

## Review Article

### Podoplanin: A Novel Diagnostic Marker

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#### ABSTRACT:

Podoplanin, a representative immunohistochemical marker for lymphatic endothelial cells, is also expressed in many other kinds of cancer cells, although its pathophysiological function is largely unknown. Various studies in the past literature have highlighted the role played by podoplanin in pathogenesis of a variety of lesions. Hence; we planned the present review to highlight some of the important aspects of podoplanin and its role as a diagnostic marker in a number of lesions.

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#### INTRODUCTION

Podoplanin is a 38 kd mucin-type transmembrane glycoprotein with extensive O-glycosylation and a high content of sialic acid that was first reported in lymphatic endothelial cells, epithelial cells of the choroid plexus, alveolar type I cells, osteoblasts, and peritoneal mesothelial cells, by Wetterwald et al in 1996, under the designation E11 antigen. This protein was subsequently identified on the surface of rat glomerular epithelial cells (podocytes) and because it was found to be involved in the flattening of foot processes in puromycin-induced nephrosis, it was named podoplanin. 2 Recent investigations have demonstrated that podoplanin, the so-called oncofetal M2A antigen expressed in testicular germ cell tumors that is recognized by the recently commercially available D2-40 antibody, and the type I alveolar cell marker hT1a-2 (also known as human Aggrus) are identical proteins.<sup>1-3</sup>

The majority of data examining the function and signaling pathways of PDPN are from studies of PDPN overexpression in tumor cells. While these studies certainly provide critical insight into cellular and molecular aspects of PDPN biology, it is important to understand whether PDPN functions similarly in non-pathological settings and in cell types where it is naturally expressed.<sup>4</sup>

#### PODOPLANIN IN DEVELOPMENT

Podoplanin is first expressed in the developing mouse embryo on day E9 in the foregut, proepicardial organ, and central nervous system. Throughout development, it is also expressed in the fetal rat kidney, choroid plexus, intestine, and esophagus. Over time, PDPN expression is increasingly restricted such that in an adult animal, PDPN is predominantly expressed in alveolar type I cells, mature osteoblasts, LECs, and FRCs in the T cell zone of lymphoid organs. PDPN is critical for normal development of some of these organs and has been well studied in PDPN-deficient animals. Pdpn<sup>-/-</sup> mice develop normally until around day E10, which coincides with the appearance of PDPN protein. From days E10–16, approximately 40% of Pdpn<sup>-/-</sup> embryos die; the ones that survive to birth die within a few days.<sup>5-7</sup>

In addition to its role in lymphatic vessel development, PDPN may play a role in the development or maintenance of lymphoid organ architecture. In the spleens of mice lacking lymphocytes, no PDPN expression is observed, although FRCs are still present as indicated by VCAM-1 and ER-TR7 staining. It appears that this lack of expression is due to a lack of lymphotoxin, but it remains unclear exactly which cell type provides that signal during development of the spleen. A more striking phenotype has been observed by Peters et al. in that Pdpn<sup>-/-</sup> mice lack

nearly all LNs, and the ones that develop are extremely disorganized. The spleens of these mice were present, but were also disorganized. It is interesting to speculate whether this phenotype indicates an important function for PDPN on FRCs and T cells; however, it is also possible that the lack of LNs is due to impaired lymph flow caused by the malformed lymphatic vessels. Thus, further work is needed to dissect this phenotype.<sup>8</sup>

### **PODOPLANIN IN CANCERS**

Induction of podoplanin expression was observed in animal tumors generated experimentally. For example, significant amounts of this glycoprotein were found both on the surface of transformed mouse keratinocytes and on the stromal cells of tumors developed as a result of treating animals with 7,12-dimethylbenz[a]anthracene (DMBA) or 12-O-tetradecanoylphorbol-13-acetate (TPA). Increased levels of podoplanin or its neo-expression were shown in many types of human cancers. It occurs in several squamous cell carcinomas, such as oral cavity, tongue and pharynx, skin and lung cancer. In oral cavity and tongue cancers, a high level of podoplanin expression was correlated with an increased incidence of metastasis to lymph nodes and shorter survival time of patients, and in lung squamous cell carcinoma - with shorter survival time of patients. Similarly, high podoplanin expression on the cells of squamous cell esophageal cancer was correlated with the severity of the disease, increased cancer cell invasion into lymphatic and blood vessels and a higher incidence of metastasis into regional lymph nodes, disease recurrences and shorter patients' survival.<sup>9,10</sup>

The presence of podoplanin in hemangioblastomas facilitates and sometimes even enables its distinction from clear cell renal cell carcinoma. Similarly, the presence of this glycoprotein on the cells of mesothelioma helps to distinguish it from lung adenocarcinoma, and in testicular germ cell tumors facilitates the distinction of seminomas from embryonal carcinoma.<sup>11</sup>

In human A431 cell line, podoplanin is a marker of cells with stem-cell-like properties, which are characterized by their high efficiency to form colonies in vitro and high tumorigenicity in nude mice model. Based on these results, it is possible that podoplanin can be a marker of cancer stem cells in squamous cell skin carcinoma.<sup>12</sup>

### **THE ROLE OF PODOPLANIN IN TUMOR PROGRESSION AND METASTASIS**

In the last decade, much data has been generated concerning the molecular mechanisms of lymphangiogenesis and its significance in pathological conditions. This was mainly due to the discovery of lymphatic endothelial cell (LEC)-specific markers, such as vascular endothelial growth factor receptor-3 (VEGFR-3), LYVE-1, Prox-1 and podoplanin. Podoplanin, originally detected on the surface of podocytes, belongs to the family of type-1 transmembrane sialomucin-like glycoproteins. Although specific for lymphatic vascular

(LV) endothelium, podoplanin is expressed in a wide variety of normal and tumor cells. The expression of podoplanin is induced by the homeobox gene Prox-1 and a specific endogenous receptor was identified on platelets. Immunohistochemical detection of podoplanin/D2-40 in LECs was used in many studies to evaluate the LV microvascular density (LVMD) in peritumoral and tumoral areas, and to correlate LVMD with lymph node status and prognosis. Podoplanin significantly increases the detection of lymphovascular invasion in different types of malignant tumors. Podoplanin expression was found in tumor cells of various types of cancer, such as vascular tumors, malignant mesothelioma, tumors of the central nervous system (CNS), germ cell tumors and squamous cell carcinomas. This expression in tumor cells is useful for pathological diagnosis and podoplanin seems to be expressed by aggressive tumors, with higher invasive and metastatic potential. Based on these data, podoplanin might be considered as an attractive therapeutic target for both LVs and tumor cells. Further studies are necessary to investigate differences in the expression of podoplanin in normal and tumor-associated lymphatics, and between the expression of podoplanin in normal non-LECs and tumor cells.<sup>13</sup>

### **PODOPLANIN IN ODONTOGENIC LESIONS**

Odontogenic Cysts & tumors originate through some aberration from the normal pattern of odontogenesis. Ameloblastoma is one of the most frequent intraosseous odontogenic tumors. However it is no longer appropriate to use the diagnosis of ameloblastoma without specifying the type. Varied-clinical entities of ameloblastoma differ in their biologic behaviour. Odontogenic cysts like dentigerous and radicular cysts are less aggressive in nature than odontogenic tumors. Recently, podoplanin commonly used as a lymphatic endothelial marker in cancers has recently been found to play a possible role in odontogenic tumorigenesis also.<sup>14</sup>

Since podoplanin is expressed on lymphatic endothelium but not on blood vessel endothelium, it is also widely used as a specific marker for lymphatic endothelial cells and lymphangiogenesis. However, expression of podoplanin is up-regulated in a number of different malignancies, including squamous cell carcinoma of the oral cavity, lung and skin, granular cell tumours and mesothelioma as well as low grade chondrosarcoma. Furthermore, podoplanin has been implicated in oral cancer progression. Recently, podoplanin expression has been described in a tooth germ and apical bud cells of a mouse incisor at the bell stage. Odontoblasts are organized as a layer of palisade cells along the interface between the dental pulp and the dentin. They are post-mitotic ecto-mesenchymal cells, which originate from the neural crest and play a central role during dentin formation and regeneration. Dentin extracellular matrix proteins synthesised in the supranuclear zone of odontoblasts are mostly secreted at the proximal front of predentin, but are also partly transported via odontoblast

processes and secreted into dentinal tubules to form intratubular dentin. Keratocystic odontogenic tumour (KCOT) is a benign uni- or multicystic, intraosseous tumour of odontogenic origin, with a characteristic lining of parakeratinized stratified squamous epithelium and potential aggressive, infiltrative behaviour. The KCOTs are lined by a regular parakeratinized stratified squamous epithelium, usually about five to eight cell layers thick and without rete ridges. There is a well-defined, often palisaded, basal layer of columnar or cuboidal cells. The parakeratotic layers often have a corrugated surface. The solid / multicystic ameloblastoma (A-S / M) is a slowly growing, locally invasive, epithelial odontogenic tumour of the jaws with a high rate of recurrence if not removed adequately, but virtually no tendency to metastasize. A-S / Ms may be unilocular or multilocular radiolucencies resembling cysts and they may revealed scalloped borders. The unicystic ameloblastoma represents an ameloblastoma variant, presenting as a cyst. Typically, the basal cells of islands of odontogenic epithel are columnar, hyperchromatic, and lined up in a palisaded fashion. Typically, their nuclei are displaced away from the basement membrane, and their cytoplasm is generally vacuolated. The central cells may be loosely arranged, resembling stellate reticulum. Adenomatoid odontogenic tumour (AOT) is composed of odontogenic epithelium in a variety of histoarchitectural patterns, embedded in a mature connective tissue stroma and characterized by slow but progressive growth. The most striking pattern is that of variably sized nodules of cuboidal or columnar cells of odontogenic epithelium forming nests or rosette-like structures with minimal stromal connective tissue.<sup>15- 18</sup>

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