

Oral Abstract

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Conditional mouse osteosarcoma, dependent on p53 loss and potentiated by loss of Rb, mimics the human disease.

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Osteosarcoma (OS) is the most common primary non-hematological malignant tumor of bone. Analysis of familial cancer syndromes and sporadic cases has implicated both p53 (Li-Fraumeni syndrome) and pRb (familial retinoblastoma) in its pathogenesis. The development of a tractable animal model of OS that mimics the genetics and pathology of the human malignancy would provide new opportunities for probing the genetics of OS, identifying candidate genes for contributing somatic events in the generation or progression of the disease, and devising new therapies based either on inactivation of specific targets or promotion of differentiation. We have generated and characterized a genetically engineered mouse model that exhibits completely penetrant short latency, malignant osteosarcoma. This model is based on the osteoblast restricted deletion of both p53 and pRb using the *Osterix-Cre* transgenic line. This model recapitulates many of the defining features of human osteosarcoma, including cytogenetic complexity, gene expression signatures, pathology, age of onset and metastatic behavior. Tumor development is strictly dependent on p53 mutation, whereas pRb mutation potentiates development of a p53-dependent disease but is insufficient in isolation to initiate osteosarcoma. This represents the first high penetrance, short latency mouse model that has been demonstrated to closely resemble human osteosarcoma. This model provides new opportunities for exploration of the molecular pathogenesis of osteosarcoma and should constitute a convenient platform in which to test or screen for novel therapeutic agents to treat the disease.