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Review Article

Comparative Aspects between Canine and Human Mesenchymal Tumors

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Abstract

Spontaneous tumors in dogs are starting to provide a crucial model of human biomedical research and particularly for cancer therapeutic strategies. One of the canine malignancies that offer the best comparative studies with humans are mesenchymal tumors. In spite of these spontaneous tumors share many characteristics with human malignancies, there are still many aspects that remain unexplored. In this review article, we will analyze the comparative features of canine mesenchymal tumors with human tumors and the new findings and therapeutic approaches in these malignancies.

Keywords: Mesenchymal stromal cells; Model animals; Oncology

Introduction

For several years, mice have long served as model for cancer research. However, these animal models do not fully represent the features that define cancer in humans since they have some limitations such as long periods of latency, genomic instability, the heterogeneity of tumor cells and their microenvironment [1,2]. Currently, several spontaneous tumors in dogs are starting to provide a relevant model of human cancer biology and for cancer therapeutic strategies [3]. However, there is still much about this aspects that remains unexplored. Several aspects of dogs make them ideal models for human cancer. First, dogs are large genetically outbreed animals and share strong genetic and physiologically similarities to humans (> 82% of homology). Second, canine spontaneous tumors share many features with their human counterparts including histological appearance, cancer progression, molecular targets, biological behavior, same environmental conditions and same response to conventional therapies. Third, as well as in humans, pet tumors are characterized by their intratumoral heterogeneity. This intrinsic heterogeneity brings to therapeutic resistances, recurrences and metastasis which provide an excellent opportunity to study many aspects with application for human cancer treatment. Finally, cancer has increased in pet dogs in recent years and, due to shorter lifespan, their progression is usually faster than in human which allows rapid accrual of progression data [1]. This latter feature lets study and tests the treatment strategies and monitor how dogs respond to the treatment and be a good chance of improving human survival rates. In this way, the National Cancer Institute has recently approved the Comparative Oncology Trials Consortia (COTC) in order to perform clinical trials on dogs with spontaneous tumors with the aim to improve the outlook for this disease in both animals and humans [4].

One of the canine malignancies that offer the best comparative studies with humans are mesenchymal tumors. These groups of tumors arise in cells of embryonic mesodermal origin and included a wide variety of different tumors. The purpose of this report is to review the comparative nature of some canine and human mesenchymal tumors and the current trends in clinical research using dogs as models for human mesenchymal tumors.

Osteosarcoma

Canine osteosarcoma is the most common primary bone tumor representing approximately 80% of all the primary bone neoplasm in dogs. This incidence is 10 to 100 times higher than in humans making the dog an attractive candidate model to study this neoplasm [4,5]. Canine osteosarcoma shares many aspects with human osteosarcoma. Both tumors represent primary cancers of bone and occurring primarily in the appendicular skeleton. Early hematogenous pulmonary metastasis is common in both species and both are chemoresponsive and radioresistant. In spite of the majority of those tumors use to be focal lesion, multiple skeletal osteosarcomas have been describe in both species. Some studies have reported that osteosarcomas can develop in association with or subsequent to other conditions at the same bony site, including infarction, fracture, and the presence of metallic fixation devices [6]. Recent data suggest that, many of the genes involved in human osteosarcoma pathogenesis appear to participate as well in the canine counterpart. Thus, alterations in oncogenes and some receptors presumably involve in human osteosarcoma pathogenesis such as P53, Rb, PTEN, ezrin protein, HER-2, c-myc, IGF-1 and mTOR have been reported also in dogs [7-12]. One of the important advantages of those similarities is the possibility to evaluate novel therapeutic agents with relevant information for new treatment strategies in human osteosarcoma. Thus, experimental protocols have been carried out in dogs with translation into human clinical trials. Mac Ewen and colleagues demonstrated in a randomized, double-blind study performed in canine spontaneous osteosarcoma that muramyl tripeptide, a macrophage activator, significantly prolonged survival in dogs after amputation [13]. Recent re-evaluation of this study in human patients found similar results with interesting therapeutic applications [11]. Other recent study in canine osteosarcoma has shown that ongoing studies of rapamycin, an mTOR pathway inhibitor, will define optimal schedules for their use in human cancer with minimal residual disease setting [14,11,4].

Soft tissue tumors

Soft tissue tumors have a high incidence, especially in companion animals. It has been estimated to account for 8-15% of all cutaneous

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and subcutaneous tumors in the dog, with a standardized annual incidence rate of 122 cases per 100.000 dogs [15]. Fibrosarcoma, hemangiosarcoma, and hemangiopericytoma are major types of soft tissue sarcomas in the dog [13]. Despite of recognized similarities between human and canine soft tissue tumors, comparative studies are very sparse. One of the canine soft tissue tumors that offer the best comparative studies are histiocytic sarcomas. Unlike humans, this tumor occurs at a much higher frequency in canine species. Particularly, in Flatcoated retriever and Bernese Mountain dogs, the incidence of histiocytic sarcomas is higher accounting around 36% of all malignant neoplasms diagnoses in these breeds [15,16]. Recent studies have suggested a heritable risk factors indicating probable genetic characteristic which may be involved in tumor initiation and progression [17,18]. Canine histiocityc sarcomas are histopathologically comparable to those in humans. A current study identified altered expression of nine genes PPBP, SpiC, VCAM1, ENPEP, ITGAD, GTSF1, Col3a1, CD90 and LUM in canine histiocytic sarcoma which help to further understanding of the propagation and oncogenesis of histiocytic cells [19]. The latest findings about that, have demonstrated that canine soft tissue tumors display histological and immunohistochemical features similar to their human equivalents and share a conserved pathogenesis. These findings provide new opportunities for developing effective therapeutic modalities for both species [20,16].

Mast cell tumors

Canine mast cell tumors are the most common cutaneous tumor in dogs representing around 16-21% of all cutaneous tumors and Boxers have the highest incidence. The higher incidence of these tumors compared to human counterpart, make them an excellent resource as models for human cancer biology and for translational cancer therapeutics. Canine mast cell tumors have been classified as well and intermediately differentiated (G1 and G2), corresponding to a benign disease, and poorly differentiated (G3), corresponding to a malignant disease [6]. Like most of the tumors, the etiology of canine mast cell tumors is also unknown. It has been demonstrated that human and canine mast cell tumors play an important role in tumor angiogenesis by means of the production of vascular endothelial growth factor [21,6]. The genetic alterations that increase the likelihood of tumors in humans are not absolutely understood in dogs. A recent study carried out by Patruno et al. (2014) has reported a link between aberrant c-kit expression, increased angiogenesis, and higher histopathological grade. Similar mutations in the oncogene KIT, a tyrosine kinase growth factor receptor, have been identified in human gastrointestinal stromal tumors (GIST) and human myelogenous leukemia and mast-cell tumors in dogs [22]. These findings provide significant opportunities to study therapeutic strategies in canine mast cell tumors using tyrosine kinase inhibitors, which can be translated to human GIST. Thus, a novel tyrosine kinase inhibitor named masitinib, that targets c-kitR has been recently developed to treat canine mast cell tumors, with the aim of translating this approach in human clinical trials [23]. Moreover, a phase I trial with spontaneous canine mast cell tumors using a multi-targeted inhibitor (Palladia, SU11654) obtained response rates of 90% providing evidence that this kinase inhibitor with activity against KI, VEGFR2 and PDGFRβ could exhibit therapeutic benefits which could be extrapolated to human tumors [21].

Despite of mesenchymal tumors, there are some other tumors which are currently being studied as potential spontaneous model tumors including lymphomas, melanomas or mammary tumors with excellent results. Several studies have strong validated dogs with spontaneous tumors to be relevant models for human studies evaluating the mechanisms involved in carcinogenesis and novel cancer therapeutics. Comparative oncology research between dog and human cancer using spontaneous tumors provide greater insight into the pathogenesis for human cancer. Translational studies will provide better understand cancer biology in order to understand cancer diagnosis, treatment and prevention in both humans and animals.

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