The molecular pathogenesis of dedifferentiated chondrosarcoma

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ABSTRACT
Dedifferentiated chondrosarcomas are cartilaginous tumors that consist of two distinguishable components, a lowgrade chondrosarcoma (chondrogenic) component and a highgrade dedifferentiated (anaplastic) component. The tumor cells in both components seem to originate from a single precursor, but there are a substantial number of genetic alterations in the anaplastic component. The underlying mechanism of dedifferentiation is unknown, but cell cycle regulators p16, p53 and retinoblastoma appear to have important roles in tumor development and dedifferentiation. In this article, molecular pathogenesis of dedifferentiated chondrosarcomas is reviewed.

Key words: Dedifferentiated chondrosarcoma, dedifferentiation, pathogenesis

INTRODUCTION

Chondrosarcomas, the second most common form of primary bone cancer, primarily affect the cartilaginous cells of the arms, shoulders, legs, spine and pelvis. Approximately, 10% of chondrosarcomas undergo dedifferentiation, a process in which a portion of the tumor undergoes an anaplastic transformation. These dedifferentiated tumors are comprised of two distinguishable, juxtaposed components: A chondrogenic component and a highgrade noncartilaginous sarcoma (anaplastic component) [Figure 1].

CLINICAL FINDINGS

Femur is the most frequently involved bone (30%), followed by the pelvis (20%), humerus (16%), ribs (7%) and scapula (7%) respectively. Majority of tumors occur in patients >50 years of age, with a mean age of approximately 60 years. Most lesions occur centrally in the medullary cavities, although there are reports of dedifferentiation in juxtacortical chondrosarcomas or from a preexisting osteochondroma.

Dedifferentiated chondrosarcomas are highly malignant tumors with a very poor prognosis. Median survival has been as short as 6 months and 5-year rates of survival range from as low as 10% to 13%. Patients rarely survive more than 2 years. Surgery is the primary form of treatment. The effectiveness of chemotherapy has not been proven, but it has been used for select cases. Metastasis, especially to the lungs, is the most common problem encountered during treatment. This article is a review of molecular studies of dedifferentiated chondrosarcoma, with an emphasis on the process and characteristics of dedifferentiation.
chondrosarcomas is associated with good prognosis. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are principally involved in the breakdown of the extra cellular matrix, as well as tumor angiogenesis. MMPs are regulated by the tissue inhibitors of MMPs (TIMPs). Upregulation of MMP2, MT1-MMP and TIMP2 has been reported in high grade malignant cartilaginous tumors, as well as in the anaplastic component of dedifferentiated chondrosarcoma. MMPs interact with the plasminogen activator system and upregulation of both the plasminogen activator system and MMPs apparently represent the malignant potential of the anaplastic component.

Oncogenesis in cartilaginous lesions
Heterozygous mutations of isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2, respectively) near or in the active sites of the enzyme that lead to the accumulation of δ-2-hydroxyglutarate have been associated with oncogenesis. Mutations occur early in oncogenesis in gliomas/glioblastomas and acute myelogenous leukemia and represent early genetic abnormalities in all cartilaginous tumors. These IDH1 and IDH2 mutations account for more than half of mutations in benign and malignant cartilaginous tumors, including dedifferentiated chondrosarcomas.

The c-Myc gene, located on chromosome 8, encodes a transcription factor that acts in the nucleus to stimulate cell growth and division. c-Myc amplification is frequently observed in high grade malignant cartilaginous tumors including dedifferentiated chondrosarcomas, while no amplification is found in benign and low grade cartilaginous tumors. In the absence of c-Myc amplification, polysomy 8 is found frequently in low to high grade malignant cartilaginous tumors. c-Myc abnormalities appear to correspond to early oncogenesis in all chondrosarcomas, particularly with high grade malignant cartilaginous tumors including dedifferentiated chondrosarcomas.

Single point mutations in the ras genes play a role in tumor development by eliminating dependence on GTPase-activation of protein regulation. A small number of cases revealed H-ras mutations in dedifferentiated chondrosarcoma, but not in low grade conventional chondrosarcomas, suggesting that the mutation may be associated with the aggressive nature of the disease rather than dedifferentiation.

Origin of dedifferentiation
The mechanism underlying dedifferentiation is controversial. There is debate as to whether the chondrogenic and anaplastic components derive from a common precursor cell. Molecular studies show that both tumor components share some genetic alterations and that the components derive from a single precursor. However, a substantial
number of genetic alterations occur in anaplastic components after the division.\textsuperscript{24,25} Therefore, it is also possible, though less likely, that the highgrade dedifferentiated component is the result of a malignant transformation within the dense fibrotic material surrounding the necrotic areas at the margin of the lowgrade chondrosarcoma component, which is the same process by which sarcoma develops in bone infarcts and chronic osteomyelitis.\textsuperscript{26}

Although the two components derive from a single precursor cell, the molecular mechanism, such as the timing of separation, has not been clarified. A possibility is that the anaplastic component originates from mature chondrosarcoma cells in the chondrogenic component as a result of direct transformation,\textsuperscript{2} or the cells of each component separate from a common single precursor cell early in tumorogenesis. The existence of a stable dedifferentiated chondrosarcoma cell line supports the premise that separation occurs early during tumor development.\textsuperscript{12}

**Chromosomal abnormalities**

Chromosomal aberrations of increasing complexity develop during tumor progression in chondrosarcoma.\textsuperscript{27,28} Dedifferentiated chondrosarcoma has a hypodiploid to hypertetraploid chromosome number and presents a heterogeneous pattern of copy number imbalances.\textsuperscript{29} Trisomy 19 has been documented in half of the dedifferentiated chondrosarcomas.\textsuperscript{30} No structural or numerical chromosomal aberrations, highly specific for dedifferentiated chondrosarcomas, have been detected. However, there is some evidence for the clustering of breakpoints in specific regions of 6q13-22 and 9p21-24.\textsuperscript{30} Chromosomal aberrations in 6q13-21 are associated with locally aggressive behavior in benign and malignant cartilaginous tumors, including dedifferentiated chondrosarcoma.\textsuperscript{27,28} Aberrations in 5q have also been reported, but the abnormality is rather more frequent in highgrade conventional chondrosarcoma (35%) than dedifferentiated chondrosarcoma (13%).\textsuperscript{28} Array-based comparative genomic hybridization studies also show that the 5q14.2-q21.3, 6q16-q25.3, 9p24.2-q12 and 9p21.3 loci are specific for highgrade conventional chondrosarcoma and dedifferentiated chondrosarcoma.\textsuperscript{31} The breakpoints in 9p21-24 are seen in anaplastic components with osteosarcoma-like features. This observation raises the possibility that each highgrade subtype may be associated with a unique set of chromosomal changes.\textsuperscript{30}

**Molecular analysis of dedifferentiation**

Defects in cell-cycle regulatory pathways play an important role in the oncogenesis of chondrosarcoma. p16 regulates cell cycle through the inhibition of cdk4 and cdk6.\textsuperscript{32} Analysis of a dedifferentiated chondrosarcoma cell line, MS0812, suggests that deletion of the p16 gene may play a major role in the malignant phenotype of dedifferentiated chondrosarcoma.\textsuperscript{12} Moreover, aberrant promoter methylation of the p16 gene has also been reported in both components of dedifferentiated chondrosarcoma.\textsuperscript{24,25} Interestingly, aberrant methylation of E-cadherin, a cell adhesion molecule, is also seen in both components. The aberrant methylation of p16 and E-cadherin may signal early oncogenesis of a dedifferentiated chondrosarcoma.\textsuperscript{25}

p53 has many mechanisms of anticancer function and plays a role in cell cycle regulation, apoptosis, genomic stability and inhibition of angiogenesis. p53 mutations are the predominant mutations present in highgrade conventional chondrosarcomas and in dedifferentiated chondrosarcoma.\textsuperscript{33,34} In dedifferentiated chondrosarcoma, p53 mutation or loss of heterozygosity (LOH) is detected exclusively in the highgrade dedifferentiated component.\textsuperscript{11,24,25} The retinoblastoma (Rb) protein controls E2F-mediated transactivation of genes whose products are important for S phase entry and cell-cycle progression. Loss of Rb function is an essential step in oncogenesis. LOH of Rb is associated with decreased Rb expression and is significantly correlated with high malignancy in cartilaginous tumors. In addition, LOH of Rb has been found only in the anaplastic component.\textsuperscript{25,35} Aberrant promoter methylation in the fragile histidine triad (FHIT) gene is seen only in highgrade dedifferentiated components. Although FHIT is involved in the regulation of apoptosis and in cell cycle control, the molecular mechanism or functional pathway is still unknown. Irregularities in Rb, p53 and FHIT in the anaplastic component may be the key abnormalities in dedifferentiation of chondrosarcomas.\textsuperscript{31,24,25,35}

**Conclusions**

Molecular studies in dedifferentiated chondrosarcomas have analyzed tumor development, as well as the mechanism of “dedifferentiation.” Among various abnormalities, cell-cycle regulation molecules p16, p53 and Rb may be important in the development of these tumors. Dedifferentiated chondrosarcomas are chemotherapy resistant, regardless of various histological features in the highgrade dedifferentiated components. Therefore, a comparative study of the anaplastic component with osteosarcoma-like features and conventional chemotherapy-sensitive osteosarcoma would be interesting, in order to identify the proteins involved in chemotherapy resistance.

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