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Osteosarcoma and its Association with Chromosomal Abnormalities

Katalin Borbély*

Department of Medicine, Medical University of Pecs and Kaposvar, Hungary

Abstract

Osteosarcoma is the most common non-hematological malignant bone disease in children and adults. The peak incidence occurs in the first 10 years and gradually decreases after the age of 50. Osteosarcoma usually occurs around the growth plate of long bones. Most osteosarcoma tumors are of high grade and are prone to develop lung metastases. Despite clinical improvement, patients with metastatic or recurrent disease have a poor prognosis. Here we review the current understanding of human osteosarcoma, focusing on the clinical aspects and chromosomal abnormalities. With the rapid expansion of knowledge of stem cell biology, it is new that osteosarcoma should be regarded as a differentiation disease caused by genetic and metamorphic changes that interfere with the differentiation of osteoblasts from mesenchymal stem cells.

Keywords: Bone; Osteosarcoma; Clinical improvement; Stem cell

Introduction

Osteosarcoma (OS) is the most common primary osteosarcoma, accounting for about 20% of all bone tumors and about 5% of all childhood tumors [1, 2, 3]. In fact, OS is the fifth most common malignancy in people aged 15 to 19 years and the second most common malignancy in adolescence following lymphoma. OS shows a bimodal age distribution, with the first peak in 20 years of life and the second peak in the elderly [4, 5]. Higher incidences have been reported in boys and African-American children. The most common sites in young adults are areas of rapid bone growth, such as the distal femur, proximal tibia, and proximal humerus. Although the development of OS is associated with several genetic predispositions, most OS tumors are sporadic and have no familial pattern [2, 3, 6, 7].

Exposure to chemical beryllium oxide [8], orthopedic prostheses [9], and FBJ virus [8] causes OS in animal models, but their role in human OS is unknown. SV40 viral DNA has been detected in up to 50% of OS tumors [10, 11], but it is unclear whether SV40 plays any role in OS tumor formation [8-13]. Radiation exposure is a well-proven risk factor for OS [8, 13], but the interval between radiation exposure and tumor development is long and therefore probably irrelevant to the development of most conventional OS tumors. Nevertheless, radiation may be involved in the development of secondary OS after radiation therapy for certain primary tumors. Despite the relatively low incidence of OS, more than 20,000 articles have been published to explain the pathogenic and clinical aspects of OS. As summarized in this study, OS exhibits a wide range of genetic and epigenetic changes, but no consistent changes have been identified in all OS tumors [1-3, 6]. With the rapid expansion of knowledge about stem cell biology and cancer stem cells [14], increasing evidence suggests that OS can be considered a differentiated disease [15, 16]. The final differentiation of osteoblasts derived from pluripotent mesenchymal stem cells is a well-coordinated process and is regulated by a cascade of regulatory signals [15, 17, 18]. The pathological and molecular characteristics of most, if not all, OS tumors strongly suggest that OS can be caused by genetic and posterior disorders of the osteoblast differentiation pathway [15, 19]. Because current chemotherapy primarily targets the proliferative aspects of OS tumors, promoting differentiation and / or avoiding differentiation defects can be used as an effective adjunct therapy to OS. We briefly review currently identified genetic alterations that may be associated with osteosarcoma pathogenesis, and then focus on recent findings that suggest potential links between defective osteogenic differentiation of mesenchymal stem cells and osteosarcoma development.

Human OS and its Clinical Aspects

This review briefly reviews the currently identified genetic changes that may be associated with the etiology of osteosarcoma and a potential association between defective bone formation differentiation in mesenchymal stem cells and the development of osteosarcoma. Focus on recent evidence that suggests.

We performed a PubMed search of the literature related to the topic using the following keywords, used individually or in combination: osteosarcoma, osteosarcoma etiology, and osteosarcoma genetics, Osteosarcoma mutation, Osteosarcoma, Osteosarcoma stem cells, Osteosarcoma stem cell differentiation and Osteosarcoma lung metastases. Publications in languages other than English, related review articles and chapters of books were not excluded from our study. Most of the cases of osteosarcoma described in the literature appear to be high-grade osteosarcoma.

OS prognostic indicators include extent of disease at diagnosis, size and location of the tumor, response to chemotherapy, and surgical remission. For those OS patients who present without detectable metastases, approximately 70% of them can achieve long-term survival. The remaining 30% will relapse, mostly within 5 years. Pulmonary metastasis is the most common form of distant spread. The average survival after a recurrence is less than 1 year. Removal of a surgically resectable recurrence or pulmonary metastasis improves survival. Thus, a major challenge in clinical management of OS is to identify poor responders to chemotherapy and/or to detect early metastatic lesions.

***Corresponding author:** Katalin Borbély, Department of Medicine, Medical University of Pecs and Kaposvar, Hungary, E-mail: katalin.b@gmail.com

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Chromosomal Abnormalities in Human OS

In contrast to other sarcomas such as synovial sarcoma, alveolar rhabdomyosarcoma, and Ewing sarcoma, no specific translocations or genetic abnormalities have been identified in OS [1-3, 6, 15, 20- 23]. Nevertheless, nearly 70% of OS tumors show a variety of cytogenetic abnormalities [4, 5]. OS ploidy scores range from haploid to nearly 6-fold. The chromosomal regions of 1p11–p13, 1q11–q12, 1q21–q22, 11p14–p15, 14p11–p13, 15p11–p13, 17p, and 19q13 are most commonly involved in structural abnormalities. Acquiring chromosome 1 and losing chromosomes 9, 10, 13, and 17 is the most common overall. The less affected chromosomal regions were 13q14 (RB1 locus), 12p12–pter (KRAS locus), 6q11–q4, and 8p23. The combination of multiple detection modalities has enabled a more accurate assessment of complex cytogenetic abnormalities in the OS. The most frequently detected amplifications include the chromosomal regions 6p12-p21 (28%), 17p11.2 (32%), and 12q13-q14 (8%). Several other relapsed chromosome loss (2q, 3p, 9, 10p, 12q, 13q, 14q, 15q, 16, 17p, and 18q) and chromosome acquisition (Xp, Xq, 5q, 6p, 8q, 17p, and 20q) was also identified, as well as multiple relapsed breakpoint clusters and non-relapsed reciprocal translocations [5]. These results further emphasize the complexity and instability of the genetic makeup of OS tumors.

Activation of Oncogenes in Human OS

The c-MYC products are involved in the regulation of cell proliferation and DNA replication [24, 25]. 7-12 percent of OS tumors show MYC amplification [26, 27, 28]. This genetic change may be more common in Pagetic OS (see below) [5]. At expression levels, OS MYC expression was elevated in 9 of 21 (42%) patients who relapsed and 4 of 17 (23%) who remained disease-free.

FOS forms a heterodimer transcription complex with specific JUN proteins that regulate target genes involved in cell growth, differentiation, transformation, and bone metabolism [29]. Injection of the viral homologous v-FOS into rodents induces OS formation. Transgenic mice that overexpress FOS in bone develop OS. In one report, 61% of OS tumors showed high FOS levels. Highest levels of FOS (and JUN) expression have been reported in traditional OS. FOS occurred in 9 of 21 (42%) patients who subsequently developed metastases. In addition, FOS was more frequently expressed in high-grade lesions than in low-grade lesions [5]. MDM2, located at 12q13, negatively regulates TP53 function by binding to the p53 protein, physically blocking the region of p53 involved in transcriptional activation of specific genes, and targeting p53 degradation. Code protein amplification leading to overexpression of MDM2 functionally suppresses p53 even in the presence of wild-type p53 protein. The 12q13 region containing MDM2 and CDK4 is amplified at 5% to 10% of the OS. However, some amplicons in this area (12q13 to q14) do not contain MDM2. Although MDM2 amplification is associated with OS progression and metastasis, MDM2 amplification and TP53 mutations did not correlate with chemotherapy response or survival. Although CDK4 gene amplification has been detected in a low percentage of OS cases, the CDK4 protein is highly expressed in 65% of low-grade OS. CDK4 forms a complex with cyclin D1, phosphorylates RB, and releases the transcription factor E2F from its interaction with RB. It has been suggested that higher levels of CDK4 as a result of amplification stoichiometrically favor RB phosphorylation, thereby impairing cell cycle control. Due to the confirmed discontinuity of the 12q13 amplicon, high CDK4 levels may promote 12q13–q15 amplification independently of MDM2. High levels of cyclin D1 (CCND1) were detected in 22% of OS and amplification of CCND1 was reported in 4% of OS. In addition, lack of expression of cyclin D1 is a strong prognostic factor as it is associated with a metastatic phenotype. ERBB2 (also known as HER2 / neu and c-erbB-2) encodes a protein that is structurally homologous to the EGF receptor without known ligands. At the time of initial biopsy, 20 of 47 OS (42.6%) showed high levels of ERBB2 expression compared to adjacent normal tissues. However, the actual role of the ERBB2 formula in OS development is unknown. One study found that increased expression of ERBB2 in tumor cells was associated with increased chances of event-free and overall survival in patients with high-grade OS without metastases, but others. Studies have previously shown OS-related cytoplasmic staining of ERBB2. Treatment at high risk for lung metastases and ERBB2-positive OS cells may represent an aggressive subpopulation of chemotherapy-resistant OS.

Conclusion

The potentially importance of chromosomal abnormalities in osteosarcoma and knowing the loss of genes and chromosomal gains identification has led to various insight on the instability during the genetic makeup. Future research should be directed towards identifying these differentiation defects in OS cells. This knowledge may help us develop efficacious differentiation therapies for OS by exploiting non-cell autonomous signals to promote differentiation state.

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Conflict of Interest

There are no conflict of interest.

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