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REVIEW

Animal models and therapeutic molecular targets of cancer: utility and limitations

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Abstract: Cancer is the term used to describe over 100 diseases that share several common hallmarks. Despite prevention, early detection, and novel therapies, cancer is still the second leading cause of death in the USA. Successful bench-to-bedside translation of basic scientific findings about cancer into therapeutic interventions for patients depends on the selection of appropriate animal experimental models. Cancer research uses animal and human cancer cell lines in vitro to study biochemical pathways in these cancer cells. In this review, we summarize the important animal models of cancer with focus on their advantages and limitations. Mouse cancer models are well known, and are frequently used for cancer research. Rodent models have revolutionized our ability to study gene and protein functions in vivo and to better understand their molecular pathways and mechanisms. Xenograft and chemically or genetically induced mouse cancers are the most commonly used rodent cancer models. Companion animals with spontaneous neoplasms are still an underexploited tool for making rapid advances in human and veterinary cancer therapies by testing new drugs and delivery systems that have shown promise in vitro and in vivo in mouse models. Companion animals have a relatively high incidence of cancers, with biological behavior, response to therapy, and response to cytotoxic agents similar to those in humans. Shorter overall lifespan and more rapid disease progression are factors contributing to the advantages of a companion animal model. In addition, the current focus is on discovering molecular targets for new therapeutic drugs to improve survival and quality of life in cancer patients.

Keywords: mouse cancer model, companion animal cancer model, dogs, cats, molecular targets

Introduction

Cancer has been characterized by several hallmarks during its multistep development: sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, tumor-promoting inflammation, induction of angiogenesis, activation of invasion and metastasis, genome instability and mutations, avoidance of immune destruction, and deregulation of cellular energetics.[1] Cancer is the second most common cause of death in the USA, exceeded only by heart disease, according to the American Cancer Society.[2] In 2014, about 585,720 Americans are expected to die of cancer, with almost 1,600 people per day and about 1,665,540 new cancer cases expected to be diagnosed in 2014. Cancer is usually detected when structural changes in a tissue or organ have occurred. The 5-year relative survival rate for all cancers diagnosed between 2003 and 2009 is 68%, up from 49% in 1975–1977.[2] Early detection of tumors and accurate monitoring of tumor response to treatment are key

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to patient survival. Discovery of tumor-specific molecular targets is required to improve detection and efficient treatment of cancer at earlier stages. Thus, the appropriate use and development of in vitro and in vivo cancer models is highly desirable.

Cancer research uses animal and human cancer cell lines in vitro to study biochemical pathways in cancer cells.[3] Almost all of the continuous cancer cell lines are derived from high-grade, high-stage cancers. The use of normal cell lines was made possible by immortalization of these cells using viral vectors.[4,5] On the way to personalized treatment protocols based on an individual's genetic profile, the use of patient-derived primary cancer cell lines instead of generic cell lines has become a valuable in vitro system for developing cancer treatment regimes.[6,7] The advantages of in vitro cancer models are highly controlled conditions, homogeneity, discovery of molecular mechanisms, and reproducibility. The main limitations of two-dimensional in vitro cell culture cancer cell lines are selection of phenotypic and genotypic cells during adaptation to in vitro conditions, accumulation of mutations in cells over time in culture, a homogeneous population of cells, and isolation of cells from the tumor microenvironment. Mimicking the interactions between tumor cells and the cellular matrix, well defined three-dimensional in vitro cancer models and coculture systems have gained acceptance for a wide variety of diagnostic and therapeutic applications.[8,9] Despite all the mentioned disadvantages, cancer cell lines have been, and will continue to be, the model in vitro system for cancer studies.

The development of in vivo animal models that recapitulate the natural history of human cancers and their clinical response to therapy constitute a major prerequisite for rapid bench-to-bedside translation of investigational anticancer therapies and imaging agents that have shown promise in in vitro models (as shown in Figure 1). This review summarizes the advantages and limitations of in vivo animal cancer models with a focus on xenograft and chemically or genetically induced mouse models of cancer, and spontaneously occurring companion animal cancer models. Spontaneous cancers in companion dogs and cats offer a unique model for human cancer biology and translational cancer therapeutics.[10] Companion animals have a relatively high incidence of cancers, with biological behavior, response to therapy, and response to cytotoxic agents similar to those occurring in humans. A shorter overall lifespan and more rapid disease progression are further factors contributing to the advantages of a companion animal model.[10–12] In addition, we discuss the current knowledge about therapeutic targets that play a major role in human and animal tumorigenesis.

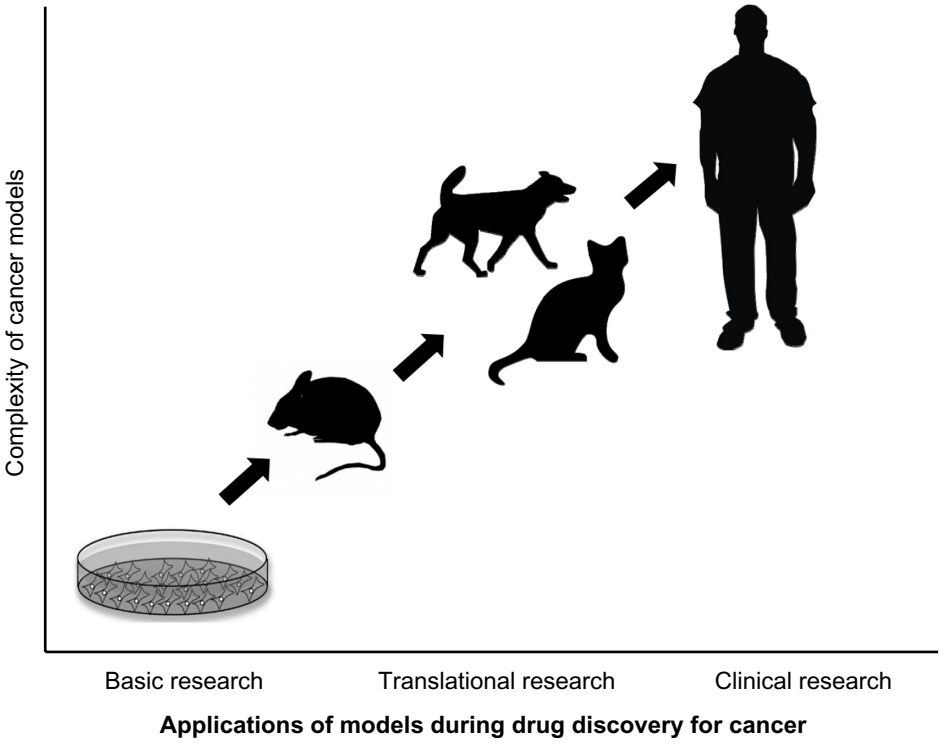

Figure 1 Importance of companion animal cancer models during drug discovery for cancer detection and treatment.
Note: Complexity of cancer models ranging from in vitro to in vivo models and correlation with their utility during the novel therapeutic and imaging agents' evaluation.

Rodent cancer models

The greatest challenge facing cancer scientists is our incomplete understanding of the genetic basis for complex human diseases, including cancer. Much of the research in human cancer genetics relies on animal models. Mouse cancer models are well known and are frequently used as models for cancer research. Mouse models have revolutionized our ability to study gene and protein function in vivo and to better understand their molecular pathways and mechanisms.[13] The most common rodent cancer models are xenografts and chemically or genetically induced cancers.[14]

Rodent xenograft cancer model

In the xenograft cancer model, human or animal cancer cells are transplanted either under the skin (ectopic) or into the organ of tumor origin (orthotopic) using immunocompromised rodents.[14–16] The most common types of immunocompromised rodents used in cancer research are athymic nude (*Forkhead box protein N1* [*Foxn1*^{nu}]) mice and severely compromised immunodeficient (SCID) mice.[17] The athymic nude mouse has a mutation of the *Foxn1* gene resulting in a severely compromised immune system. SCID rodents have a single nucleotide polymorphism within the DNA-dependent protein kinase of catalytic polypeptide (*Prkdc*) gene, resulting in complete failure of their immune system due to absent or atypical T and B lymphocytes.

Xenograft animal cancer models are a relatively inexpensive method for generating in vivo tumors using human and animal cancer cell lines. These models enable in vivo testing and development of successful cancer therapy and imaging agents identified in vitro.[18,19] The major disadvantages of the xenograft rodent cancer models that limit the rapid translation of research to the human clinic include; effectiveness of specific anticancer drugs toward only certain cancer tumors, the superficial vascularization of xenograft tumors, and the lack of stroma-tumor interactions. The major limitation of xenograft cancer models is that the mice and rats used have compromised immune systems, so do not represent the behavior of naturally occurring cancers in humans.[18,20]

Chemically induced rodent models of cancer

Chemically induced rodent models of cancer are developed by exposure to carcinogens, eg, N-butyl-N-(4-hydroxybutyl) nitrosamine,[21–24] 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone,[25,26] N-ethyl-N-nitrosourea,[27] azoxymethane,[28,29] benzopyrene,[30] urethane,[31] and asbestos fibers.[32] Chemically induced cancer rodent models help in the study of the complex traits of cancer, but require high-throughput sequencing to identify the mutations, making the method laborious and time-consuming.

Genetically engineered mouse models of cancer

In the past, conditional and inducible systems were used to allow tissue-specific and time-specific induction of various oncogenes or suppression of tumor suppressor genes, leading to the development of spontaneous cancers.[33] The most commonly used systems are *Cre-Lox*,[34] tetracycline-dependent promoter regulation,[35] and *Flp*-mediated site-specific and spontaneous recombination methods.[36] Genetically modified mice are created by microinjection of DNA in the pronuclei of fertilized zygotes and the transgene is integrated into the genome.[37,38] Transgenic mice generated to carry cloned oncogenes[39] and knockout mice lacking tumor suppressor genes[40] have provided good models of human cancer. Several transgenic models have been developed for sporadic cancers, eg, via suppression of the *Apc* gene in an animal model of human familial adenomatous polyposis.[41,42] Those genetically engineered animal models have had a high impact in oncology drug discovery and preclinical translational biology.[31,43–45] The major disadvantage of these models is the inability to control the level and pattern of gene expression. Random integration of a transgene can also result in unexpected phenotypes.[13]

Companion animals

Companion animals with spontaneous neoplasms are still an underexploited approach for making rapid advances in the treatment of human and veterinary cancers by testing new compounds and delivery systems that have shown promise in vitro and in vivo in mouse models. A mouse model has several advantages, including short gestation times, small size, relatively inexpensive maintenance, and easy manipulation of gene expression.[46] However, the average rate of successful translation from rodent models to clinical cancer trials is less than 8%.[47] Another major disadvantage of the mouse model is that mice can tolerate higher drug concentrations than human patients, and mouse bone marrow may be less sensitive to many cytotoxic agents.[48] Considering the vast species differences between mice and humans, it is important to utilize other animal models, such as companion animals with naturally occurring cancers.

Comparative oncology integrates companion animals with naturally occurring cancers to study cancer biology. Clinical trials with companion animals promote advances in humans,

as well as animal oncology including testing new diagnostics and therapeutics that will benefit both humans and companion animals. In 2014, there will be an estimated 1.6 million human patients diagnosed with cancer in the US.[2] Roughly 6 million dogs and similar number of cats are diagnosed with cancer each year in the US. This large population of pets with cancer provides the opportunity to study spontaneous cancers similar to those that occur in humans.[49] Naturally occurring tumors in dogs and cats have more clinical and biological similarities to human cancers than any other animal cancer model.[46] Dogs develop tumor at twice the frequency of humans, and cats at half the frequency of humans.[12] The average age of a dog developing a spontaneous cancer is 8.4 years, which corresponds to an average human age of 50 years, suggesting that, as in humans, spontaneous cancers in dogs are influenced by age and the environment.[50] Companion animal cancers occur in animals with an intact immune system. The tumors are heterogeneous, develop recurrent and drug-resistant disease, and metastasize to distant sites. These tumors capture the essence of human cancer better than any other model system.[51] Animal tumors are histologically very similar to human cancers, and respond similarly to conventional therapies. The significantly shorter lifecycle involved is a major advantage for performing clinical trials, because it allows more rapid collection of survival data.[46] The disease-free interval in dogs treated for cancer is 18 months, whereas 7 years are needed to assess treatment outcomes in humans.[50]

High coverage dog genome sequencing has enabled better understanding of the genetics of cancer and allows comparisons in canines and humans.[52] Recent studies have shown stronger similarities between the canine and human genome as compared with the mouse genome.[50] The same tumor oncogenes and suppressor genes contribute to development of cancer in humans and dogs.[50] The sequence homology between human and dog cancer-associated proteins, eg, p53, Rb, MDM2, BRCA1, and BRCA2,[53,54] is similar, as shown in Table 1. A phylogenetic tree of the various cancer-related genes, including *p53, c-Myc, cyclooxygenase-2 (COX-2)*, and *c-KIT*, shows that the dog and cat genes are more similar to human genes than to mouse genes, as shown in Figure 2. There are similarities in the cytogenetic abnormalities in human and canine cancers like fusion of the *Abl* gene (*Abelson tyrosine kinase*) to a part of the *BCR* (*breakpoint cluster region*) gene, which results in constitutively active BCR-Abl tyrosine kinase in leukemia,[55] or presence of *c-KIT* mutations in gastrointestinal tumors[56] in humans and canines. Dogs can develop a wide range of cancers, the most common being lymphoma, hemangiosarcoma, osteosarcoma (OSA), mast cell tumors, melanoma, squamous cell carcinoma, mammary carcinoma, apocrine gland carcinoma (anal sac), transitional cell carcinoma, and soft tissue sarcoma.[50,57] Several types of cancer that might be suitable models for human cancer, along with the estimated percentage of all new cancers in dogs and cats in the USA, are summarized in Table 2.

Table 1 List of major molecular targets with their sequence percentage identities to human proteins

	Mouse (%)	Cat (%)	Dog (%)
p53	77	80	79
c-Myc	91	93	94
COX-2	87	90	90
c-Kit/CD117	82	89	88
K-RAS	97	99	99
EGFR	88	89	89
PDGFR-α	94	91	98
β-catenin	99	99	99
PTEN	99	100	100
BRCA1	56	72	74

Notes: The sequences identified in various species were compared using the Basic Local Alignment Search Tool from the National Center for Biotechnology Information.

Abbreviations: BRCA1, breast cancer type 1 susceptibility protein; c-Kit/CD117, tyrosine-protein kinase Kit/cluster of differentiation 117; c-Myc, cytoplasmic-myelocytomatosis oncoprotein; COX-2, cyclooxygenase-2; EGFR, epidermal growth factor receptor; K-RAS, Kirsten rat sarcoma viral oncoprotein; p53, tumor suppressor p53; PDGFR-α, platelet-derived growth factor receptor-α; PTEN, phosphatase and tensin homologue.

Lymphoma

Lymphomas are lymphocyte cancers that can arise anywhere lymphocytes are found, including the bone marrow, lymph nodes, the spleen, intestines, and other areas of the lymphatic system. Leukemia is a cancer of blood-forming cells arising in the bone marrow. Leukemias and lymphomas are classified according to the type of cell that is exhibiting uncontrolled growth. There are an estimated 731,277 people living with or in remission from lymphoma in the USA, and approximately 79,990 new cases of lymphoma are expected in the USA in 2014.[58] Lymphomas are among the most common types of tumors in dogs, with the highest incidence of non-Hodgkin lymphoma making up 83% of all hematopoietic cancers in dogs.[59] Feline lymphoma accounts for 50%–90% of all hematopoietic tumors in cats, and since hematopoietic tumors represent approximately one third of all feline tumors, it is estimated that 200 per 100,000 cats are at risk.[60] Feline leukemia virus was the most common cause of lymphoma from 1960 to 1980, when approximately two thirds of lymphoma cases were associated with feline leukemia virus antigenemia.[60] The causes of canine lymphoma are mostly genetic, but environmental factors such as herbicides are also suspected.[61] There are strong similarities between canine and human lymphomas, including cytogenetic and clinical features, tumor biology, tumor behavior, and genetic aberrations, making dogs an important animal model to study disease progression and

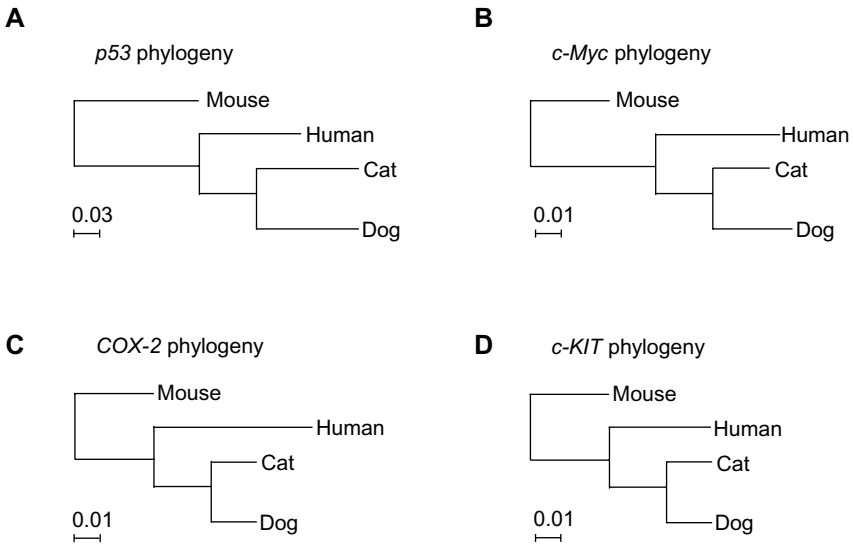

Figure 2 Phylogenic trees of genes for different species.
Notes: Phylogenetic trees of several cancer-related genes. (**A**) *p53*, (**B**) *c-Myc*, (**C**) *COX-2*, and (**D**) *c-KIT/CD117*, show that dog and cat genes are more similar to human genes when compared with those of the mouse. Sequence homology was compared using the Basic Local Alignment Search Tool from the National Center for Biotechnology Information and the phylogenetic trees were constructed based on the COBALT Multiple Sequence Alignment Tool with "neighbor joining" as the tree construction method.
Abbreviations: *c-KIT/CD117, tyrosine-protein kinase Kit/cluster of differentiation 117; c-Myc, cellular myelocytomatosis oncogene; COX-2, cyclooxygenase-2*; *p53*, tumor suppressor *p53*.

therapeutic options.[46,59] The incidence of canine non-Hodgkin lymphoma is similar to that in humans,[62] with an estimated population of more than 75 million dogs at risk in the USA.[63] Humans and dogs have similar non-Hodgkin lymphoma histology, with diffuse large B-cells and a similar treatment regimen of combination chemotherapy including cyclophosphamide, doxorubicin, vincristine, and prednisone.[64] Lymphomas are becoming increasingly resistant to commonly used therapies, so it is important to understand the disease and discover novel therapies in suitable animal models. Canine models have been successfully used to develop new chemotherapeutic strategies, eg, asparaginase.[65]

Head and neck cancers

Cancers arising from squamous cells that line the moist, mucosal surfaces inside the head and neck are collectively known as head and neck cancers (HNC). Approximately 42,440 new cases of HNC are expected in 2014. Incidence rates are more than twice as high in men when compared with women.[2] HNC is aggressive, locally invasive, and frequently diagnosed late in its development, so current treatment strategies including surgery, radiation, and chemotherapy are often ineffective for HNC.[66]

HNC account for 20% of all oral malignancies in dogs.[67] Dogs with HNC have been used as experimental models for evaluation of radiation therapy.[12] Similar to human HNC caused by tobacco exposure and human papillomavirus infection, HNC in companion animals have also been associated with exposure to environmental tobacco smoke[68] and canine and feline papillomavirus.[69,70] HNC account for 75% of all oral tumors in cats.[71,72] The incidence of HNC in cats is similar to that in people, accounting for up to 10% of all feline cancers.[73] In cats, the cancer metastasizes to the regional lymph nodes (14.8%–18%) and lungs (12%) later in the course of the disease, and most affected cats are euthanized due to poor quality of life.[74,75] Second-hand tobacco smoke[76] and papillomavirus are associated with feline HNC.[70] Both feline and canine HNC are locally invasive, with metastasis and local disease recurrence.[76] Due to the very similar risk factors for oral cancers in humans, dogs, and cats, it is important to study cell lines from companion animals with naturally occurring cancers to better understand human disease.[7]

Table 2 Estimated percentage of all new cancers in dogs and cats in the USA

Type of cancer	Dogs	Cats
Lymphoma	24%[46]	>30%[60]
Head and neck carcinoma	6%[60]	10%[73]
Bladder cancer	2%[82]	Rare[60]
Osteosarcoma	5%[86]	Rare[90]
Mammary cancer	3.4%[92]	12%[147]
Prostate cancer	0.3%–0.6%[148]	Rare[149]
Lung cancer	1%[12]	Rare[12]
Melanoma	Relatively common[60]	Rare[60]

Bladder cancer

Bladder cancer is the fourth most common cancer in men and the eighth most common malignancy in women in the

USA according to the American Cancer Society. An estimated 74,690 new cases of bladder cancer are expected to occur in 2014 in the USA. An estimated 15,580 bladder cancer-related deaths will also occur in this period.[2] Precise early detection of tumors and accurate monitoring of tumor response to treatment are key to patient survival.[77] Up to 70% of patients with non-muscle-invasive bladder cancer will develop local recurrence after transurethral resection of the tumor.[78,79]

The histologic and biologic characteristics of bladder cancers in dogs are similar to those of bladder cancers in humans.[80–82] Compared with humans, transitional cell carcinomas in dogs can be low-grade with a superficial papillary appearance or be high-grade invasive tumors that spread through the bladder wall to lymph nodes and to other organs, predominantly the liver and lung.[80,83,84] The exact cause of transitional cell carcinoma in dogs is still not known; however, a genetic predisposition, pesticides, insecticides, and second-hand smoke are considered to be major risk factors.[80,83,84] Bladder cancer in cats is very rare.[60]

One of the examples of using dogs diagnosed with transitional cell carcinoma as a cancer model is for evaluation of novel imaging agents to detect bladder cancer. Specific uptake of fluorocoxib A by primary canine transitional cell carcinoma lines in vitro[19] as well by naturally occurring transitional cell carcinoma during scoping of dogs has been described.[19,85]

Osteosarcoma

OSA is the most common type of bone cancer in children and adolescents. There are about 800 new cases of OSA in the USA each year, and about 400 of these are in children and teens.[2] OSA is the most common primary bone tumor found in dogs.[86] It accounts for up to 85%–98% of all canine bone tumors,[87] and >80% of reported cases are in the giant and large breeds, including the Rottweiler, Scottish Deerhound, German Shepherd, Doberman, Great Dane, and Greyhound.[88] The usual treatments for OSA include limb amputation and chemotherapy, with a 1-year survival rate of less than 50%, and 20% or less surviving 2 years or longer. The major problem is metastasis occurring before limb amputation. Dogs with OSA represent a unique model for the disease in humans due to similar histopathology, clinical presentation, and molecular targets, along with similar metastatic sites and survival rates.[87] Dogs have been a valuable model of OSA and have been used in clinical trials pioneering limb salvage techniques that are now used in humans.[89] OSA in cats is rare; however, feline and canine skeletal OSA share similar histologic features, although have different prognostic characteristics.[90]

Breast cancer

Breast cancer is the second most frequently diagnosed cancer in women. Over 230,000 new cases of invasive breast cancer are expected to be diagnosed in the USA during 2014.[2] Mammary neoplasms are the most common tumor in unspayed female dogs, representing 52% of all neoplasms.[12] Canine mammary tumors are similar to those in humans in many aspects, including hormonal dependence, a metastatic pattern, age, and role of environmental factors in onset of the disease.[12] Up to 60% of human cancers and 45% of dog breast cancers are estrogen receptor-positive,[64] and early spaying prevents the development of breast cancer in dogs.[91,92] The most common treatment option for breast cancer in dogs is surgery, and chemotherapy is rarely used.[12] Mammary tumors are the third most common neoplasia in cats, following lymphoid and skin cancers, with 80%–90% being malignant tumors, most of which are adenocarcinomas.[12] Only 10% of feline mammary tumors are estrogen receptor-positive, so spaying has very little effect on recurrence of cancer or survival rates in cats.[93]

Prostate cancer

Prostate cancer is the most frequently diagnosed cancer in men apart from skin cancer, with over 230,000 estimated new cases diagnosed in 2014 in the USA.[2] Dogs are the only large mammals other than humans with a significant incidence of spontaneous prostate cancer.[94] The common occurrence of bone metastases and androgen-independent disease in dogs with prostate cancer represents a model for study of therapies for advanced, hormone-nonresponsive prostate cancers in humans.[94] Treatment options for prostate cancer include local and systemic therapies, as well as nonsteroidal anti-inflammatory drugs, to improve quality of life.[95] Very few cases of prostate cancer have been reported in domestic cats, most of which are high-grade carcinomas with lymph node and lung metastases.[93]

Lung cancer

Lung cancer accounts for most of the cancer deaths in men (28%) and women (26%), with over 220,000 estimated new cases in 2014 in the USA.[2] Dogs and cats rarely develop lung cancer; the total incidence is 1%, with most being adenocarcinomas.[12,96] Surgical excision remains the primary treatment for lung cancer in dogs. Studies have shown a significant increase in the numbers of malignant respiratory tract tumors in dogs exposed to cigarette smoke,[97] so dogs can be used to study the effects of environmental factors in carcinogenesis as a epidemiologic model, as well as a diagnostic and therapeutic model of lung cancer.

Melanoma

Another type of cancer that is a valuable model for human cancer is canine melanoma. In the USA, it is estimated that in 2014 there will be 43,890 and 32,210 new cases of skin melanoma in men and women, respectively.[2] Chemotherapy has provided little benefit in patients with melanoma, but development of targeted (proto-oncogene B-Raf, extracellular signal-regulated kinase [ERK], or c-Kit inhibitors) and new immune approaches has radically changed the prognosis.[98] Unlike genetically engineered models, sporadic canine melanocytic neoplasms share several characteristics with human melanoma,[99] making dogs a more relevant preclinical model for design of clinical trials.[100] Canine melanomas rarely arise in sun-exposed sites, and mostly occur in the oral cavity, mimicking human mucosal melanoma. The spectrum of canine melanocytic neoplasia includes benign lesions somewhat analogous to nevi, as well as invasive primary melanoma and widespread metastasis.[99] Melanoma is common in dogs[60,101,102] but rare in cats.[60,103]

Other types of cancer

In 2014, it is estimated that there will be approximately 12,000 and 23,380 new cases of human soft tissue and brain cancers, respectively, in the USA.[2] Soft tissue sarcomas are a heterogeneous population of mesenchymal tumors that comprise 15% and 7% of all skin and subcutaneous tumors in dogs and cats, respectively. Hemangiosarcomas, chondrosarcomas, lipomas, brain tumors, and soft tissue sarcomas in dogs are valuable models for human soft tissue cancers.[60]

Molecular markers for detection and treatment of cancer

Development of tumor-specific molecular imaging and therapeutic drugs is required to improve detection and treatment of cancer at earlier stages.[1] In contrast with conventional chemotherapy that interferes with all rapidly dividing cells, targeted therapy takes an individualized approach to suppression of tumor cells based on inhibition of the identified tumor-driving signaling pathways. The increased complexity of the interaction between signaling pathways and datasets from various cancer types has led to development of new computational models to predict activity of targeted signaling pathways, responses to therapy, and the prognosis in patients with cancer.[104]

There are several major oncogenic signaling pathways that play a role in tumor growth and progression: receptor tyrosine kinase, ie, growth factor receptors, such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), platelet-derived growth factor receptor, fibroblast growth factor receptor, c-Met, and insulin-like growth factor 1 receptor; Src; Ras/Raf/mitogen-activated protein kinase/ERK; phosphatidylinositide 3-kinase; G protein-coupled receptor; pRb; Hedgehog; Wnt-β-catenin; transforming growth factor-β; nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB), including its target COX-2; and Notch signaling pathways.[105] Because those molecules are expressed at high levels in cancers, but not in surrounding normal tissues, they are attractive targets for selective detection and treatment of cancers. Most targeted therapies are either small-molecule drugs or monoclonal antibodies. Candidates for small-molecule drugs are usually identified in drug screens assessing the effects of thousands of test compounds on a specific target.

The first molecular target for targeted cancer therapy was the estrogen receptor in breast cancer. Several drugs have been approved by the US Food and Drug Administration for treatment of estrogen receptor-positive breast cancer, including tamoxifen, fulvestrant, toremifene, and aromatase inhibitors.[106] The tyrosine kinase receptor (TK) family plays an important role in the regulation of cancer. The EGFR,[107] c-Kit, platelet-derived growth factor receptor-α/β, Src-family kinases,[7,108] PI3K/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways,[109] and VEGFR[110] are commonly overexpressed and are effective molecular targets for treatment of cancer. They are called signal transduction inhibitors, and include imatinib mesylate (TK), dasatinib (TK), nilotinib (TK), trastuzumab (human epidermal growth factor receptor 2 [HER-2]), pertuzumab (HER-2), gefitinib (EGFR), erlotinib (EGFR, other TK), cetuximab (EGFR), vandetanib (VEGFR), and sorafenib (VEGF).[111] Other targeted therapies modify the function of proteins that regulate gene expression and other cellular functions, such as vorinostat (a histone deacetylase inhibitor). Further targeted therapies induce tumor cell apoptosis, such as bortezomib (proteasome)[112,113] and other groups target the immune system to help destroy cancer cells, such as rituximab (CD20).[114,115] Another class of targeted therapies includes monoclonal antibodies that deliver toxic molecules to cancer cells specifically, such as ibritumomab (targets $CD20^+$ non-Hodgkin B-cell lymphoma [B-cells NHL] by delivering radioactive 111-indium or 90-yttrium).[116]

Inflammation is a hallmark of cancer and has been shown to play a key role in the initiation and progression of the disease.[1] Many types of cancer that overexpress EGFR have also been shown to overexpress COX-2,[117] which is downstream of the NFκB signaling pathway. COX-2 increases in inflammatory and premalignant lesions[118–120] and is expressed at even higher

levels in carcinomas.[81,121,122] Genetic studies in transgenic mice overexpressing COX-2 confirmed increased development of metastatic tumors,[123,124] and COX-2$^{-/-}$ mice showed decreased development of intestinal and skin tumors.[125,126] Similarly, when COX-2 activity was shut down pharmacologically by nonsteroidal anti-inflammatory drugs (NSAIDs), the development of mammary carcinomas in tumor-prone transgenic mice was strongly suppressed.[127] NSAIDs are among the most widely used prescription and nonprescription drugs in the world.[128,129] Identification of the second isoform of the COX enzyme, COX-2, led to discovery of a new class of COX-2 selective inhibitors, ie, the COXIBs, including rofecoxib, celecoxib, valdecoxib, etoricoxib, and lumiracoxib.[128,130] The use of radioactively or fluorescently labeled COXIBs as a new class of imaging agents is based on selective uptake by COX-2-expressing neoplastic lesions.[26,117,131,132]

Cancer vaccines and gene therapy are often considered to be targeted therapies, because they interfere with the growth of specific cancer cells, according to the National Cancer Institute.[111]

Targeted therapy has allowed substantial progress in the treatment of cancer and shown promising results in combination with other therapies.[133–145] Targeted therapy is well tolerated, although a variety of side effects are still commonly observed, including rash, diarrhea, hypertension, hypothyroidism, proteinuria, hepatotoxicity, depigmentation, ocular toxicity, hyperglycemia, and dyslipidemia.[146]

Conclusion

In this review, several preclinical cancer models are described that could be used for diagnosis, therapy, or prognosis. The focus is on their strengths, weaknesses, utility, and significance during development of novel therapeutic drugs and imaging agents for clinical application. The decision regarding which model of cancer to use depends on the stage of drug discovery (see Figure 1). However, the final proof of concept for efficacy and safety of novel therapeutic and imaging drugs lies in humans. The personalized medicine approach is still in its early stages, but shows the early benefits of selective targeted therapy protocols for individual cancer patients. Further investigations with regard to novel molecular target identification, novel drug development, identification of appropriate patients who might benefit from therapy, timing of drug administration for combined therapies, reducing the side effects of treatment, and better understanding of drug resistance are still needed.

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Author contributions

MC designed, acquired and interpreted the data, wrote, and approved the final manuscript, designed figures, and agreed to be accountable for all aspects of the work. KR acquired and interpreted the data, wrote and approved the final manuscript, prepared figures, and also agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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