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NEOPLASTIC DISEASE

Immunohistochemical Validation of Spontaneously Arising Canine Osteosarcoma as a Model for Human Osteosarcoma

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Summary

Osteosarcoma (OS) originates from bone-forming mesenchymal cells and represents one of the primary bone tumours. It is the most common primary bone tumour in dogs and man. The characterization of an appropriate natural disease animal model to study human OS is essential to elucidate the pathogenesis of the disease. This study aimed to validate canine OS as a model for the human disease by evaluating immunohistochemically the expression of markers known to be important in human OS. The immunohistochemical panel included vimentin, alkaline phosphatase (ALP), desmin, S100, neuron-specific enolase (NSE), runt-related transcription factor 2 (Runx2) and bone morphogenetic protein 4 (BMP4). Immunohistochemistry was conducted on formalin-fixed, paraffin wax-embedded tissue sections from 59 dogs with confirmed primary OS. Vimentin, ALP, Runx2 and BMP4 were highly expressed by all tumours, while desmin, S100 and NSE were expressed variably. The findings were similar to those described previously for human OS and suggest that canine OS may represent a useful model for the study of the human disease.

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Keywords: dog; immunohistochemistry; man; osteosarcoma

Introduction

Osteosarcoma (OS) is a malignancy that originates from bone-forming mesenchymal cells (Brodey and Riser, 1969) and is the most commonly diagnosed primary bone tumour in both man and dogs (Brodey and Riser, 1969; Mirabello *et al.*, 2011). OS occurs frequently in children, young and old adults, taller people and in young, large and giant breed dogs (Owen, 1984; Mirabello *et al.*, 2011).

Worldwide, human OS has a bimodal age distribution with the highest incidence in children and young adults (0–24 years) and a second peak in the elderly (>60 years) (Mirabello *et al.*, 2009a). People with localized OS have 5-year survival rates of around 65%, while patients with metastatic OS have a worse prognosis (5-year survival rates of 20%) (Li and Ye, 2014). In dogs treated with amputation and adjuvant chemotherapy, the 2-year survival rate for localized OS is approximately 20% (Bielack and Carrle, 2008).

In the USA, fewer than 1,000 new cases of human OS are diagnosed annually (Dorfman and Czerniak, 1995). The incidence of OS in dogs is significantly higher (>8,000 cases/year) (Jongeward, 1985). Canine OS represents 85–98% of all canine bone cancers (Dernell *et al.*, 2007). Similar to human OS,

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canine OS is also known to have a bimodal age distribution of 18–24 months and 7–9 years. Interestingly, the incidence is significantly higher in older dogs compared with that occurring in younger dogs (Dernell *et al*., 2007). In both man and dogs, OS mostly affects the ends of long bones near the metaphyseal regions (Owen *et al*., 1975; Mirabello *et al*., 2011; Guil-Luna *et al*., 2015). The molecular nature of OS is not yet fully understood (Bayani *et al*., 2003; Lau *et al*., 2004; Man *et al*., 2004; Gorlick, 2009) because of the complexity of OS genetics and an inability to elucidate related pathways (Gorlick, 2009).

The use of animal models in cancer research has a long history (Hewitt, 1978; Herberman, 1983). Such models are useful for the study of the biology of cancers and to discover new therapeutic targets, but defining the most suitable animal models is often difficult. Animal models commonly used to study human OS are the dog, mouse and rat (Guijarro *et al*., 2014).

People and dogs share a similar basis of global gene expression signatures (Paoloni *et al*., 2009), environmental conditions (Owen *et al*., 1975; Guil-Luna *et al*., 2015), physiological characteristics (Gordon and Khanna, 2010), OS biological behaviours (Owen, 1969), histological morphology, molecular targets, tumour progression and response to conventional treatments (Guil-Luna *et al*., 2015). In addition, canine OS is 10–100 times more common than human OS (Mueller *et al*., 2007; Paoloni and Khanna, 2008), it is a naturally occurring tumour (Brodey, 1979; Vail and MacEwen, 2000) and metastasis initiates in a shorter period than in human OS (Owen, 1967), which offers better opportunities to investigate the effects of potential therapies (Dernell *et al*., 2007; Mirabello *et al*., 2009b). Furthermore, dogs have shorter lifespans and faster OS progression than people (Owen, 1967; Gordon and Khanna, 2010). The latter characteristic provides an opportunity to study the response to different therapies that could improve human survival time (Guil-Luna *et al*., 2015). All of these aspects of canine OS make it an attractive animal model for study of human OS (Owen *et al*., 1975; Paoloni *et al*., 2009; Morello *et al*., 2011).

Detection of specific tumour markers in OS is important for accurate diagnosis, prediction of prognosis, metastases and response to chemotherapy (Selvarajah and Kirpensteijn, 2010). Despite the aetiology of OS being complex, some tumour markers are expressed at low levels or are overexpressed in canine and human OS (Trieb *et al*., 2003; Barger *et al*., 2005; Won *et al*., 2009). Tumour markers that are generally expressed in human OS include vimentin, S100, osteonectin, osteocalcin, smooth muscle actin (SMA), CD99 and neuron-specific enolase (NSE) (Trihia and Valavanis, 2012). In human OS, vimentin (Rosenberg, 1995), alkaline phosphatase (ALP) (Rosenberg, 1995), runt-related transcription factor 2 (Runx2) (Andela *et al*., 2005) and bone morphogenetic protein 4 (BMP4) (Rosier and Bukata, 2007) are highly expressed. In addition, desmin (Coffin and Belchis, 2006), S100 (Coffin and Belchis, 2006) and NSE (Rosenberg, 1995) are weakly expressed in some human OSs.

A pilot study was conducted to investigate if the tumour markers currently used to classify human OS are applicable to canine OS, using five samples of canine OS tissue. It was found that similar to human OS, this panel of antibodies (vimentin, CK7, desmin, neurofilament protein, CD45, NSE, CD57 and S100) could be used to differentiate canine OS from other canine tumours. This was the first demonstration of the presence of CK7, desmin and S100 in canine OS (H. J. Gunn, RMIT University, Melbourne, Australia; unpublished data). This panel of antibodies was modified for the purpose of cost benefit and the size of some of the canine OS tissue samples available for the present study. Neurofilament protein and CD45 were excluded because they are not expressed in human OS. CK7 and CD57 were also excluded because they are not mesenchymal cell markers. Antibodies specific for ALP, Runx2 and BMP4 were added.

Demonstrating differences or similarities in expression profiles of specific protein markers in canine and human OS could help in therapeutic and comparative histopathological studies to improve our understanding of this tumour. Therefore, the aim of this study was to validate canine OS as a model for human OS by investigating and analyzing the expression of the selected marker proteins in spontaneously arising canine OS. The expression profiles were then compared with those previously obtained for human OS (Rosenberg, 1995; Andela *et al*., 2005; Coffin and Belchis, 2006; Rosier and Bukata, 2007).

Materials and Methods

Tumour Samples

This study was conducted using 59 formalin-fixed, paraffin wax-embedded (FFPE) primary canine OS tissues collected between 1991 and 2015. These tissue blocks originated from the archival collection of the Pathology Unit, School of Veterinary Sciences, University of Bristol, UK. The OS tumours were histopathologically confirmed according to the veterinary classifications of domestic animals (Thompson and Dittmer, 2017).

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