REVIEW ARTICLE

Podoplanin: A Novel Diagnostic And Prognostic Marker In Oral Tumors: A Brief Review

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ABSTRACT

Every cell type has a unique molecular signature, referred to as biomarkers, which are identifiable characteristics such as levels or activities of a myriad of genes, proteins or other molecular features.With the explosion of molecular technology and understanding of the biology of oral tumors, a wide variety of biological agents have been found to identify prognostic factors in oral tumors. One such protein is podoplanin.Podoplanin is a 38kDa type-1 transmembrane sialomucin -like glycoprotein which consists of 162 amino acids. Recently, podoplanin commonly used as a lymphatic endothelial marker in cancers has recently been found to play a possible role in odontogenic tumorigenesis also.Therefore the purpose of this review paper is to highlight the multifaceted role of podoplanin in oral cancers as well as in oral tumors.

Key-words:podoplanin, odontogenic tumors,protein, squamous cell carcinoma(SCC), head and neck squamous cell carcinoma(HNSCC)

How to cite this article: Singhal N, Barman I. Podoplanin: A Novel Diagnostic And Prognostic Marker In Oral Tumors. A Brief Review Int J Cont Med Res. 2014;1(2):56-60

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Source of Support: Nil

Conflict of Interest: None

INTRODUCTION

Every individual has a cell type having a distinct set of genes or proteins, referred to as biomarkers, which have unique identifiable characteristics.A biomarker can be defined as a characteristic that is evaluated as an index of normal biologic processes, pathologic processes, or pharmacologic responses in an individual to a therapeutic intervention.[1] Diagnostic and prognostic biomarkers are quantifiable traits that help clinical oncologists to identify who is at risk, diagnose at an early stage, select the best treatment modality & monitor response to treatment.[2]

With the explosion of molecular technology and understanding of the biology of oral tumors, a wide variety of biological agents have been found to identify prognostic factors in oral tumors. One such protein is podoplanin. Podoplanin is a 38kDa type-1 transmembrane sialomucin -like glycoprotein which consists of 162 amino acids. In normal human tissue, podoplanin is expressed in kidneypodocytes, in skeletal muscle,placenta, lung and heart ,in myofibroblastsof the breast and salivary glands, in osteoblasts and mesothelial cells .It is also expressed on the apical surface of rat alveolar type I cells.[3]Occasionally, focal expression of podoplanin can be found in circumscribed areas of the basal layer of the human epidermis.[4] As podoplanin is expressed on lymphatic but not on blood vessel endothelium, it is widely used as a specific marker for lymphatic endothelial cells and lymphangiogenesis inmanyspecies.Wetterwald et al first identified podoplanin in LECs & some other normal cells in the year 1996 in the murine osteoblastic cell line MC3Y3-E1.[5,6] The term podoplanin was assigned to the gene because of its lowlevel expression seen in the podocytes of the murine renal corpuscle. Podoplanin is a 38 kD a mucoprotein which lead to the flattening of foot processes,

therefore playing a role in maintaining the unique shape of podocytes.[7]In the past much literature has been reviewed on podoplanin and most of the information is available on its role in squamous cell carcinomas where it is highlighted as a lymphatic vessel prognostic marker.We therefore wish to provide our readers with a review which elucidate the role of podoplanin in odontogenic tumorigeneis also which is a recent topic.

PHYSIOLOGICAL ROLE OF PODOPLANIN

The physiological function of podoplanin is still unknown.Podoplanin plays an important role in preventing cellular adhesion and is involved in the regulation of the shape of podocyte foot processes and in the maintenance of glomerular permeability. Moreover, podoplanin is involved in lymphatic vessel formation and does not influence formation of blood vessels. Podoplanin knockout mice have lymphatic defects associated with diminished lymphatic transport, congenital lymphoedema and dilation of lymphatic vessels. Podoplanin can induce platelet aggregation in vitro.[3] Podoplanin has also been linked to tooth development. Recently, podoplanin expression has been described in a tooth germ and apical bud cells of a mouse incisor at the bell stage.[8]

PODOPLANIN EXPRESSION IN TUMOR CELLS

Podoplanin is invariably expressed in some tumors, such as lymphangioma, seminoma & follicular dendritic cell tumor, but tumor cell expression of podoplanin is highly variable in squamous cell carcinoma (SCC).[3]This expression in tumor cells is useful for pathological diagnosis and podoplanin seems to be expressed by aggressive tumors, with higher invasive andmetastatic potential. Based on these data, podoplanin might be considered as an attractive therapeutic target for both lymphatic vessels and tumor cells.

PODOPLANIN &ORAL SQUAMOUS CELL CARCINOMAHNSCCs are malignant tumors of the head and neck region which can occur in the lip, oral cavity , nasal cavity, paranasal sinuses, pharynx, and larynx. The different anatomic sites of HNSCC correspond to distinct clinical classifications having different clinical presentations and treatment outcomes. These cancers are frequently aggressive in their biologic behaviour and spread via the lymph nodes of head & neck region. Thus, lymph node metastasis can be used as one of the independent prognostic parameters in patients with HNSCC. However, cervical lymph node metastasis cannot always be predicted from the size and extent of invasion of the primary tumors. Aggressiveness of a tumor is chiefly determined by its underlying molecular features. Podoplanin is widely used as a specific marker to evaluate lymphatic vessel invasion because it is specifically expressed by the lymphatic endothelium.[9]

POTENTIAL ROLE OF PODOPLANIN IN TUMOR INVASION AND METASTASIS

A role for podoplanin in invasion and metastasis has been suggested.It was found that about 80% of human SCCs podoplanin expressed – often in a one-cell layer – at the invasive edge of the tumours. The restricted expression of podoplanin at the front of human squamous cell carcinomas prompted the question whether factors of the surrounding tissue could influence podoplanin expression. Indeed, podoplanin expression can be induced by epidermal growth factor, basic fibroblast growth factor (FGF2) and tumour necrosis factor a in MCF7 breast cancer cells, and by bradykinin in 3T3 fibroblasts.[10,11]
Podoplanin by passes EMT(epithelial mesenchymal interactions). Podoplanin does not suppress the cadherin switch or EMT, but is able to mediate an independent pathway of tumour cell invasion.Cancer cell migration and invasion depend on an active remodelling of the actin cytoskeleton. Podoplanin might favor tumor invasion through its ability to remodel actin in the cytoskeleton of tumor cells, contributing to their increased motility. The association between podoplanin and the actin cytoskeleton seems to be mediated by ezrin, which is markedly phosphorylated in the presence of podoplanin overexpression.[7]Membrane proteins are linked via ERM proteins (ezrin, radixin and moesin) to the actin cytoskeleton. One of the ERM proteins,

ezrin, has been shown to mediate filopodia formation and to induce metastasis. Podoplanin physically associates with ezrin thus suggesting a role of podoplanin expression in the rearrangement of the actin cytoskeleton.It has been reported that podoplanin increases the activities of Rho GTPases, mainly RhoA, contributing to cytoskeletal reorganization, suggesting an important role of podoplanin in tumor invasion and metastasis.[3]

PODOPLANIN IN ODONTOGENIC LESIONS

It has been observed in the recent literature that podoplanin expression is also seen in odontogenic tissues like in secretory ameloblasts, developing & mature odontoblasts, Tomes' fibres & pulp cells.[12] A myriad of odontogenic tumors and cysts occurring in the oral and maxillofacial region arise histogenetically from the odontogenic apparatus and their remnants.This multiformity reflects the complex development of dental structures since these lesions originate through some aberration from the normal pattern of odontogenesis.[13] Podoplanin which is frequently used as a lymphatic endothelial marker in OSCCs has recently been found to play a possible role in odontogenic tumorigenesis also.
Various scientific studies have shown strong expression of podoplanin in the epithelial odontogenic cells in the peripheral areas of the odontogenic tumors such as ameloblastomas, keratocystic odontogenic tumors, adenomatoid odontogenic tumors, odontomas ,calcifying epithelial odontogenic tumors.[12,14-16] Interestingly, both mitotic activity and podoplanin expression within the ameloblastoma are restricted to the peripheral cells. It can be concluded that podoplanin is expressed during intense proliferative activity in odontogenic cells and once the cells reach state of maturity as in stellate reticulum like cells , there is lack of immunoreactivity.[17]However, in benign odontogenic cysts, such as dentigerous cysts &odontogenic orthokeratinized cysts ,it is observed that the epithelial cells do not express podoplanin except when associated with inflammatory infiltrate.[12]This therefore justifies the possible role of podoplanin in odontogenic tumorigenesis.

DISCUSSION

In the recent past podoplanin – a small mucin-like protein has evolved in different physiological and pathological conditions including the phenomenon of cell invasion. Therefore it is said to have potential implications for diagnosis and prognosis. Although the protein has been considered as a specific marker for lymphatic endothelial cells , its expression has also been demonstrated in various normal as well as neoplastic cells. F.N. Bartuli et al (2012)[18] analysed podoplanin overexpression in 20 patients with oral cancer, by immunohistochemical analysis. Podoplanin was not expressed in normal oral epithelial cells. High podoplanin expression was found more frequently in the oral cavity cancers associated with lymph node metastasis. They observed an increased podoplanin expression in the early stages of tumourigenesis thus supporting a potential role of podoplanin in the initiation but not in the progression of oral cancer. So they concluded that podoplanin can be used as a prognostic factor for lymph node metastasis in the patients affected by oral cancer.Frederico Omar et al (2012)[19] investigated angiogenesis and lymphangiogenesis in mucoepidermoid carcinoma measuring the density of neoformed and lymphatic vessels using CD105 and D2-40 antibodies. They also investigated the expression of D2-40 in neoplastic cells. The presence of podoplanin in tumor cells correlated significantly with the increase in intratumoral neoformed vessels. Tjioe KC et al (2013)[20] immunohistochemically observed that podoplanin was expressed in the peripheral odontogenic epithelium of the tumourslike ameloblastomas, adenomatoid odontogenic tumours, KCOTS, OOCs, calcifying epithelial odontogenic tumour, ameloblastic fibromas, ameloblastic fibro-odontomas and calcifying cystic odontogenic tumours. KCOTS exhibited intense positive podoplanin expression while in OOC it was absent or weak. They therefore co-related podoplanin to the proliferative activity& aggressive biologic behaviour of KCOTS. Eri

Okamoto et al (2010)[12] immunohistochemically analysed podoplanin expression in odontogenic keratocysts which include Keratocystic odontogenic tumors KCOTs and orthokeratinised odontogenic cysts (OOCs) and few dentigerous cysts (DCs) .Podoplanin was strongly expressed in KCOTs in comparison with OOCs. Therefore they suggested that the pattern of staining for podoplanin in KCOT could be related to its neoplastic nature, and suggested a role of the protein in tumor invasiveness. Wei Mai (2014)[21] revealed the clinicopathological significance of podoplanin immunoreactivity in esophageal squamous cell carcinomas by analysing the podoplanin positive lymphatic vessels in intratumoral and peritumoral tissues and showed that it can be used as a marker to predict lymph node metastasis, recurrence, and worse prognosis in ESCC. Patricia Gonzalez Alva (2011)[22] analysed the expression of podoplanin in compound as well as complex odontomas immunohistochemically. They exhibited positive podoplanin expression in developing & mature odontoblasts, Tomes' fibres & in secretory ameloblasts but not in mature ameloblasts. Thus they revealed that the development of tooth germ affects the pattern of podoplanin staining further describing that the protein may participate in the process of differentiation.

CONCLUSION

Despite being an expensive and immunostaining technique sensitive biomarker, podoplanin in the present scenario may serve as a multifaceted, novel prognostic & diagnostic marker which on one hand can be used as a specific marker for lymph node metastasis in HNSCCS & on the other hand can also be used as a marker to determine the process of local invasion in aggressive odontogenic tumors. However, some important questions concerning the function of podoplanin in tumours remain open. The function of podoplanin where the expression of podoplanin is often more diffuse and not restricted to the tumour front, needs to be elucidated. The role of podoplanin expression in carcinoma *in situ* also has to be addressed. As no expression of podoplanin was found in many biopsies and these cancers often exhibit the morphological characteristics of collective cell migration. Further studies need to be carried out to understand the exact molecular mechanisms by which podoplanin plays a role in oral tumors which will help to devise new and more efficient strategies to reinforce the importance of this molecule in cell migration, local invasion and aggressive behaviour.

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