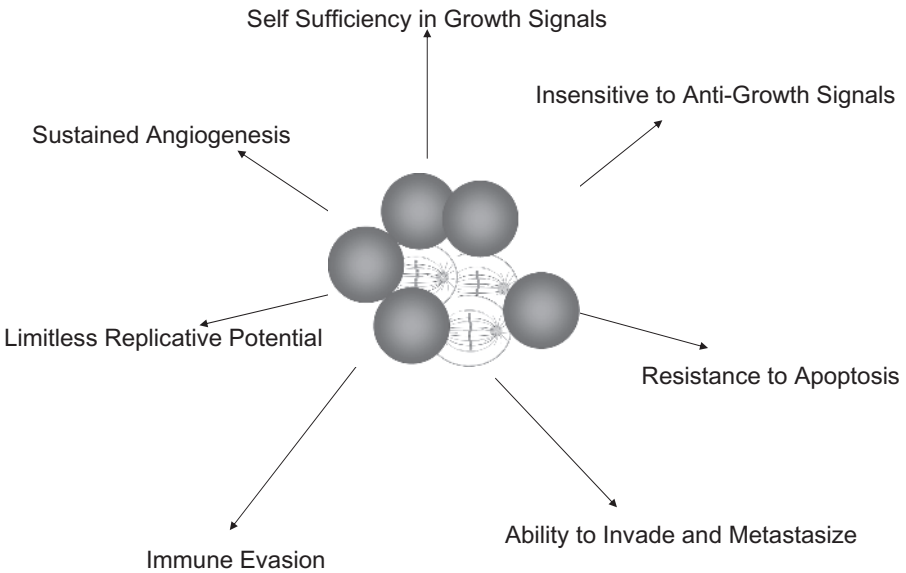

Figure 1.5. The pathways to cancer. Despite the complexity of cancer as a disease, it can be defined on the basis of the acquisition of seven fundamental characteristics: self sufficiency in growth, an insensitivity to antigrowth signals, an ability to evade programmed cell death (apoptosis), limitless replicative potential (mainly through reactivation of telomerase), an ability to sustain angiogenesis, an ability to invade and metastasize, and an ability to evade host immunity. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

Key Points
- The pathways for cells becoming malignant are highly variable.
- Mutations in certain oncogenes can occur early in the progression of some tumors, and late in others.
- As a consequence, the acquisition of the essential cancer characteristics may appear at different times in the progression of different cancers.
- Irrespective of the path taken, the hallmark capabilities of cancer will remain common for multiple cancer types and will help clarify mechanisms, prognosis, and the development of new treatments.

The Importance of the Microenvironment

- Tumor formation is a consequence of genetic changes in the target cell.
- However, the formation of a tumor is also directly reliant on an appropriate environment for tumor growth.
- Several studies have demonstrated that the supporting stroma (e.g., fibroblasts), blood vessels and local environmental conditions (e.g., tissue hypoxia), have a direct effect on the ability of a tumor to grow and survive.
- Consequently, the tumor microenvironment also represents a target for therapy.

A Challenge to the Accepted Model of Carcinogenesis: The Cancer Stem Cell Theory

For completeness we mention here a challenge to the accepted model of carcinogenesis:
- The accepted model of carcinogenesis has been a stochastic model whereby any cell in the body has the potential for malignant transformation. A challenge to the stochastic model is the cancer stem cell theory, which suggests that cancer is, in fact, a true stem cell disease.
- The cancer stem cell theory states that malignant transformation occurs in the adult stem cell and gives rise to a cancer stem cell. This would reconcile how a cell would survive long enough to acquire the appropriate number of genetic changes, as stem cells are long-lived.
- This has given rise to the concept that tumors are composed of both cancer stem cells, which have a large proliferative capacity, and a daughter population of cells, with a limited proliferative potential.
- If a population of cancer stem cells is responsible for the propagation of a tumor, this has immense implications for therapy. The evidence suggests that daughter cells, which make up the bulk population of tumors, may be sensitive to the effects of conventional treatments such as radiation and/or chemotherapy. However, stem cell populations tend to harbor strong resistance mechanisms, entering periods of quiescence during which they are resistant to strategies aimed at eradicating cycling cells.
- If conventional therapies are not appropriate for killing cancer stem cells, it would follow that alternative pathways in these cells need to be identified (Figure 1.6).
- The identification of cancer stem cells in both humans and dogs has been a defining moment in cancer research. If the theory is correct, future efforts must be made to characterize these cells with a view to identifying therapeutic targets.

The Causes of Cancer

- In many circumstances, exposure to one tumor-inducing agent or carcinogen provides only one hit toward the development of the malignant phenotype.
- The nature of tumor-inducing agents has been crucial to our understanding of cancer formation because they all have the common property of being able to affect host DNA via genetic or epigenetic means.
- In particular, seminal experiments in animal retroviruses led to the discovery of oncogenes, which was a turning point in our understanding of cancer biology.

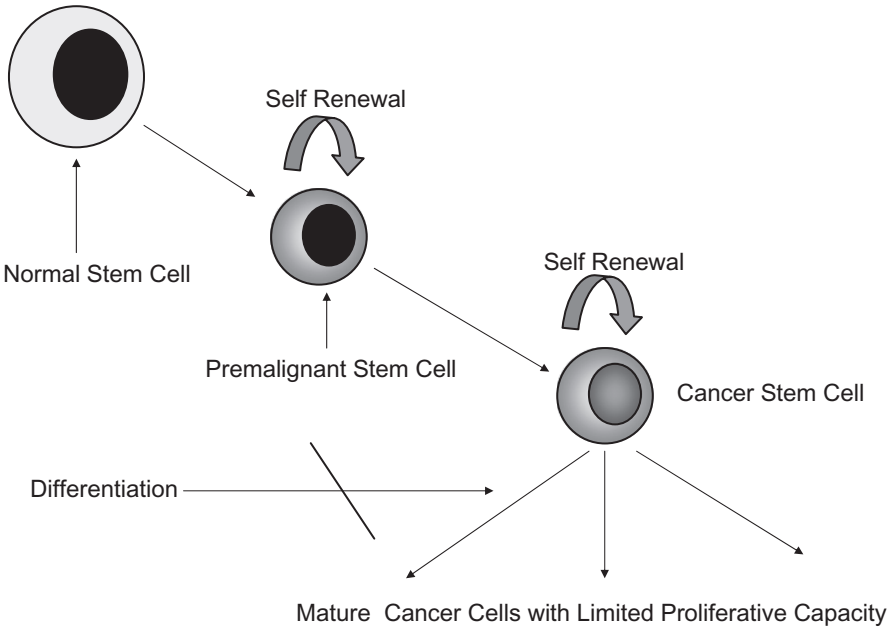

Figure 1.6. The cancer stem cell theory. This theory challenges the stochastic model presented in Fig. 1.1 and suggests that malignant transformation is restricted to adult stem cells. Progression to a full malignant cell then leads to the formation of an asymmetrically dividing cancer cell capable of self-renewal and the production of daughter cells. In a similar way to the production of committed cells from normal stem cells, daughter cancer cells have a limited proliferative capacity. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D. J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

- These cancer-causing agents can be broadly divided into
  - The oncogenic viruses
  - Chemical carcinogens
  - Physical agents such as radiation

The Oncogenic Viruses

- Oncogenenic viruses provided the first evidence that genetic factors play a role in the development of cancer.
- These viruses are a diverse group of pathogens that include all the major families of the DNA viruses and a class of RNA viruses known as *retroviruses*.
- Although diverse, one almost universal feature is the importance of a DNA stage in the replication of the viral genome.

Retroviruses and Cancer

- Retroviruses are important oncogenic viruses of cats, cattle, and chickens, the studies of which have been seminal to our understanding of viral and nonviral oncogenesis.
- The structure and basic replication cycle of a typical retrovirus is shown in Figure 1.7.
- Retroviruses become integrated into the genome of the cell and can promote carcinogenesis through the activation of cellular oncogenes adjacent to them.
- **For example, *myc* is an oncogene intimately associated with cell cycle progression and proliferation. When there is viral insertion close to the *myc* locus, the gene becomes controlled by the powerful viral promoters**

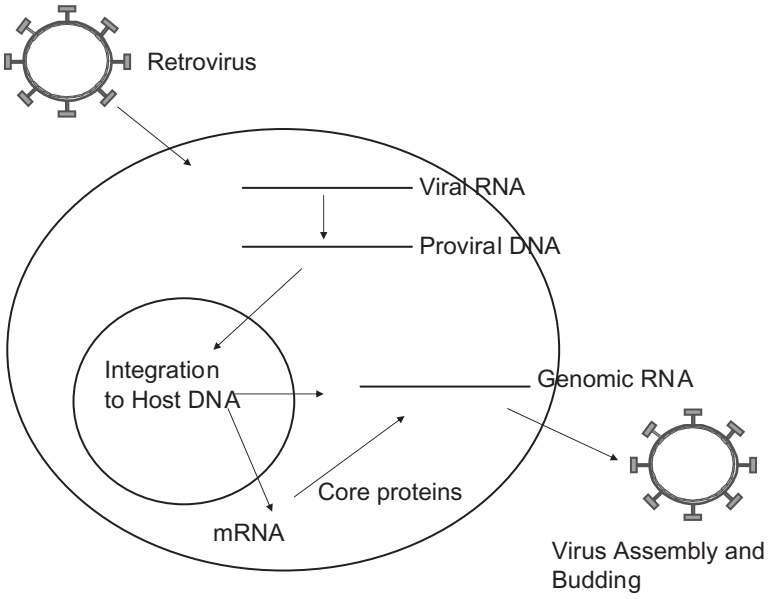

Figure 1.7. The structure and replication life cycle of a typical retrovirus. The retrovirus is a double-stranded RNA virus, which, on entry to the cell, reverse transcribes into proviral DNA. This DNA can integrate into the host genome. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D. J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

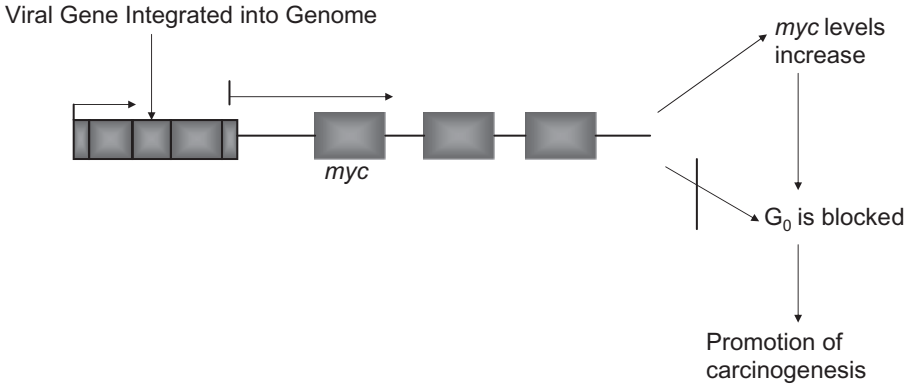

Figure 1.8. Oncogenesis through insertional mutagenesis. In this scenario, the *myc* gene comes under control of the integrated retroviral promoters. There is a failure of cells to enter G_o of the cell cycle, leading to uncontrolled proliferation. Reprinted from "From Viruses to cancer stem cells: Dissecting the pathways to malignancy" by Argyle D.J. and Blacking T.M. (The Veterinary Journal, 2007) with kind permission from Elsevier.

leading to unregulated *myc* expression. Uncontrolled *myc* protein production prevents cells from entering G_0, the resting phase of the cell cycle, and thereby promotes unregulated cellular proliferation, a common occurrence in FeLV-associated lymphoma in cats (Figure 1.8).

Feline Leukemia Virus (FeLV)

- Hemopoietic tumors are the most commonly diagnosed neoplasms of the cat accounting for around 30–40% of all tumors and this is directly related to FeLV infection.

- FeLV isolates are classified into three distinct subgroups (A, B, and C) on the basis of viral interference with superinfection. These subgroups most likely define viral envelope subtypes that use different cellular receptor molecules for viral entry.
- FeLV A is ecotropic (can infect only feline cells) and represents the dominant form of FeLV.
- FeLV B is polytropic (can also infect human cells) and is overrepresented in cases of virally induced lymphoma in cats. FeLV B isolates are thought to arise de novo, from recombination events between FeLV A and feline endogenous sequences present in the feline genome.
- FeLV C is also thought to arise de novo by mutation of the *env* gene in FeLV A and are not transmitted in nature. They are uniquely associated with the development of pure red cell aplasia (PRCA) in cats.
- Persistently viremic cats are the main source of infection. The virus is secreted continuously in the saliva and is spread by intimate social contact. The virus can also be spread congenitally from an infected queen to her kittens. In the first few weeks after viral exposure, interactions between the virus and the host's immune system determine the outcome of infection. The potential outcomes of infection include persistent viral infection, latent infection, and the establishment of complete immunity and viral clearance. It is the persistently viremic cats that go on to develop FeLV-associated diseases (Chapter 10).
- Malignant diseases associated with FeLV include lymphomas and leukemias.
- Lymphoma is the most common tumor of cats and can present most commonly in thymic, multicentric, and alimentary forms.
- Tumorigenesis is thought to occur through immunosuppression of the host and insertional effects of proviral DNA on cellular oncogenes such as *myc*.
- However, it is important to note that FeLV is not isolated from all cats with lymphoma. Only 80% of cats with thymic lymphoma are viremic; only 60% and 30% are viremic in the multicentric and alimentary forms, respectively. There is some evidence to suggest that these viruses may be involved as an initiating event before being cleared by the animal's immune system.
- The incidence of FeLV-related lymphoproliferative neoplasia has decreased since routing vaccination protocols were implemented in the 1980s.
- FeLV is also associated with nonmalignant diseases such as bone marrow failure, immunosuppression, and reproductive failure. The pathogenesis of these conditions is poorly understood.

Feline Immunodeficiency Virus (FIV) and Cancer

- In contrast to the oncogenic retroviruses, FIV is a lentivirus.
- These are retroviruses that classically cause diseases with a slow incubation period and include FIV, HIV, maedi visna, and equine infectious anemia.
- FIV has also been associated with neoplastic disease in cats, especially lymphomas. These can largely be explained by the immunosuppression caused by the virus, however, a direct effect associated with viral insertional mutagenesis has been postulated.

The DNA Viruses

- Many DNA viruses have been associated with the development of cancer in animals and humans. In particular, the papilloma viruses (which are small DNA viruses) have long been known to cause wart lesions, which can become malignant depending on a number of several other predisposing factors.
- Most often, wart lesions are overcome by the immune system and disappear from the animal over a 6-month period. The life cycle of the virus is tightly coupled with the differentiation process of the epithelial cell and, in certain circumstances, the benign wart can persist and ultimately become transformed to become a malignant tumor, squamous cell carcinoma.
- The most extensively studied of the papilloma viruses are the bovine papilloma viruses (BPV). Papilloma viruses have been used as model systems to study the role of co-carcinogens in the development of cancer.

- In contrast to the papilloma viruses, herpes viruses are large DNA viruses and are known to cause Mareks disease in chickens. The herpes viruses are the subject of extensive studies in man through their involvement in Epstein-Barr virus (EBV) – associated lymphomas and Kaposi's sarcoma.

Chemical Carcinogenesis

- In 1775 Sir Percival Potts perceived the relationship between the high incidence of scrotal cancer in chimney sweeps and their chronic exposure to soot. He also noted that skin cancer in the general population was a disease of middle to late age, whereas the chimney sweep boys, who often were exposed to soot at the age of 4 years, developed cancer in their teens.
- These observations demonstrated the link between chemicals such as hydrocarbons and the development of cancer. Since this time, the role of chemical carcinogens has been extensively studied in human and, to a lesser extent, in veterinary medicine.
- The role of tobacco smoke and asbestos are well documented from epidemiological studies in human cancer patients, but their role in veterinary cancer medicine is still unclear.
- Examples of chemically induced carcinogenesis playing a role in veterinary cancers include the following:
  - Bracken fern has been shown to provide a cofactor for malignant transformation with papilloma viruses in cattle.
  - Some epidemiological studies have linked the use of herbicides with the development of canine lymphoma. However, the data presented for the latter has been questioned and the role of herbicides and pesticides in domestic animal cancers still remains unclear.
  - Food substances can also be carcinogenic and notable is aflatoxin, an alkaloid produced by Aspergillus species, which grows on badly stored peanuts. A classical veterinary case involved an epizootic of liver cancer in trout reaching up to 60% incidence in Denmark and Kenya. The trout had been fed on a batch of moldy peanuts in hatcheries in Denmark.
  - Of major importance is the use of chemicals that induce **chronic inflammation**. The use of cyclophosphamide for treatment of cancer patients can lead to chronic inflammation of the bladder due to renal excretion of a metabolite of cyclophosphamide called *acrolein*. Although not common, there are case reports of transitional cell carcinoma of the bladder in dogs after treatment with cyclophosphamide.

Chronic Inflammation, Bacteria, and Cancer

- There is still little known about the role of inflammation, chronic irritation, or trauma in the development of cancer, and many reports have largely been anecdotal. However, there are a number of important observations that have been made that warrant further investigation:
  - There is epidemiological evidence to suggest that primary bone neoplasia may occur at the site of a previous fracture or repair. In most documented cases, there has been a complication of surgery such as low-grade osteomyelitis that may contribute to the development of cancer. In addition, the presence of microfractures through increased mechanical stress in the growing long bones of the giant breeds may contribute to the higher incidence of bone cancer in these dogs.
  - There have been case reports that have described the development of squamous cell carcinomas at the sites of both burns and scar tissue in horses. The development of tumors at the site of previous burns in humans is well recognized.
  - It has been suggested that the development of cutaneous epitheliotropic lymphoma (mycosis fungoides) in dogs may be through persistent antigenic stimulation in the skin. Although c-type retroviral particles have been isolated from canine lymphoma cells in culture, their role in tumorigenesis is still speculative. It is possible that persistent stimulation of lymphoid cells in the skin may allow the selection of malignant cells and the establishment of the tumor. A similar situation occurs in human gastric lymphoma associated with helicobactor pylori infection.
  - There is still uncertainty surrounding the carcinogenic trigger in injection-site sarcomas in cats. Numerous theories have been suggested, including the role of the adjuvant and the vaccine itself (chemical carcinogenesis). However, malignant transformation may not be a reflection of what is injected or applied, but

rather may result from the local irritation/inflammation that is adding another "hit" to a cell that is on its way to malignancy.
- Although not well studied in animals, *Helicobactor pylori* has emerged as a highly important pathogen of man, especially in its association with gastric ulcer disease and gastric carcinoma. The role of this bacteria in this disease is now undisputed and it is regarded as a causal agent of cancer in man. Further, it is also associated with the development of gastric lymphoma in man, through chronic inflammation. It is incredible that simple treatment of these tumors with antibiotics can lead to regression.

Parasitic Infections

- A paucity of information exists regarding the role of parasites in carcinogenesis.
- The most quoted example is that of the helminth infection *Spirocerca Lupi*. This parasite is endemic in Africa and Southeast U.S. and causes esophageal tumors (fibrosarcoma or osteosarcoma) in dogs and foxes). Worm eggs develop into larvae in an intermediate host. In the dog, ingested larvae migrate to the esophagus via the aorta and form highly vascular fibroblastic nodules. These nodules can undergo malignant transformation to form either fibrosarcomas or osteosarcomas.

Physical Agents

- Radiation is a well-known carcinogen in animals and man. This is due to DNA damage that is caused directly by the radiation or indirectly through radiation-mediated intracellular production of oxygen free radicals. DNA damage can lead to genetic mutations that play a role in tumorigenesis. For this reason, the use of diagnostic and therapeutic radiation should be thoughtful and planned. Unnecessary exposure to radiation should be unconditionally avoided.
- In terms of ultraviolet radiation, the association between sunlight and the development of malignancies has been recognized for over a hundred years and has been one of the most extensively studied physical causes of cancer.
- In man, the association between the frequency and severity of sunburns during childhood and the eventual development of malignant melanoma has been proven in epidemiological studies.
- In domestic animals, the best-documented examples of this kind are in the development of squamous cell carcinomas in white cats, whiteface cattle, and possibly in gray horses.
- In white cats, the pinnae and the nasal planum are susceptible to chronic inflammatory dermatitis that may be initiated by excessive exposure to direct sunlight containing UV radiation (especially UVB). A photon of UVB can cause malignant transformation of skin cells by its subcellular effects on DNA.
- It has also been suggested that a contributing mechanism may be immunosuppression as a consequence of UV exposure. In this, UV-B photons can convert transurocyanic acid in the skin to cisurocyanic acid that can have profound effects on antigen-presenting cell function and T cell activity.

Hormones and Cancer

- In man, cancer of the breast, endometrium, ovary, and prostate occur in hormone-responsive tissues, and these tumors may require hormones for their continued growth.
- Hormones can influence cancer development by enhancing cellular replication in cells that may have already acquired a number of genetic hits toward malignancy.
- Estrogen in bitches is known to influence the development of benign vaginal fibromas that regress after a season or ovariohysterectomy.
- It is well documented that early ovariohysterectomy in bitches is protective for mammary carcinoma. The hormonal influences on breast cancer are far better defined for women than dogs. The complete role of estrogens and progesterones, and the significance of receptor expression on canine mammary tumors are still under investigation.

Genetic Predisposition to Cancer

- In man, there are a number of inherited syndromes that give rise to familial cancer syndromes. The best characterized are Li-Fraumeni syndrome (inheritance of an abnormal copy of a p53 allele) and retinoblastoma (inheritance of an abnormal copy of a Rb allele). In both of these cases, the defect occurs in a tumor suppressor gene and therefore both alleles must be affected for abnormal function of the gene to be expressed. Affected individuals are more likely to develop cancers at a younger age.
- Other inherited cancers include Wilm's tumor (WT1), familial adenomatous polyposis (FAP), and breast cancer (BCRA 1 and BCRA 2).
- It is well recognized that certain breeds of dogs have a predisposition to certain cancers.
- The publication of the canine genome, and the development of appropriate linkage maps, is now allowing the opportunity to identify specific genetic changes in breeds that allow their susceptibility to certain cancers.

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