IMMUNOLOCALIZATION OF NOTCH SIGNALING PROTEIN MOLECULES IN A MAXILLARY CHONDROSARCOMA AND ITS RECURRENT TUMOR


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Abstract

Background: Notch receptors are critical determinants of cell fate in a variety of organisms. Notch signaling is involved in the chondrogenic specification of neural crest cells. Aberrant Notch activity has been implicated in numerous human diseases including cancers; however, its role in chondrogenic tumors has not been clarified.

Method: Tissue samples from a case of primary chondrosarcoma of the maxilla and its recurrent tumor were examined immunohistochemically for Notch1-4 and their ligands (Jagged1, Jagged2 and Delta1) expression.

Results: Both primary and recurrent tumors were histopathologically diagnosed as conventional hyaline chondrosarcoma (WHO Grade I). Hypercellular tumor areas strongly expressed Notch3 and Jagged1 in spindle and pleomorphic cells suggesting up-regulation of these protein molecules at sites of tumor proliferation. Expression patterns were distinct with some overlap. Differentiated malignant and atypical chondrocytes demonstrated variable expression levels of Jagged1, and weak to absent staining for Notch1, 4 and Delta1. Protein immunolocalization was largely membranous and cytoplasmic, sometimes outlining the lacunae of malignant chondrocytes. Hyaline cartilage demonstrated a diffuse or granular precipitation of Jagged1 suggesting presence of soluble Jagged1 activity at sites of abnormal chondrogenesis. No immunoreactivity for the other Notch members was observed. Calcified cartilage was consistently Notch-negative indicating down-regulation of Notch with cartilage maturation. Stromal components namely endothelial cells and fibroblasts variably expressed Notch1, 3 and Jagged1 but were mildly or non-reactive for the other members.

Conclusions: Results indicate that Notch signaling pathway may participate in cellular differentiation and proliferation in chondrosarcoma. Findings implicate Notch3 and Jagged1 as key molecules that influence the differentiation and maturation of cells of chondrogenic lineage.

Key words: Chondrosarcoma, Immunohistochemistry, Notch receptors, Notch ligands

INTRODUCTION

Chondrosarcoma is a rare malignant mesenchymal tumour characterized histopathologically by the production of cartilaginous tissue and the absence of production of bone tissue by the tumour cells [1-2]. It ranked as the second most common bone malignancy where it forms approximately 11% of all primary bone cancers [2-3]. Chondrosarcoma mostly affects long bones especially the pelvis, femur and humerus. It is uncommon in the head and neck region where its frequency of occurrence ranges from 1-12% of all chondrosarcomas [3-7]. Of these, 10% occur in the jaws, bones [6,7] and most of these arise in the maxilla with a predilection for the anterior maxillary region [3-4].

Chondrosarcomas are sub-classified into the conventional (hyaline/myxoid), dedifferentiated, clear cell, and mesenchymal subtypes [3-5]. Conventional chondrosarcoma, the most common subtype, is composed of either hyaline cartilage, myxoid cartilage or a combination of both of these matrices. The hyaline subtype is characterized by hypercellular hyaline cartilage containing cytologically atypical chondrocytes within lacunae. In contrast, the atypical chondrocytes of the myxoid subtype do not reside in lacunae but instead are enmeshed in a flocculent myxoid matrix. The mesenchymal subtype is known to display a more anaplastic appearance. According to the World Health Organization (WHO) grading system, three categories of chondrosarcoma were identified: grade I (well differentiated), grade II (moderately differentiated) and grade III (poorly differentiated) [1-2]. The biological behaviour of these tumors is characterized by progressive enlargement and subsequent compression or invasion of local structures such as cranial nerves. Complete surgical resection of these tumors is the most acceptable treatment of choice [7]. Radiotherapy and chemotherapy as adjunctive or palliative therapy remain controversial.