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ADAM10 localization in temporomandibular joint disk with internal derangement: an ex vivo immunohistochemical study

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ABSTRACT

The purpose of this study was to determine the presence of ADAM10 in temporomandibular joint disk with internal derangement. Twenty-five paraffin blocks of displaced temporomandibular joint (TMJ) disk specimens from earlier investigations were retrieved from the archives of the University of Catania. Of these 16 had been removed from females and 9 from males; 11 with anterior disk displacement with reduction (ADDwR) and 14 with anterior disk displacement without reduction (ADDwoR). The sections were dehydrated, embedded in paraffin and cut. Then they were incubated in 0.3% H_2O_2/methanol and half of sections from each sample were incubated in diluted rabbit polyclonal anti-ADAM10 antibody. Then biotinylated anti-mouse/anti-rabbit IgG was applied to the sections, followed by avidin–biotin–perioxidase complex. The results were analyzed and the results were that ADAM10 was overexpressed in the posterior band of sections from patients with ADDwR compared to the other bands of both ADDwR and ADDwoR sections. Overexpression correlated with severe histopathological degeneration. We believe these results have the potential to provide insights into the pathogenesis of TMJ disk degeneration and to help design new therapeutic approaches targeting the proteolytic events that lead to tissue degeneration. Early therapeutic block of ADAM10 activity could succeed in limiting aggrecan-rich matrix breakdown without affecting normal physiology.

1. Introduction

Temporomandibular joint disorders (TMDs) are divided into those involving alterations of joints (e.g. internal derangement, degenerative processes) and of muscles (e.g. myalgias, muscle contractures) (Maglione et al., 2013). Derangement is both a clinical feature of TMDs and the result of an abnormal relationship of the articular disk to the mandibular condyle and articular eminence. Internal derangement (ID) is among the most common disorders of the temporomandibular joint (TMJ) (Loreto et al., 2013). The most frequent type of ID is anterior disk displacement (ADD) with or without reduction (ADDwR and ADDwoR, respectively). In ADDwR the disk slides into and out of its normal functional position as the jaw opens and closes, whereas in ADDwoR it glides anteriorly to a lower resting position, remaining stuck in the anterior joint recess, and failing to return to its normal position with condylar movement (Loreto et al., 2012).

Normal articular disk has an anterior band, in front of the condyle head; a thin intermediate band interposed between the anterior region of the condyle head and the inclined back side of the articular eminence; and a thicker posterior band interposed between the condyle head and the roof of the mandibular fossa. An altered relationship between these structures can cause disk compression or injury.

The human TMJ disk consists of compact fibrous tissue with rare fibroblast-like cells scattered among dense, regularly arranged collagen fibers and an extracellular matrix (ECM) composed of collagen and proteoglycan complexes (Leonardi et al., 2002; Matsumoto et al., 2008). The ECM is a major disk component,

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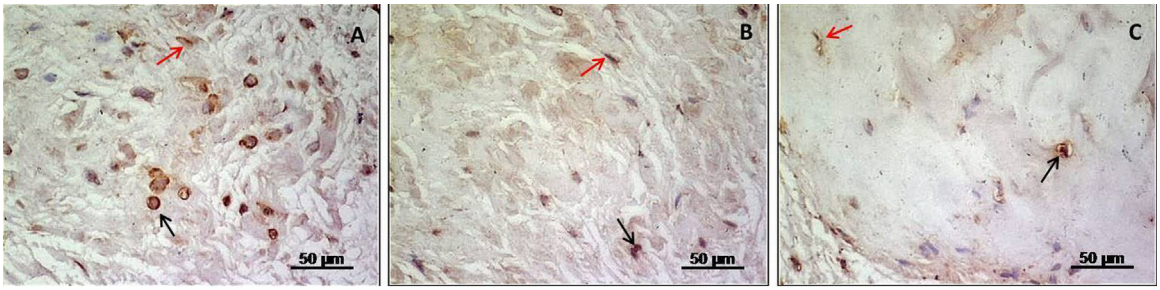

Fig. 1. ADAM10 immunoexpression in sections from patients with ADDwR. A: posterior band (400X). Scale bar: 50 µm. B: intermediate band (400X). Scale bar: 50 µm. C: anterior band (400X). Scale bar: 50 µm. Red arrows: fibroblast-like cells; black arrows: chondrocyte-like cells. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

providing resistance to tension, compression, and shear forces (Gepstein et al., 2002).

ADAMs, a disintegrin and metalloproteinase (adamlysins), are closely involved in cell development, adhesion, migration, and inflammation as well as cancer. Since they are responsible for proteoglycan degradation, they have also been suggested to have a major role in the pathogenesis of intervertebral disk degeneration (Pockert et al., 2009; Rogerson et al., 2008; Verma and Dalal, 2011). ADAMs are sheddases, because they can cut off or shed extracellular portions of transmembrane proteins (Loreto et al., 2012). ADAMs share several similarities. They belong to the same molecule family as ADAMTs (a disintegrin and metalloproteinase with thrombospondin motif), and differ from them only by the absence of one or more thrombospondin motifs and for the presence of an Epidermal Growth Factor (EGF) repeat, a transmembrane domain, and a cytoplasmic tail.

The human genome contains 25 ADAM genes, of which four seem to be pseudogenes. In humans and other vertebrates, ADAM2, 7, 18, 20, 21, 29 and 30 are chiefly expressed in testis, in line with their involvement in spermatogenesis and sperm function; ADAM9, 10, 12, 15, 17 and 19, are widely expressed in body tissues, whereas ADAM28 and 33 show a limited tissue range, and ADAM8 is active mainly in hematopoietic cells (Edwards et al., 2008).

Regulation of ADAM activity is a complex process. In many cases ADAM10 is either constantly shedding or activated by Ca^{2+} influx (Kleino et al., 2015). However, the regulation of activation and sub-

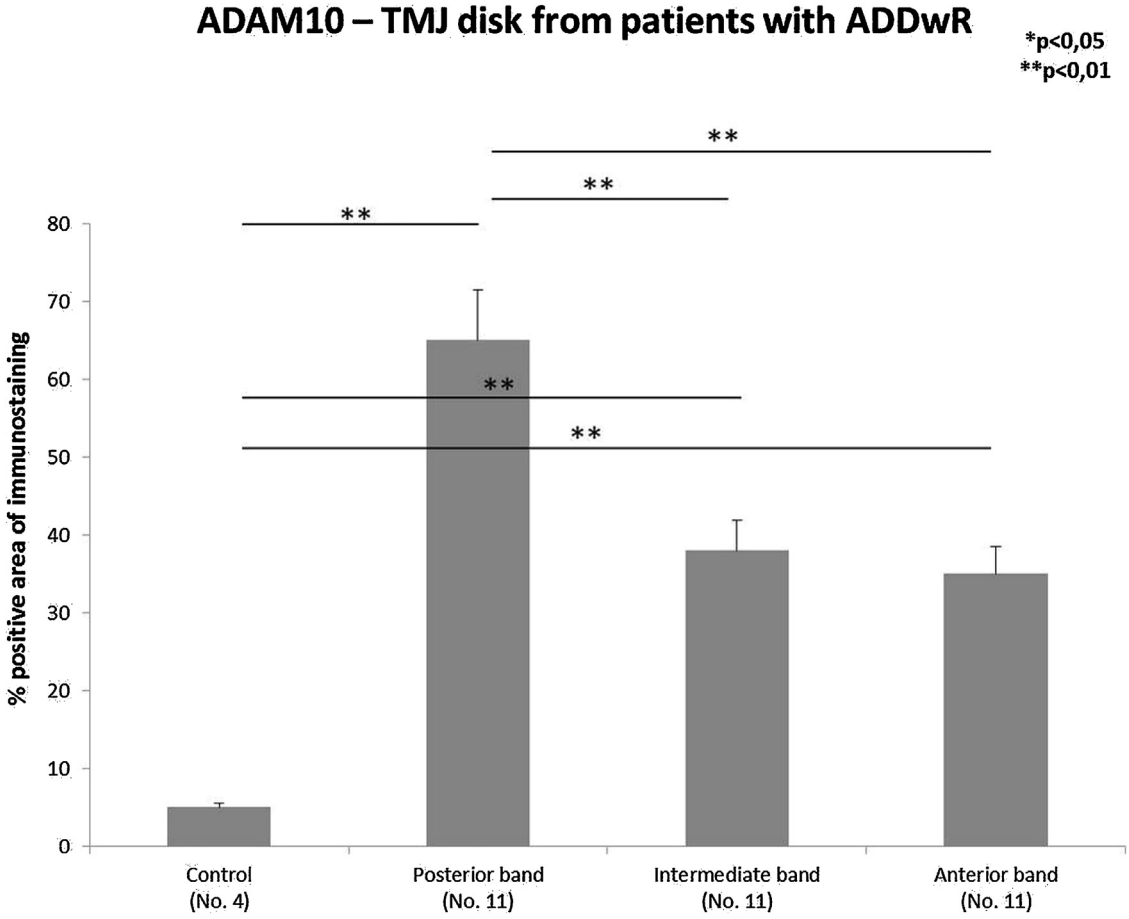

Fig. 2. Immunohistochemical analysis of sections from patients with ADDwR: percentage area of ADAM10-positive immunostaining in the anterior, intermediate, and posterior band of TMJ disks from patients with ADDwR (No. 11) correlated to control disks (No. 4). All experiments were performed at least in triplicate. *P* values < 0.01 were considered statistically very significant $^{**}p < 0.01$.