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Review

Cell–extracellular matrix interactions in oral tumorigenesis: Roles of podoplanin and CD44 and modulation of Hippo pathway

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ABSTRACT

Background: Although many studies have examined the crosstalk between tumor cells and extracellular matrix during tumorigenesis, the role of this crosstalk is incompletely understood. This crosstalk is regulated by dynamic reciprocal interactions among tumor cells, stroma, and stromal cells in the tumor microenvironment. Our recent findings have led us to focus on selected adhesion molecules and signaling pathways, specifically podoplanin, CD44, and Hippo pathway, that regulate cell–extracellular matrix interactions. Our studies have shown that interactions among these molecules and the Hippo pathway modulate the behavior of specific tumors and stromal cells.

Highlight: Podoplanin, a transmembrane sialomucin-like protein, is localized on cell surface facing the intercellular space or on basolateral cell surface facing extracellular matrix in tumor cells of odontogenic tumors, salivary gland tumors, and oral squamous cell carcinoma. Podoplanin and CD44 attach oral squamous cell carcinoma cells to hyaluronan-rich extracellular matrices and promote their proliferation. CD44, an alternatively spliced, multi-domain, multifunctional transmembrane protein, regulates vascular endothelial cell survival by modulating adhesion molecules CD31 and vascular endothelial (VE) cadherin through Hippo pathway. Endothelial cells lacking these adhesion molecules escape contact inhibition and show abnormal proliferation. In murine hemangioendothelioma cells, reduced expression of CD31 and VE-cadherin modulates Hippo pathway, resulting in their prolonged survival, proliferation, and invasion.

Conclusion: Signaling pathways initiated by adhesion molecule-mediated crosstalk between tumor cells and extracellular matrices play important roles in driving and maintaining tumor-specific tissue architecture and contributing to tumor survival, growth, and metastasis.

Contents

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1. Introduction

During tumorigenesis, parenchymal cells interact with stromal cells and molecules in the extracellular matrix (ECM) through various surface receptors. These cell–cell and cell–extracellular matrix interactions result in tumor-specific tissue architecture. However, molecular pathways induced by the crosstalk between tumor parenchymal cells and ECM-rich stroma that influence the behavior of these cells are incompletely understood. In this review, we describe several specific cell adhesion molecules involved in crosstalk among tumor cells, stromal cells, and ECM.

Our studies on oral tumors and ECM (specifically perlecan) [1–8] suggest that crosstalk between oral tumor cells and ECM regulates phenotypic expression and proliferative potential of these cells and results in a tumor-specific tissue architecture. We have applied this hypothesis to experimental and translational research for the differential diagnosis of oral tumors [2,5,9,10].

We have focused on podoplanin as a candidate molecule that mediates signaling between tumor parenchymal cells and stroma and have elucidated its function as a CD44-associated adhesion molecule via hyaluronan-rich ECM [11–13]. We have documented an important role of Hippo pathway, a conserved signaling pathway essential for regulating organ growth and modulating tumor-specific tissue composition and architecture [14–21]. We have also documented the roles of some specific endothelial cell adhesion molecules involved in microvascular endothelial cell survival [22] and have shown that dysregulation of these adhesion molecules and Hippo pathway-mediated cell survival is responsible for vascular tumorigenesis [23].

In this review, we discuss the application of specific molecular interactions based on our findings of the roles of cell adhesion molecules and ECM in cell survival and behavior to understand the fundamentals of tumorigenesis.

2. Expression of podoplanin in oral tumors

One of the difficulties in histopathological diagnosis of head and neck lesions is the differential diagnosis of cystic jaw lesions, including odontogenic tumors. This is because small biopsy specimens do not always show a representative histology, e.g., enlargement of cystic spaces or inflammation. In such cases, routine hematoxylin–eosin staining is not always applicable for the differential diagnosis of cystic jaw lesions [5,24–26]. To seek practical aids in solving this confusion, we have utilized immunohistochemical approach for the accurate differential diagnosis of odontogenic cystic lesions [2,5,9,10,26]. We observed that in tumor parenchymal cells, podoplanin was localized to the cell surface facing the extracellular stroma [5,10,11]. Therefore, we

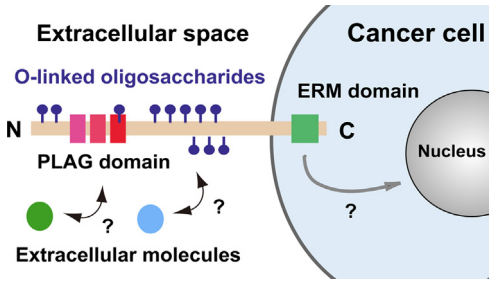

Fig. 2. Schematic diagram of podoplanin and its hypothetical function. Podoplanin is a transmembrane glycoprotein containing a large extracellular domain with many O-glycosylation sites, a single transmembrane domain, and a short cytoplasmic tail. The extracellular domain contains a platelet aggregation–stimulating (PLAG) domain that interacts with C-type lectin-like receptor-2 involved in hematogenous dissemination of cancer. The cytoplasmic tail contains an ezrin–radixin–moesin (ERM) domain that interacts with the actin cytoskeleton via ERM family proteins, which are involved in cell motility. We hypothesized that podoplanin interacts with extracellular molecules on the ectodomain and contributes to the adhesion, proliferation, or migration/invasion of oral tumor cells.

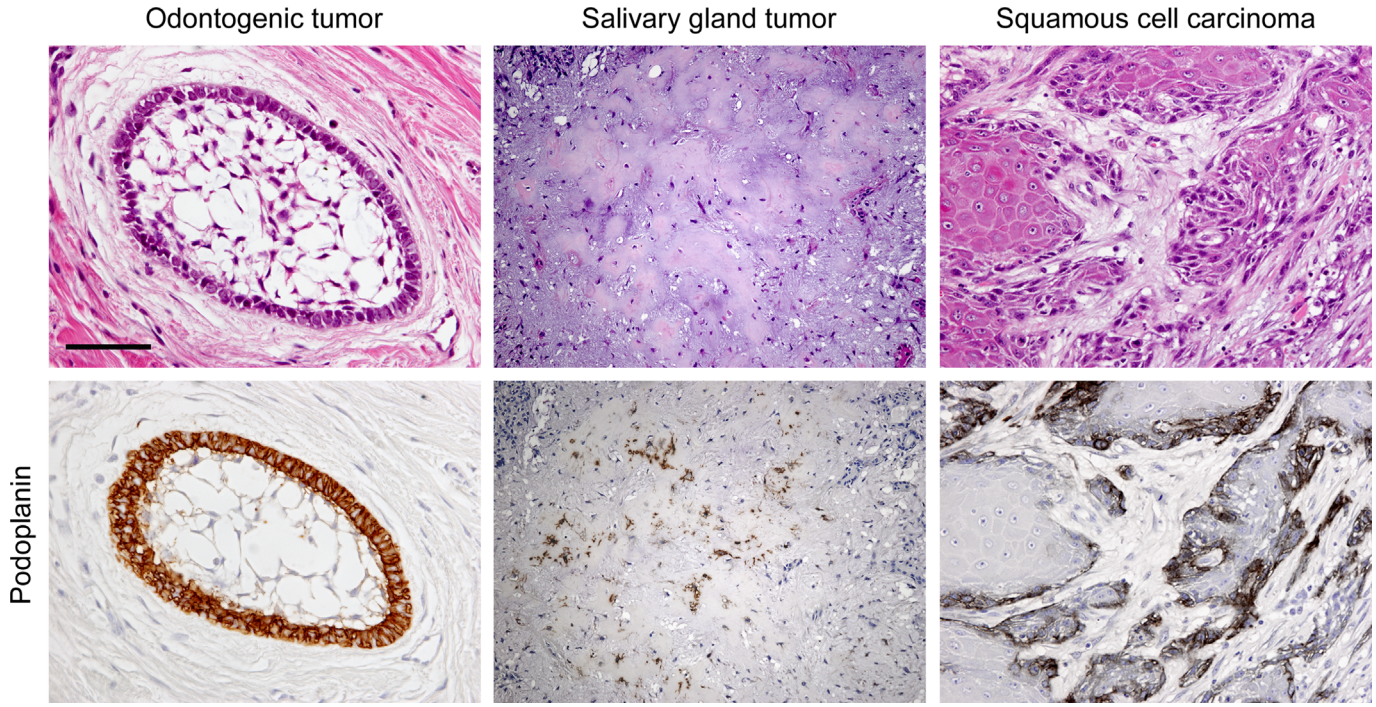

Fig. 1. Podoplanin expression profiles of oral tumors. Left column: odontogenic tumor (ameloblastoma); middle column: salivary gland tumor (pleomorphic adenoma); right column: oral squamous cell carcinoma. Top row: sections stained with hematoxylin and eosin; bottom row: sections stained with immunoperoxidase and counterstained with hematoxylin for podoplanin. Scale bar: 100 μm. Podoplanin is localized on the surface facing the ECM-rich stromata in tumor parenchymal cells. All figure panels have been compiled from our data published in *Pathology-Research and Practice* [11], *Virchows Archiv* [12], and *Laboratory Investigation* [13].