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NEOPLASTIC DISEASE

A Review of the Association between Osteosarcoma Metastasis and Protein Translation

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Summary

The malignant transformation of mesenchymal cells within the bone leads to the development of osteosarcoma (OS), but the genetic underpinnings of these events are not understood. From a clinical perspective, primary tumour management can be achieved successfully in most patients. However, the development of metastasis to the lungs represents the most common cause of death in OS patients. A clearer understanding of metastasis biology is required to improve cancer mortality and improve outcomes. Modelling the genetics, biology and therapy of OS can be accomplished through research involving a number of species. Most notable is the naturally occurring form of OS that develops in dogs. Through a cross-species and comparative approach important questions can be asked within specific and suitable models to advance our understanding of this disease and its common metastatic outcome. A comparative perspective on the problem of OS metastasis that utilizes a cross-species approach may offer unique opportunities to assist in this prioritization and generate new hypotheses related to this important clinical problem.

Keywords: dog; metastasis; osteosarcoma; protein translation

Osteosarcoma

Osteosarcoma (OS) is an uncommon tumour of bone, arising from the malignant transformation of mesenchymal cells, which differentiate towards the formation of osteoid and bone (Malawar *et al.*, 2005; Kansara and Thomas, 2007). While OS can arise in any bone, the most common sites of primary tumours are the distal femur, proximal tibia and proximal humerus. Beyond primary tumour growth in the appendicular and less commonly the axial skeleton, a defining feature of OS biology is its high propensity for pulmonary metastasis (90% of metastases are to the lung; Krishnan *et al.*, 2005). These defining features of OS are shared between human and canine OS patients. This cross-species review describes the disease with an emphasis on metastasis biology and our interest in the potential linkage between efficient protein translation and metastasis.

Human Osteosarcoma in Paediatric Patients

OS may occur at any age; however, it has a peak incidence in the second decade of life with a second smaller peak of incidence in the elderly population (>50 years of age) (Hayden and Hoang, 2006; Kansara and Thomas, 2007). Although rare, it is the most common paediatric bone malignancy in the USA (Gurney *et al.*, 1999). Approximately 800–1,000 cases of OS are diagnosed in the USA each year and about half of these patients are teenagers (Wang, 2005; Kansara and Thomas, 2007). OS occurs most frequently during the adolescent growth spurt in areas of rapid bone growth, suggesting a relationship between tumour formation and rapid growth and/or growth factors expressed at this time in life (American Cancer Society, http://www.cancer.org/

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docroot/home/index.asp). OS may occur more frequently in males than females (60% versus 40%) and slightly more often in African Americans than Caucasians (Gurney *et al*., 1999).

Fifty years ago, when surgery was the only available treatment, a diagnosis of OS was often fatal. Patients had only a 15–20% chance of cure (Dahlin and Coventry, 1967; Hayden and Hoang, 2006). Fortunately, advances in chemotherapy, including the introduction of single agent and combination chemotherapy, and advanced orthopaedic surgical techniques in the 1980s and 1990s increased survival rates dramatically. Today, patients with localized disease at presentation have a 65–70% chance of 5-year relapse-free survival (Bielack *et al*., 2002; Hayden and Hoang, 2006; Kansara and Thomas, 2007; Meyers, 2009). Unfortunately, the remaining patients will relapse (with pulmonary metastasis) within the first 5 years, attesting to the fact that these patients have undetectable metastatic disease at diagnosis. Indeed, up to 20–25% of newly diagnosed patients have detectable metastases at diagnosis (Hattinger *et al*., 2010). Patients presenting with metastases have a poor prognosis, with long-term survival rates of 10–30% (Meyers, 2009). Other prognostic indicators for early relapse include the size and location of the primary tumour, the response to preoperative (neoadjuvant) chemotherapy and surgical success (Bielack *et al*., 2002). Current chemotherapy treatment plans are based on neoadjuvant chemotherapy followed by surgical removal of the tumour and post-operative (adjuvant) chemotherapy. The use of neoadjuvant chemotherapy has the advantage of down-staging the size of the primary tumour and as such providing a more successful opportunity for primary tumour resection with limb salvage. Pathological analysis of the definitive resection provides an opportunity to evaluate histologically chemotherapy-induced tumour necrosis in the resected specimen.

The Huvos grading system (Huvos *et al*., 1977) is a non-invasive quantitative estimate of the percentage of tumour cell necrosis (death) observed in the tumour after surgery. Patients showing tumour necrosis in at least 90% of the resected tumour specimen are classified as good responders (Huvos score 3 or 4) and have more favourable prognoses than patients with less necrosis. Patients with low necrosis scores (Huvos score of 1 or 2) are often selected to receive alternative and more aggressive chemotherapy protocols in the adjuvant setting. Patients who achieve a good histological response to preoperative chemotherapy have considerably better survival than those who have a poor response. Five-year survival for those with good response is approximately 75–80%, compared with 45–55% for those with poor response (Whelan *et al*., 2000; Bielack *et al*., 2002). Exemplary of this approach, the European and American Osteosarcoma Study (EURAMOS) group, has launched, and now nearly completed, the EURAMOS I study. In this study histological response (Huvos score) following preoperative chemotherapy (http://www.ctu.mrc.ac.uk/euramos) is used to assign patients to distinct treatment groups. The current treatment backbone used as first-line therapy in patients includes cisplatin, doxorubicin and methotrexate. The EURAMOS objectives are: (1) to examine whether the addition of ifosfamide and etoposide (IE) to postoperative chemotherapy improves event-free survival for patients with a poor histological response to preoperative chemotherapy and (2) to examine whether the addition of interferon (IFN)-α as maintenance therapy after post-operative chemotherapy improves event-free survival for patients with a good histological response to preoperative chemotherapy.

Despite sophistication of trial designs and multimodality treatments for OS, improvements in long-term survival in the last 20 years have been modest at best. The primary cause of death for patients continues to be the development of metastasis. In order for patient outcomes to improve, we must improve our understanding of the biology of metastasis. Given the complexity of metastasis, there remains a need to develop or to identify reliable animal models of OS. An ideal model would include development of spontaneous primary bone tumour and pulmonary metastases within an immunocompetent host. This type of model would provide the best opportunity to identify key regulatory pathways involved in the development and metastatic progression of OS, as well as the ability to investigate activities of novel antimetastatic therapeutics.

Comparative Studies in Animals

Cross-species comparative opportunities to understand OS biology and therapy are strong. Current animal models of OS include rats, mice and dogs. Each model provides unique strengths. Rat OS models play an important role in evaluating new surgical and molecular methods of treatment for appendicular OS (Blouin *et al*., 2005). Mouse models of OS are used commonly to study tumour biology and develop new approaches for treating OS. Transplantable mouse OS models include syngeneic (genetically identical or closely related, so as to allow successful tissue transplant), xenograft (derived or obtained from an organism of a different species, as a tissue graft; human explants), heterotopic (pertaining to the injection of