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Research Article

Expression of β-Catenin in Nerves: A Biological Marker

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Abstract

β-catenin is a protein associated with the intercellular adhesion molecule E-cadherin and belongs to a family of molecules including α and γ-catenins, found at adherent junctions between epithelial cells. Cytoplasmic β-catenin participates in transduction of wingless-Wnt signals and activates transcription by forming complexes with DNA-binding proteins. It promotes proliferation at high cell density, attenuates the radiation-induced G1/S cell cycle block, and inhibits anoikis. β-catenin is an important protein in multistage carcinogenesis. It represents a valuable prognostic marker in pharyngeal squamous cell carcinoma, participates in melanoma progression, in the progression from pancreatic adenoma to carcinoma and other functions. β-catenin is a crucial signal in neural crest development. With an immunohistochemical method we precisely identified nervous tissue with antibody for β-catenin.

Keywords: β-Catenin; Nervous System; Immunohistochemistry

Introduction

β-catenin is a 92-97kD protein associated with the intercellular adhesion molecule E-cadherin [11]. Through this association, β-catenin plays an important role in strong cell-cell adhesion as it links E-cadherin to the actin cytoskeleton through the protein β-catenin. This protein belongs to a family of molecules including α and γ-catenins, found at adherent junctions between epithelial cells [11]. Recently, it has been demonstrated that cytoplasmic β-catenin participates in transduction of wingless-Wnt signals and activates transcription by forming complexes with DNA-binding proteins [5].

Increasing roles for β-catenin are being recognized, since it promotes proliferation at high cell density, attenuates the radiation-induced G_1/S cell cycle block, inhibits anoikis (suspension-induced apoptosis with epithelial cells deprived of attachment to an extra cellular matrix for an extended period of time) [10].

Hughson., *et al.* [7]. in 1998 showed the presence of β-catenin, NCAM, and cadherins in the CG-4 cell line (derived from primary cell rat Oligodendrocyte O-2A, arised during development in the sub-ventricular regions of the central nervous system). Hari., *et al.* [4] in 2002 identified β-catenin as a crucial signal in neural crest development. In the central nervous system cadherins are thought to be involved in axon outgrowth, axon fasciculation, and target recognition [1]. With a carefully validated immunohistochemical method for β-catenin we identified nervous tissue (Figure 1). This study was therefore undertaken to show this possible novel biomarker for neural tissue.

Materials and Methods

The sample analyzed in the study were obtained from the Department of Pathology at the Bauru Dental School of University of São Paulo. The 7 cases (2 pleomorphic adenomas and 5 minor salivary glands) were obtained from the archives of the Department. The tissue samples were fixed in 10% formalin solution and embedded in paraffin. These specimens were diagnosed according to the World Health Organization's international histologic classification of tumors section on histologic typing of salivary gland tumors. On light microscopic examination of conventionally prepared sections stained with HE were observed some nervous fibers.

The expression of β-catenin (BD Transduction Laboratories) was analyzed by immunohistochemistry. Formalin-fixed, paraffin embedded specimens were used for the immunohistochemical analysis by the avidin-biotin-peroxidase complex method. Briefly, 3µm sections of tumors and glands were dewaxed and rehydrated prior to antigen retrieval. Antigen retrieval was performed by incubating the slides in steamer at 100°C for 40 min. These preparations were incubated in H_2O_2 for 5 min to block endogenous peroxidase. Then they were incubated overnight at 4°C with primary mouse monoclonal antibody β-catenin (DAKO). Chromogenic detection was with 3,3-diaminobenzidine (DAB). Counterstaining was briefly performed with Mayer's hematoxylin. Negative controls for immunostaining were carried out by substituting the primary antibodies with PBS. For a positive control there was immunopositivity on ducts of salivary glands and sometimes, mucosal epithelium.

Results

All samples had positive control. Higher β-catenin index rates were seen in all nerve fibers (Figure 1). Intercalated, striated and interlobular duct cells were also positive. The inflammatory, acinic, vascular and muscle cells did not demonstrate expression of β-catenin. The mucosal epithelium, when present, were strongly positive.

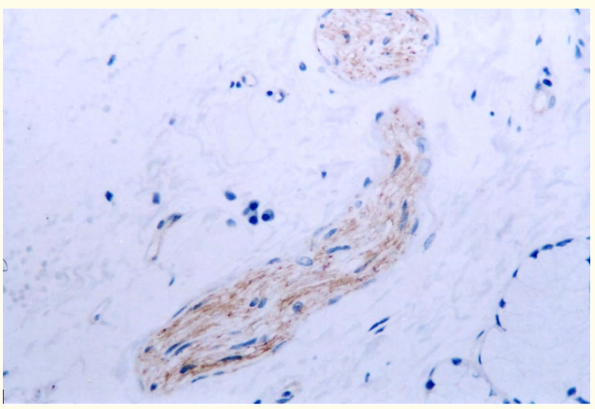

Figure 1: β-catenin immunopositivity in a nervous fiber of a minor salivary gland.

Discussion and Conclusion

β-catenin has being identified as an important protein in multistage carcinogenesis. Some aberration on APC gene or metabolism results in nuclear translocation and accumulation of this protein. Its nuclear expression in pharyngeal squamous cell carcinoma predicts short overall survival representing a valuable prognostic marker in this tumor [14]. Genetic defects that result in up-regulation of β-catenin may play a role in melanoma progression [15]. The loss of E-cadherin-mediated cell adhesion that involves β-catenin, is one rate-limiting step in the progression from pancreatic adenoma to carcinoma [12]. A mutation on exon 3 of the β-catenin gene promotes accumulation of mutant β-catenin in thyroid cell that probably contributes to the development of the cribiform morular variant of the papillary thyroid carcinoma [18]. The aberrant expression of the molecule can play an important role in the histologic differentiation and tumor staging of mucoepidermoid carcinoma [16].

But β-catenin also participates in the morphogenesis [13]. and the catenin-cadherin interactions are important in the regulation of bone cell and chondrocytes activity. Abnormalities of expression or function of these molecules may be important in the formation of bone tumors and their clinical behavior [9]. The absence of β-catenin significantly reduces the capacity of endothelial cells to maintain intercellular contacts and causes a defective vascular pattern and increased vascular fragility [2].

HARI., *et al*. [4]. in 2002´ study indicated that β-catenin plays a role in specifying the melanocyte lineage from neural crest cells, most likely due to its function in mediating Wnt signaling. β-catenin has an early function in neurogenesis. It controls the early specification of ngn2-dependent sensory neurons by mediating Wnt signaling rather than cadherin-dependent cell adhesion. Thus, β-catenin as a component of the Wnt signal transduction pathway can be added to the list of signals, such as TGFβ family members, Notch, and NRG, that regulate cell fates in neural crest development [4].

The E-cadherin, a calcium-dependent adhesion molecule is expressed in myelinating schwann cells in the peripheral nervous system and is involved in forming adherents junctions between adjacent loops of membrane at he paranode. During nerve development β-catenin and E-cadherin are localized to the paranodal region after the onset of myelin compaction [8].The dynamic expression pattern of β-Catenin (partner of β-catenin) and the biochemical evidences of its association with N-cadherin plays a role in neuronal migration, neurite outgrowth and synapse formation and plasticity [3].

The S-100 protein is an antibody used to mark schwann cells and schwannomas, as Leu-7. Glial fibrillary acidic protein marks some schwann cells - possibly unmyelinated, myelin basic protein stains myelin, neurofilament proteins reveal the localization of axons and the perineurium is shown by epithelial membrane antigen (EMA). Silver stains can also be used to identify the twisted and disoriented axons. Neurofibromas have mast cells that can be stained by toluidine blue or Giemsa techniques. The S-100 protein, Leu-7 and EMA are immunocytochemical markers for this tumor, as neurofilament proteins and Silver stains. Neurofibromatosis, neuronal tumors, solitary circumscribed neuromas and malignant peripheral nerve sheath tumors or malignant schwannomas also can have their neural cells stained by these antibodies [17]. HOWNG., *et al* [6]. 2002, were the first to suggest that β-catenin, E-cadherin and Wnt-signaling might be involved in brain tumorigenesis.

With a carefully validated immunohistochemical method for β-catenin we identified nervous tissue (Figure 1). Probably the marked cells are schwann cells. This study tend to show

this possible biomarker for neural tissue and to suggest new experiments to clarify the pattern of staining β-catenin in normal and tumor neural tissues.

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