Cancer Genetics

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Overview of the Issue

Cancer is a disease of genes. Although the vast majority of cancers occur sporadically, risk is variably influenced by heritable factors. Dogs and people share a common environment and are susceptible to a similar range of cancers, although there are some significant differences between both species. This lecture will review the genetic basis and pathology for cancer in general, and will discuss advances in the search for cancer susceptibility genes in dogs.

Additional Detail

Introduction

Cancer is the leading cause of death in humans under the age of 85, as well as the leading cause of disease-related death in dogs. As such, it has gained exceptional importance in our society. Both genetic and environmental factors have major effects on the temporal occurrence of cancer, and there is thus a new emphasis to learn more about how these factors influence cellular and molecular changes in cancer. Dogs and people are susceptible to many of the same types of cancer and the natural history (incidence, age of onset, location, progression, outcome) of many cancer types is similar in both species. Our pet dogs share our environment closely, allowing us to examine not only the heritable risk factors, but also those associated with the environment. Moreover, when compared to humans, dogs have shorter generational life spans (as many as five or more related generations frequently co-exist), extended pedigrees with detailed family histories, and more homogeneous genetic backgrounds, which provide unique opportunities to address questions about the origin and behavior of cancer. The answers we obtain studying cancers of dogs will contribute to our ultimate goals to design strategies for prevention and treatment of cancer in both dogs and people.

Cancer is a "genetic" disease

To understand the implications of cancer, one must first realize that cancer is not a simple disease. Rather, the term cancer describes a large number of diseases whose only common feature is uncontrolled cell growth and proliferation. A very important concept that is now universally accepted is that "*cancer is a genetic disease, although it is not always heritable*." Tumors arise from cells that accumulate mutations which eliminate normal constraints of proliferation and genetic integrity. These mutations provide cells a selective growth advantage within their environment. This is essentially the same evolutionary phenomenon that we call "natural selection", albeit on a microscopic scale. Various theories have been proposed to explain the genetic basis of cancer. One explanation invokes stochastic (random) events - the inherent error rate of enzymes that control DNA replication during each division introduces about 1 in 1,000,000 to 1 in 10,000,000 mutations for each base that is replicated during each round of replication. The genome consists of many millions of base pairs, so each daughter cell is likely to carry at least a few mutations in its DNA. In other words, *the single most important risk factor for cancer is life*. Yet, most of these mutations are silent; that is, they do not present any problems to the cell's ability to function, but others can disable tumor suppressor genes or activate proto-oncogenes that respectively inhibit or promote cell division and survival. An alternative hypothesis is that mutations are not stochastic, but rather "directed" due to the presence of a "mutator phenotype," where the factors that control DNA replication and repair are inherently prone to more errors than would be expected by simple stochastic events in particular individuals. This leads to different cancer predispositions, which would be higher than the mean in such individuals, and might explain why not all people (or dogs) exposed to similar environmental carcinogens develop the same forms cancer at the same rate. There is evidence to support both mechanisms (stochastic and directed) in people and animals.

In both cases, loss of function of tumor suppressor genes and gain of function of oncogenes appear to contribute disproportionately to the origin of tumors. Tumor suppressor genes encode proteins that constrain cell division, promote cell death, or are essential to maintain the integrity of DNA. These genes can even help eliminate renegade cells that have initiated the path to cancer; thus, mutations that disable tumor suppressor genes contribute to the development and progression of tumors. In a broadly oversimplified approach, tumor suppressor genes can be grouped in three categories. One that includes *p53* and *ATM*, among others, is responsible for controlling DNA repair. Cells can undergo spontaneous mutations, and these tumor suppressor genes must ensure that the mutant cells do not divide until the errors in their DNA sequence are repaired. Another that includes various cyclin-dependent kinase inhibitors such as *INK4* and even some proto-oncogenes such as *Ras* (see below) controls cellular aging. Each cell in the body has the potential for a finite number of divisions, and these genes prevent further replication when that number has been reached. A third serves to counteract the function of growth-promoting genes and survival genes. Among these are *RB* and *PTEN*. Inactivation of tumor suppressor genes such as those listed above increases the risk of cellular transformation that can result in various types of cancer. Moreover, cancers that arise due to other mutations but that retain the function of these tumor suppressor genes may respond more favorably to therapy, making these promising targets for genetic therapy of cancer. Proto-oncogenes are the polar opposites of tumor suppressor genes. They encode proteins that promote cell growth and survival. In most cases, these genes are "turned on" and "turned off" as needed to maintain an adequate balance of cell division. However, when these genes are targets of mutation, they may gain independent function that cannot be "turned off", leading to the development of cancer. It is very important to note that, even though there are numerous prototypical tumor suppressor genes and oncogenes (or cellular proto-oncogenes), many different genes can function in one or the other category (and sometimes both), depending on the context in which they are expressed!

Genetics of Canine Cancer

A Heritable Cancer Syndrome of Dogs

We seek to define genetic lesions that underlie the pathogenesis of cancer in dogs. Mutations of specific genes that increase the probability, or risk, that an individual (actually a cell) will develop a tumor. In some cases, mutations occur in reproductive cells and are passed on in the germ line. Identification of such mutations should help us predict relative cancer risk in individuals (or the likelihood of individuals to produce progeny with elevated cancer risks), allowing us to invest in practices to modify the environment that may reduce or eliminate the risk (cancer prevention). The investigation of cancer susceptibility in families or breeds of dogs is of critical importance to dog breeders and dog owners alike. Unlike other heritable conditions, genetic susceptibility to cancer may not manifest in disease until a dog has reached middle age, and long after it has achieved breeding potential. When present, this genetic susceptibility may be due to a process called loss of heterozygosity. Individuals inherit two copies of each gene upon conception, one from the sire, and one from the dam. Each of these gene copies is called

an "allele." A family or breed may have through the course of time, lost a functional allele of a "tumor suppressor gene" through mutation. The affected individuals are heterozygous (that is, they have two different alleles, and only one is functional). These individuals may not develop disease (cancer), unless the second, functional copy of the gene in question is mutated in a cell that retains the capacity to divide. Even in the best of circumstances, genetic analysis can only predict the probability or provide a relative risk, rather than a definitive assessment of whether or not the individual will in fact develop cancer. In an elegant series of research papers, Ostrander's and Lingaas's groups recently reported an example of a heritable cancer syndrome (renal cystadenoma and nodular dermatofibrosis or RCND) in German Shepherd Dogs, where the gene defect was traced to a novel tumor suppressor gene called *BHD* (folliculin)[1,2]

Cancer Syndromes with Significant Heritable Influence

There are various cancers whose prevalence in specific breeds indicates the risk is modulated in large part by inherited factors. Perhaps the best studied among these is bladder cancer in Scottish terriers. Recent work by Knapp, Glickman, and others[3,4] shows that the risk for this disease is almost 20-fold greater in Scottish terriers than the average for all dogs. However, the occurrence of the disease seems to be influenced by environmental factors such as exposure to herbicides, as well as by body composition. The genes that modulate risk in this breed remain to be determined, and are possibly linked in a complex mode of inheritance that could make their identification challenging. For this reason, mapping studies comparing risk among Scottish terriers and other susceptible breeds might be a fruitful endeavor.

Cancer Syndromes Mediated by Somatic Mutations

In most cancers of dogs and humans, mutations occur "sporadically", that is, they alter the DNA of non-reproductive (somatic) cells. Generally, these mutations arise in susceptible individuals upon exposure to certain environmental insults; but the risk is not necessarily shared by relatives of the affected individual. Nevertheless, identifying the patterns of mutations associated with specific tumor types is likely to provide information to obtain a more accurate prognosis, and to develop more effective treatments. One example of this process has been extensively studied by London and her colleagues, who described a common mutation of the c-Kit protein in canine mast cell tumors. Although the presence of this mutation is associated with a worse prognosis, it offers a potential target for treatments to improve the outcomes of dogs with this disease[5,6]

Cancer Syndromes Associated with Environmental Factors

Perhaps the best example of this type of cancer is mammary tumors of female dogs. More than 30 years ago, Dorn and colleagues showed a significant association of mammary tumors with intact hormonal status in female dogs. Based on their work and others, it is estimated that ovariectomy can reduce the risk of this disease by more than 200-fold, demonstrating the key role of estrogen (and possibly progesterone) in the pathogenesis of malignant mammary tumors in the dog. While in many ways this resembles mammary tumor biology of women, the story in cats is vastly different[7]. Recent work focuses on the role of other oncogenes, such as IGF-1 in these tumors[8]

Cancer Syndromes with Complex Inheritance Patterns

Another approach that has been successfully used to identify genes that contribute to cancer is the study of recurrent chromosomal abnormalities. Historically, this approach is responsible for the identification of the vast majority of tumor-associated genes (in humans). Until recently, major technical obstacles dampened the study of canine chromosomes, but many were overcome by the work of Breen and his colleagues, who developed reagents and adapted techniques to define a consensus karyotype for the dog[9-11]. Using this information, our groups have documented breed specific prevalence (and hence, presumed patterns of inheritance) for canine non-Hodgkin lymphoma (NHL)[12]. As importantly, we have shown that pathognomonic molecular abnormalities of both NHL and leukemias of dogs and humans are conserved, indicating the underlying basis for these diseases is firmly embedded in the genome and may result from peculiar aspects of mammalian evolution.

Summary

We can confidently state that the genetic basis of cancer is now beyond question. It is estimated that at least five mutational events are required for overt malignant transformation, and genomic instability seems to be necessary to establish a self-renewing population of cells (possibly cancer stem cells) whose progeny expand to cause clinical disease. Ultimately, a subpopulation endowed with metastatic properties that is drug resistant leads to death of the cancer patient. A major focus of contemporary cancer genetics is to define whether such properties are inherent to cancer stem cells or whether they arise by natural selection and clonal evolution. Current knowledge and available molecular tools allow us to predict prognosis and response to therapy in some cancers of companion animals, and we believe the availability and usefulness of such tools in clinical practice will expand rapidly. Hence, as we improve our understanding of fundamental mechanisms that account for malignant transformation and tumor progression, we will be able to design even better strategies for cancer prevention and therapy.

References/Suggested Reading

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