Paws to consider

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Newsletter of the Program in Canine Cancer at the AMC Cancer Research Center

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The beginning of a new year and the arrival of spring bring hope and renewal to the spirit. This is true for our research group working in the shadow of the beautiful Rocky Mountains. In recent months, our work and that of our collaborators has continued to yield steady progress and new discoveries that we hope will be useful in our fight to prevent and treat cancer in both dogs and their human companions. As always, we thank all of you who have contributed to our studies, both financially and by allowing your pets to participate. Your support makes our work possible.

Sincerely,

Jaime, Susan, Stacie, Ashley, Angie, Heather, and Susie

Why Cancer Happens

Cancer is the leading cause of disease-related death in dogs, and as such, it has gained exceptional importance in our society. Both genetic and environmental factors contribute to the occurrence of cancer and are the basis of research on the causes of cancer (pathogenesis), as well as on prevention, diagnosis and treatment. A new emphasis has developed to learn more about genetic and environmental factors that influence cellular and molecular changes in canine cancer. Dogs and people are susceptible to many of the same types of cancer and the natural history of many cancer types appear to be similar in both species. Studies that address causative issues of cancer in dogs will ultimately be important for both dogs and people.

Cancer is a "genetic" disease. The term cancer refers to a large number of diseases whose common feature is uncontrolled cell growth and proliferation (multiplication). This loss of cell growth control results from an accumulation of mutations (errors in the DNA code) in genes that control cell division and cell survival. The most common cause of mutations in the DNA of somatic cells (non-reproductive cells) is the inherent error that occurs during normal cell division. In mammalian cells, there is an error rate of about 1 in 1,000,000 to 1 in 10,000,000 bases during each round of cell division. The genome consists of many millions of bases, so each daughter cell is likely to carry at least a few mutations in its DNA. Most of these mutations are silent; that is, they do not present any problems to the cell's ability to function.

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However, some mutations can disable tumor suppressor genes, whose normal function is to keep cell growth under control. Other mutations activate oncogenes, which promote cell growth and division, and allow too many cells to survive. A cell that accumulates sufficient mutations in genes which restrain proliferation and maintain genetic integrity can give rise to a tumor. Because of the mutations, this cell and its progeny acquire a "selective growth advantage" within their environment. This is essentially the same phenomenon that we call "natural selection", albeit in a microscopic scale. Given the fact that most mutations occur during cell division, it is not surprising that the most common cancers arise from cells that divide frequently in the performance of their function. The origin of these cancers, then, is "genetic" because it lies in the malfunction of genes that control growth and survival, but these cancers are considered to be "sporadic" - that is, they are largely independent of heritable risk factors. Ultimately, the probability of cancer arising is a result of the complex interplay between cancer susceptibility genes (tumor suppressor genes, oncogenes, and genes that control the integrity of the genome) and the environment. Environmental mutagens (for example, constituents of tobacco smoke, sunlight, or other agents that damage DNA) can tip the balance of genetic risk to overt cancer, or they can accelerate the arousal of the disease.

Cancer risk can be inherited. Mutations that contribute to cancer can also be inherited. An inherited mutation in a single gene that is important in cell growth control can increase the risk of that individual developing cancer. This can be due to reducing the overall number of acquired mutations that must accumulate before a cell becomes cancerous, or it can be due to disabling a critical safeguard gene that normally prevents cells from becoming tumors. In humans, it is estimated that approximately 5% of cancers are occur in people who have known heritable risk factors. In dogs, there appears to be a predisposition among certain breeds or families to develop specific types of cancer, suggesting that a hereditary component may be important in the development or progression of the disease. However, the existence of heritable cancer syndromes in dogs remains to be conclusively proven.

How is cancer kept at bay? Although both heritable factors and behavioral (environmental) factors are known that increase the risk of cancer in people, similar information for dogs is limited. Dogs (like other higher vertebrates) have developed built-in safeguards which mandate that abnormal cells be destroyed. It is only when these safeguards are disabled by mutations (or other mechanisms) that cancer cells can overwhelm normal cells. Despite the alarming incidence of cancer in older dogs, the reliability of these systems is evident in the fact that many of our pets do not develop cancer until they reach an advanced age if at all. We know, for example, that neutering has a protective effect on hormone related cancers (mammary cancer and prostate cancer) and this information has been used extensively to reduce the prevalence of these tumors in the non-breeding population of pet dogs. But little is known regarding specific factors that influence the risks for other cancers. A major goal of our program (and those of our collaborators) is to define genetic factors that influence cancer risk in pet dogs as a means to devise rational strategies for treatment and prevention.

Andy

Tegwen

New Studies

The AKC Canine Health Foundation recently launched a "Cancer Initiative" to raise almost one million dollars to support cancer research projects. These projects seek to define markers of heritable cancer risk, identify markers that improve the ability of veterinarians to predict responses to available treatments, and develop new strategies for therapy based on known genetic anomalies peculiar to tumors. The research project "*Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma*" (AKC CHF Grant 2254) is a collaborative effort between Dr. Jaime Modiano at the AMC Cancer Research Center in Denver, CO and Dr. Matthew Breen at North Carolina State University in Raleigh, NC that seeks to determine how genes impact the development of cancer in dogs. Specifically, the researchers will study abnormalities in genes and chromosomes in lymphoma and osteosarcoma to determine if these abnormalities are inherited, and to assess their clinical significance (that is, if they are predictive regarding response to treatment and prognosis). In the short term (few years), this study may help identify "genetic pawprints" in tumors that can be used to predict if they are likely to respond to conventional therapy, allowing owners of affected dogs to make more informed decisions regarding treatment for their pets. In the long term, we anticipate that this and other studies may define specific gene markers that define cancer risk for individuals and their progeny that can be used for judicious breeding decisions to reduce the incidence of cancer in dogs.

Because the study design will address issues on breed predilection and heritability, participation is restricted to Golden Retrievers, Rottweilers, and Mastiffs. For complete eligibility criteria and additional details about the study, please contact the Health Committee Representative for each of the breed clubs or contact Dr. Modiano directly.

Pablo

Research Progress: Focus on Lymphoma

We noticed that Bailey had a "lump" on her neck last weekend... It did not seem to bother her, but we took her to the vet nonetheless to have it checked out. We never expected to hear our vet say, "Bailey has cancer." There was a life-draining effect to the finality of this diagnosis. Our shock and despair was compounded because Bailey, our dog, friend, and family member was otherwise happy and in perfect health!

Stories such as this happen to many families across the country every day. Lymphoma (cancer of the lymph glands) is one of the most common cancers seen in dogs. Although there are breeds that appear to be at increased risk for this disease, lymphoma can affect any dog of any breed at any age. It accounts for approximately 20% of all canine tumors, and >80% of cancers originating from blood cells. Most of the time, lymphoma appears as "swollen glands" (lymph nodes) that can be seen or felt under the neck, in front of the shoulders, or behind the knee. Occasionally, lymphoma can affect lymph nodes that are not visible or palpable from outside the body, such as those inside the chest or in the abdomen. In these cases, dogs may accumulate fluid in the chest that makes breathing difficult, or they may have digestive problems (diarrhea, vomiting, or painful abdomen). If left untreated, dogs with lymphoma will generally succumb to the disease within 3 to 4 weeks. Treatment with prednisone (a corticosteroid) alone generally can induce short-lived remissions (usually less than 8 to 12 weeks), but frequently renders the disease resistant to further treatment. Durable remissions are achievable in lymphoma, so the disease is considered "treatable." Multi-agent chemotherapy consisting of L-asparaginase, vincristine, cyclophosphamide, doxorubicin, and prednisone, which is the standard of care for this disease, will induce remissions of 12 to 18 months in many cases. However, there are various subtypes of lymphoma that exhibit different behaviors, and some of the more aggressive types are unresponsive to any available treatment. For example, the median survival for dogs with lymphoma originating from B cells treated with multi-agent chemotherapy is approximately 14 months, whereas the median survival for dogs with lymphoma originating from T cells treated with multi-agent chemotherapy is approximately 6 months. However, there remains a lot of variability in the responses seen even when tumors are classified into these subtypes.

This uncertainty and the inevitable outcome of the disease are the forces that have driven a long-term collaboration between the laboratories of Dr. Jaime Modiano at AMC and Dr. Stuart Helfand at the University of Wisconsin to study canine lymphoma. In a recent study published in the Journal of Immunotherapy (January 2002), the research team showed that canine lymphomas (and many leukemias) express a protein on their surface that may provide a new target for therapy. But, before the research team could get to this point, many years were spent studying normal canine lymphocytes. In part, this was done to define differences between normal cells and cancer cells. But also because there are parallels between the normal dividing cells and cancer cells (which divide constantly) that could be exploited to treat the disease.

One protein that is expressed only in dividing lymphocytes is the receptor for interleukin-2 (IL-2R). Interleukin-2 (IL-2) is a *cytokine* or cellular messenger that orchestrates the function of the immune system. When IL-2 is present in the extracellular environment, the cells that bear IL-2R on their surface become activated and are driven to divide. Although the tumor cells divide without the need for IL-2, we hypothesized that these tumor cells may not know any better and still have IL-2R on their surface.

There was a small obstacle, though. There were no reagents or information on the canine form of the *alpha subunit*, which a critical component of the IL-2R. With this in mind, Dr. Erin Dickerson, a member of Dr. Helfand's laboratory and the first author of this paper, used sophisticated molecular biology techniques to clone the gene encoding the *alpha subunit* in the dog. Reagents in hand, she was able to verify that the tumors in each of 13 dogs with lymphoma and 6 dogs with leukemia expressed components of the IL-2R. This is significant because it may allow the researchers to devise therapies aimed specifically at killing the malignant cells by targeting the IL-2R, somewhat akin to a guided missile. Similar strategies are in the experimental stages for some types of lymphoma in people with promising results.

A project funded in Dr. Helfand's lab through the Cancer Initiative seeks to generate additional reagents that may not only be useful to improve the timing and precision of lymphoma diagnosis, but also may provide better alternatives to treat some types of aggressive canine lymphoma.

A Brief History of the AMC Cancer Research Center

History and Background. AMC Cancer Research Center is a national not-for-profit research institute dedicated to the prevention and control of cancer and other chronic diseases. For nearly a century, AMC has dedicated itself to the relief of human suffering and the treatment of major diseases. It started in the early 1900's with the scourge of tuberculosis (TB). It was believed that an effective treatment for TB was clean, fresh air and sunshine, for which Denver provided the perfect climate. Jewish patients, many of who were poor immigrants from eastern Europe, flocked to Denver in search of a cure for their TB. Unfortunately, hundreds of people were literally dying in the streets of Denver. In response to the poor and dying, Dr. Charles Spivak opened a free tuberculosis sanatorium - the Jewish Consumptives Relief Society (JCRS) in 1904.

In the beginning, patients were housed in individual "tents" or small cottages, since TB was a highly contagious disease. But JCRS rapidly expanded and became its own city. Established essentials included a dining hall, farming and dairy herds, a laundry, a pharmacy, treatment rooms, two operating rooms, labs, and dental office. An extensive 9,000-volume library, regular cultural events, production of a literary magazine and the Spivak, Colorado Post Office were added. The buildings that supported this “city” now house AMC Cancer Research Center scientists and their programs.

By the early 1950s, tuberculosis was brought under control, so in 1954, on the occasion of its 50th anniversary, the institution reincorporated as the American Medical Center at Denver and entered into a new battle - the eradication of cancer, an insidious and devastating disease about which little was known. Thus, AMC became one of the first dedicated cancer institutions in the nation. As it reached its 75th anniversary, the AMC Cancer Board resolved that since the control of cancer could only come through research, all of AMC's resources and efforts should be directed toward improving the tools with which to aggressively fight cancer. In 1984, the organization abbreviated its name to AMC Cancer Research Center and cancer research became the principal focus. Five years later, the Center's leadership reaffirmed the innovative spirit first established by Dr. Spivak that continued for nearly a century: they dedicated the institution's total scientific resources to research into the prevention and control of cancer, making AMC the first cancer research center in the United States with such a specific and exclusive mission.

The spirit of commitment and excellence that guides AMC today had its origins in those early years of historic and medical frontiers. AMC Cancer Research Center is now a national independent not-for-profit research institution. Its scientists and physicians work in the laboratory, clinics, communities, and healthcare settings, impacting research across the country. AMC is highly recognized in the field of cancer prevention and control research. The program on Canine Cancer Genetics is the latest addition to the comprehensive research portfolio of AMC scientists. We are proud to continue our 100-year old mission to improve the health, well-being, and quality of life of families everywhere, and we look forward with anticipation to upcoming changes that will strengthen our affiliation with the University of Colorado Health Sciences Center. Stay tuned!

Casey

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