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Osteosarcoma and its Association with Chromosomal Abnormalities

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Abstract

Osteosarcoma is the most common non-hematological malignant bone disease in children and adults. The peak incidence occurs in the ýrst 10 years and gradually decreases after the age of 50. Osteosarcoma usually occurs around

Chromosomal Abnormalities in Human OS

In contrast to other sarcomas such as synovial sarcoma, alveolar rhabdomyosarcoma, and Ewing sarcoma, no speci c translocations or genetic abnormalities have been identi ed 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. e 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. e less a ected chromosomal regions were 13q14 (RB1 locus), 12p12–pter (KRAS locus), 6q11–q4, and 8p23. e combination of multiple detection modalities has enabled a more accurate assessment of complex cytogenetic abnormalities in the OS. e most frequently detected ampli cations 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 identi ed, as well as multiple relapsed breakpoint clusters and non-relapsed reciprocal translocations [5]. ese results further emphasize the complexity and instability of the genetic makeup of OS tumors.

Activation of Oncogenes in Human OS

e c-MYC products are involved in the regulation of cell proliferation and DNA replication [24, 25]. 7-12 percent of OS tumors show MYC ampli cation [26, 27, 28]. is 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 speci c JUN proteins that regulate target genes involved in cell growth, di erentiation, 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 speci c genes, and targeting p53 degradation. Code protein ampli cation leading to overexpression of MDM2 functionally suppresses p53 even in the presence of wild-type p53 protein. e 12q13 region containing MDM2 and CDK4 is ampli ed at 5% to 10% of the OS. However, some amplicons in this area (12q13 to q14) do not contain MDM2. Although MDM2 ampli cation is associated with OS progression and metastasis, MDM2 ampli cation and TP53 mutations did not correlate with chemotherapy response or survivaln in t. ese results

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