DIAGNOSTIC AND HISTOGENETIC SIGNIFICANCE OF S 100 PROTEIN IN ORAL DISEASES

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Abstract

S-100 protein, although originally isolated from brain tissue, has since been shown to be present in a wide variety of tissues and cell types. S 100 protein is present in cytoplasm and nucleoplasms of a wide array of cells. It's role in cell functioning is not clearly understood. S 100 protein is present in number of tumours occurring in maxillofacial region., including chondroid tumours, granular cell tumours, schwannomas, oral mucosal melanomas, salivary gland tumours, histiocytosis and some odontogenic tumours also. S 100 protein has been used to study the histogenesis of certain tumours such as osseous and chondroid tumours and salivary gland tumours such as pleomoerphic adenoma. A review of the role of S 100 protein in diagnosis and histogenesis of certain oral and maxillofacial tumours is done here

Key Words: S-100 protein, tumor

Introduction

S 100 protein was first isolated from bovine brain and so called because of it's solubility in 100% saturated solution of ammonium sulphate at neutral PH.S 100 proteins are low molecular weight proteins. Although initially thought to be a specific feature of neural crest origin, S 100 is now known to have wider distribution. S 100 is a calcium binding protein initially identified in the brain of several mammals[1]. At present at least 21 different type of S 100 proteins has been identified[2]. S 100 protein initially detected in neurogenic tumours were later on found in many non neurogenic tumours including malignant melanomas, meningiomas, teratomas and lymphomas as well[3]. Today altered levels of S 100 proteins has been found to be associated with cardiomyopathies, neurogenerative disorders, inflammatory disorders and cancer.[2] Altered levels of S 100 protien has been reported in oral diseases such as , oral melanomas, salivary gland tumours, granular cell myoblastoma and oral lichen planus. [4,5,6,7]

Structure and Function of S 100 protein

S 100 is one of the "EF" hand family of low molecular weight protein. The E and F refer to two polypeptide alpha helices joined by calcium iron binding loop forming the conformation of hand when illustrated diagrammatically. The monomers (of 10-12kDa) are either alpha or beta subunits or are each composed of two "hands". The dimer of two alpha subunits is termed S 100b and the heterodimer of one alpha and beta subunit is S 100a. S 100 protein is highly conserved in all vertebrates, up to 95% in the case of beta subunit. This suggest that the biological function of S 100 protein is important and similar between species. S 100 is diffusely distributed throughout the cytoplasm and is present in some cell organelles.[8] The role of S 100 is not fully understood, but it's function is probably attributable to calcium binding properties.[9]. S 100 is also a constituent of microtubules in centrioles and cilia and, invitro has the ability to control microtubule assembly and disassembly in the presence of

calcium and zinc.[8] It does this by complexing with proteins associated with the formation of microtubules.[10]

Although present in nucleoplasm S-100 is absent from cristae nucleoli.[3] The observation that S 100 is present in nucleoplasm has led to the notion that it is involved in cell cycle control. The S 100 beta subunits stimulates expression of growth associated proto-oncogenes, raising the possibility of an autocrine role and thus S-100 is implicated in cell division.[10] Dimers of S 100 can invitro, promote neurite extension[10]. After it was discovered that the beta subunit of S 100 is encoded on chromosome 21, it was postulated that triplication of this gene may account for some of the neurological abnormalities of Down syndrome.[11] S 100 protein may be important in other capacities for example immunity and regulation of PH and water and electrolyte balance.[10]

Role of antibody to S 100 protein in diagnostic pathology

H.J Khan et al had examined normal tissues and various tumours for S 100 protein using protein antiserum in an immunoperoxidase reaction. Positive staining was observed in the case of glial cells of the central nervous system, some neurons, schwann cells of the peripheral nervous system, melanocytes, Langerhans cells of the epidermis, sweat glands and ducts of the skin, myoepithelial cells, occasional ducts of the salivary glands, breast serous glands and hyaline cartilage of bronchi and the larynx. Fetal neuroblasts, sustentacular cells of adrenal medulla, interdigitating reticulum cells of lymph node, spleen and thymus and chondrocytes showed positive. Normal nerves and nerve complexes throughout normal tissues stained positively.

Among the neoplastic tissues, gliomas, neurilemommas, neurofibromas and malignant melanomas is positive for S 100 protien.[12, 13] In mixed tumours, chondroid areas, myxoid areas and epithelial cells stained positive for S 100 protein.[12, 14] Both mono and multi nuclear histiocytes in histiocytosis which characteristically may contain Langerhan's cells and birbeck granules stained positively for S 100 protein.[12] Positive staining was seen in medullary carcinoma of the breast, bronchio alveolar carcinoma and pheochromocytoma.[12]

Although S 100 protien was positive in a variety of tumours, it could not be detected in a large number of other neoplasms surveyed. These included tumour of epithelial derivation (adenocarcinomas, squamous cell carcinomas and basal cell carcinomas of skin), lymphomas (Hodgkin's and non Hodgkin's) and sarcomas (rabdomyosarcomas, leiomyosarcoma and fibrosarcoma. In some of the lymphomas, single or focal aggregates of cells stained positive for S 100 [12].

S 100 protein in tumours of cartilage and bone

Chondrocytes can be either of neural crest or mesodermal origin. Those derived from fetal skull and visceral cartilage are described as being of neural crest origin, whereas chondrocytes found elsewhere in the body have been considered as mesodermal origin. In contrast, although bone is formed in two ways, through either intramembraneous or endochondral ossification, all bones are thought to be of mesodermal origin.

Steffanson and his associates [15] found S 100 protein in normal human chondrocytes, in areas representative of both neural crest and mesodermal orgin. They suggested that mesodermal chondrocytes may be developmentally closer to neuroectoderm than previously thought.

Chondroid tumours, both benign and malignant stained positive for S 100 protien.[16] In periosteal chondroma and endochondroma, the chondrocytes stained positive. There was no reactivity in the surrounding chondroid or fibrous tissue. Adjacent normal bone tissue was also negative. In chondroblastoma S 100 positivity

was detected in well differentiated chondrocytes. Immunoreactivity was negative for multinucleated giant cells in chondroblastoma.

In mesenchymal chondrosarcoma immunoreactivity for S 100 protein was found in cytoplasm and/or nucleus of well differentiated chondrocytes.[16,17] There was no immunoreactivity in the surrounding chondroid matrix or the mesenchymal tumour cells.

In case of osseous tumours, osteoma and osteoblastoma stained negative for all components of the tumour. In case of osteosarcoma S 100 was negative for all components except for small foci of cartilage. The giant cell tumour of bone showed positivity in all components. Ewings tumour is negative for S 100 staining.[16] Nakamura et al concluded from their study that the presence of S 100 protein in chondroid cells and their absence in osseous cells suggest that chondroid cells are developmentally closer than osseous cells to neuroectoderm.[16]

S 100 protein in granular cell tumour

The granular cell tumour, previously known as granular cell myoblastoma, a rare tumour of unknown cause consist of unique granular cells. Although a varied origin for tumour has been suggested, it is now believed to be of neural origin, predominantly on the basis of immunohistochemical studies. A related tumour, congenital gingival granular cell tumour, having identical microscopic appearance to that of granular cell tumour is believed to be having different histogenesis.

A consistent S 100 positive reaction has been seen in granular cell tumour[18]. The nuclei and cytoplasm of the granular cell tumour stain positive for S 100 protein. The reaction of nuclei is more intense than that of cytoplasm[19].

Kaiserling et al[20] studied granular cell tumour and congenital granular cell tumour to compare the immunophenotype of these tumours. The granular cell tumour was positive for S 100 protien. The congenital granular cell tumour was only weakly reactive for S 100 protein. At the same time both were reactive for macrophage markers. These finding suggest that, rather than having a neural origin congenital gingival granular cell tumour may be derived from pericyte or a related cell with potential smooth muscle differentiation

S 100 protein in soft tissue tumours derived from schwann cells and melanocytes

In routine practice of surgical pathology it is often difficult to determine the cell origin of tumour arising in soft tissues. By permitting detection of cell specific antigens immmunohistochemistry adds a new dimension to identification of cells not recognizable by morphological features alone. Steffanson et al[21] in their study found out all tumours arising from schwann cells stained positive for S 100 protien.. This included schwann cells in traumatic neuromas and cutaneous neurofibromas. S 100 positive reaction was found in Antoni A and Antoni B type tissues of neurilemmomas. Plexiform and cutaneous neurofibromas stained positive for S 100 protein. Jon Ohno et al[22] has reported a case of solitary neurofibroma of gingiva with prominent differentiation of meissner's bodies. The meissner's bodies stained intensely positive for S 100 protein. The presence of S 100 protein on meissner's bodies has been reported in previous studies[23]

S 100 protein in oral mucosal melanoma (OMM)

Primary oral malignant melanoma comprises only 0.2-8% of all melanomas. Nevertheless, aggressive nature of these neoplasms attracts frequent interest. OMM differs from its cutaneous counterpart in incidence, geographical distribution and clinical and pathological features. OMM like melanomas may be difficult to distinguish from other anaplastic tumours on morphological grounds and so immunohistochemical analysis may be used to aid diagnosis. S 100 protein is consistently

positive in OMM[24]. Cells of the advancing front of a vertical growth phase were often more strongly positive than superficial cells, and epitheloid cells were more strongly positive than spindle cells. Oral nevus cells were positive for alpha and beta S 100, when mono clonal antibodies were used.[25]. Fitzgibbon et al [26] had studied four oropharyngeal melanomas for S 100 protein reactivity. With polyclonal antiserum S 100 was positive in all four cases. With monoclonal antibody only two were positive. The inconsistent staining of melanomas may be explained by the fact that some melanocytic tumour cells lack S 100 beta DNA or that S 100 profiles alter as the disease progress. Although a number of new monoclonal antibodies has been used in the diagnosis of mucosal melanomas, S 100 remains the most sensitive marker for oral mucosal and desmoplastic mucosal melanomas.

S-100 protein in histiocytes and Langerhan's cells

The human lymphoreticular system consists of dendritic histiocytes, such as langerhan's cells (LC), interdigitating reticulum cells (IDCs) and follicular dendritic cells. Although macrophages and histiocytes are generally thought to originate from blood monocytes, the origin of dendritic histiocytes remain controversial. S 100 protein has found to be positive in LCs and IDCs but negative in monocytes and macrophages. Therefore some authors consider LCs and IDCs not to be monocytic in origin. Takahashi et al[27] had found S100 immunoreactivity in skin LCs, IDCs and histiocytosis X cells. This suggest that they are independent of the monocytic macrophage system even though they are all derived from common stem cells of the bone marrow. Welsh W et al[28] had done a quantitative evaluation of Langerhan's cells in median rhomboid glossitis. They have found that median rhomboid glossitis is associated with a reduced S 100 positive langerhan cell count which has suggested to result in a focal defect in immuno surveillance which results in colonization by candida. In oral lichen planus(OLP) S 100 positive intraepithelial dendritic cells are increased in lesional tissue in comparison to it's normal counterpart.[7] In OLP the highest dendritic cell counts are seen where the lymphocyte and macrophage infiltrate is heaviest.[7]

S 100 protein in salivary gland tumours

While there has been general agreement on the clinical aspects associated with these lesions, variation has been noticed in histologic typing and classification. This is most likely due to difficulties in histopathologic and histogenetic inter pretation. The application of immuno histochemistry to salivary gland pathology has shown that materials similar or identical to proteins once thought to be nervous system specific are present in some salivary gland tissue. Because of the essential role of myoepithelial cells in salivary gland pathology, the expression of S 100 protein in these tumours is claimed to have a major histogenetic implications.[30] The reports are conflicting regarding the presence of S 100 proteins in the myoepithelial cells of salivary gland. Myoepithelial cells are recorded as positive[31] in some studies while negative in certain other studies.[32] Dardick et al[33] in their immunohistochemical and electron microscopic study have concluded that S 100 protein is absent in myoepithelium of normal salivary gland. Pleomorphic adenoma and myoepithelioma are lesions in which S 100 protien has been demonstrated immunohistochemically and by certain immunological mechanisms. The lack of S 100 protein in myoepithelium of normal salivary gland and it's presence in neoplastic tissue reflects an equally important aspect of acquisition of ectopic proteins in salivary gland neoplasms.

S 100 Protein in Odontogenic cysts and tumours

In odontogenic tumours, which develop at various stages of tooth formation,

both ectodermal and mesenchymal odontogenic components show an elaborate proliferation and mutual stimulation. Therefore, odontogenic tumours show a variety of characteristic features dependent on the tumour cell origin and the stage of tumour cell differentiation. Ectome senchymal part of tooth germ is believed to originate from the neural crest cells. So this is one aspect that has been investigated with S 100 protien antibodies. In case of odontogenic cyst the inflammatory component in the connective tissue contains langerhan's cells. Some investigations with S 100 protein has been carried out regarding this aspect of odontogenic cyst.

Akhlaghi et al had carried out a retrospective study on Langhans cells in 142 odontogenic cyst and has found out S 100 protein positivity in all 142 cases.[35] Murase et al has demonstrated S 100 protein positivity of Langhans cells in ameloblastomas, radicular cysts and dentigerous cysts, where a significant inflammatory component was present.[36] In a study done by Takeda et al on ameloblastic fibroma(AF) and ameloblastic fibrodentinoma(AFD) few s 100 positive cells were found on epithelial component of both AF and AFD. Mesenchymal dendritic and spindle cells were positive for S 100. The same investigators has suggested the possibility of the expression of neural proteins probably related to neural crest related cells in dentinogenesis under certain pathologic conditions in odontogenic tumour.[37] S 100 positivuty has been observed in a pigmented calcifying cystic odontogenic tumour[38], probably indicating the presence of dendritic melanocyte and neuroectodermal origin of the tumour.

Conclusion

S 100 protein, first believed to be of neural crest origin is now found to have a wider distribution. Though S-100 protein is now frequently used to aid in diagnosis of uncertain histological appearance, it's lack of specificity has produced confusing and often inconsistent data. Histogenesis of oral and maxillofacial lesions can be investigated with S 100 protein. But caution should be there in interpreting the results as the possibility of ectopic S 100 proteins are formed in neoplastic tissues. The current significance of S 100 in Oral Pathology is that provided the limitations of S 100 immunhistochemistry is recognized, expression of this protein can still confirm a difficult diagnosis which is suggested by routine histological staining.

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