THE ROLE OF PODOPLANIN IN CANCER INVASION AND METASTASIS IN ORAL SQUAMOUS CELL CARCINOMA

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OBJECTIVES

Podoplanin is a transmembrane receptor glycoprotein that is upregulated in transformed cells, cancer associated fibroblasts and inflammatory macrophages, which contributes to cancer progression. Podoplanin is expressed by endothelial cells of lymphatic vessels but not by blood vessels including high endothelial venules. In solid tumors podoplanin has been proposed as a specific marker for lymphatic endothelium and can be used to predict the malignant transformation of potentially malignant disorders and the metastatic tendency in OSCC. The study has been performed in 150 cases of OSCCs, included in a Tissue Micro Array (TMA) with a long time follow-up (mean 8 years).

GRAPHS & TABLES RESUS
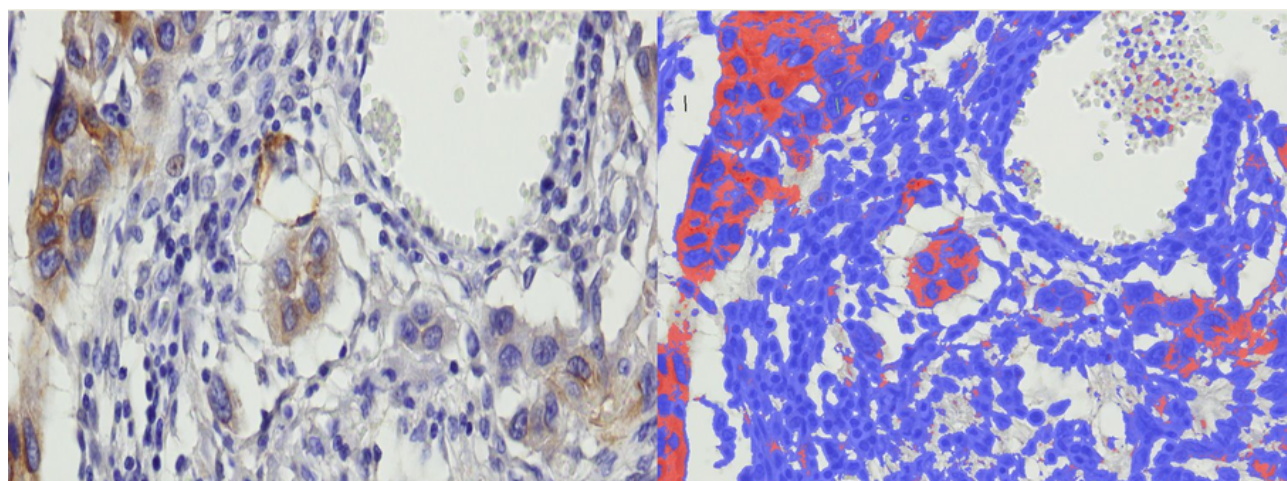
Podoplanin expression and lymphvascular invasion

PODOPLANIN	P (Anova test)
Gender	0.033 (increase in Male)
Age	0.037 (increase in over 65)
T (TNM AJCC 2017)	0.045 (increase in T4)
Stage	p<0.001 (in III and IVB stages)

PODOPLANIN	MMP9	P
Cancer %	Cancer %	0.032 (up-regulation)
Cancer%	Cancer %	Spearman's test: p<0.001
Average vessels	Phlogosis	Spearman's test: p<0.01
Deep margin	Phlogosis	0.031 ANOVA
Deep margin	Phlogosis	Spearman's test: p<0.05
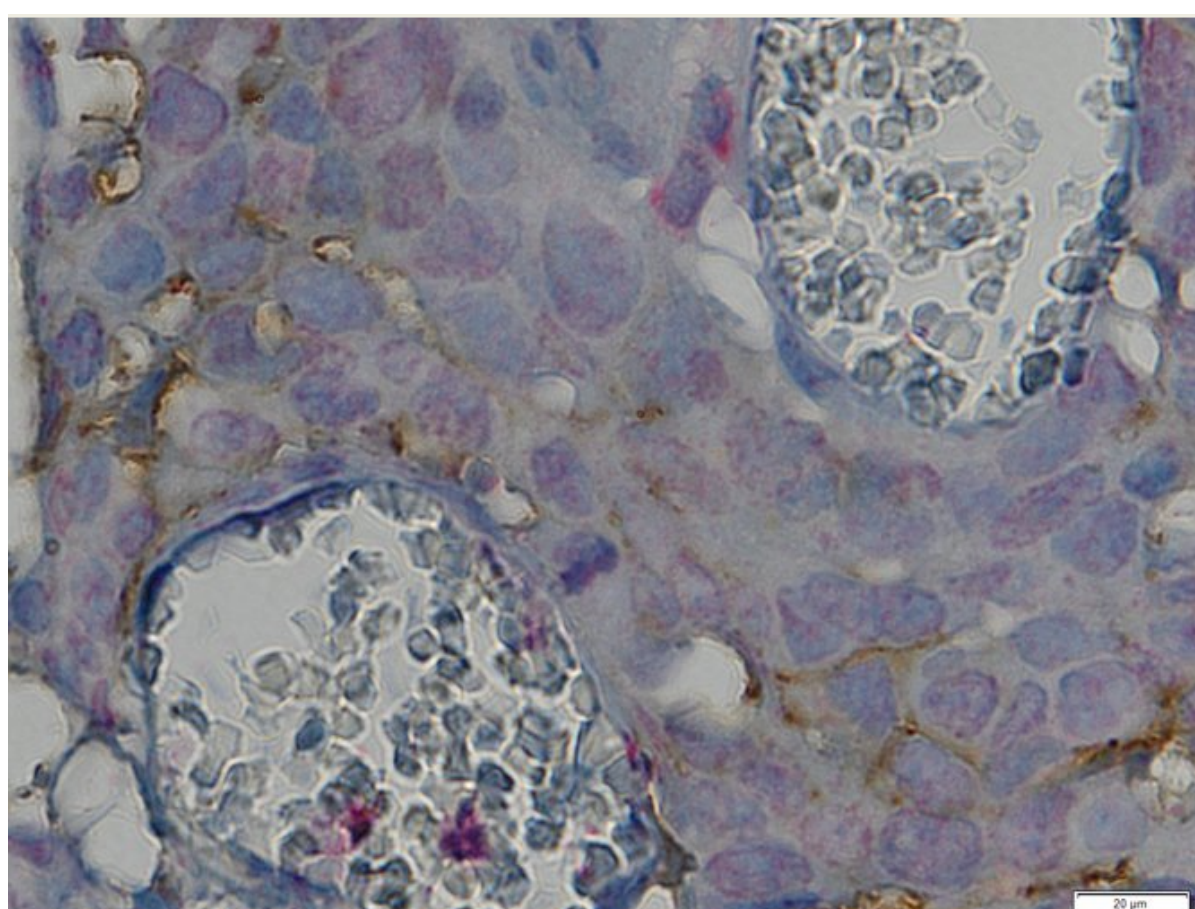
Representative double immunoistaining for podoplanin (brown) and MMP9 in OSCC

METHODS

Tissue-microarray based immunohistochemistry was performed using D2-40 and MMP-9 monoclonal Abs and standard automatized technique (Ventana Benchmark®). Further serial sections have been stained with Abs related cell cycle, apoptosis inhibition, phlogistic carcinogenesis, growth factors, and genes representative of key pathways in oral cancerogenesis and lymph node metastasis. Immunostained spots were digitally counted using CellSens V1.9® Olympus image analysis software. In brief, four HPH-20x microscopic picture (145.675,65 µm2 x HPF) were captured and analyzed for each TMA spot. Lymphatic Microvessel Density (LMD) was expressed as the average of four × 200 field counts of podoplanin-positive endothelial cells corresponding to the entire TMA spot (582.702,6 µm2 = 582,7 mm2). Data have been analyzed by SOFA Statistics 1.4.3 (for Windows). Pearson's test and ANOVA statistical analysis have been used to correlate podoplanin expression to clinicopathological parameters.

RESULTS

The study of clinicopatological data showed upregulation podoplanin has a high statistical significance and it is overexpressed in stage IVB with p <0.001 in moderately advanced or very advanced local disease (tumor invadeing through cortical bone- mandible or maxilla- or involveng the inferior alveolar bone, floor of mouth or skin of face) according to AJCC edition VIII 2017. Furthermore the study shows a linear correlation between Podoplanin and a tissue metastaticic tissue microenvironment as demonstrated by association between neoformed lymphvascular channels (D240+) and and MMP9 expressed in phologosis and between Podoplanin and MMP9 in cancer cells. Moreover a significative role of podoplanin in invasione process has been demonstrated by up-regulation of podoplanin in tumor with DOI >10mm.

CONCLUSION

The lymphatic marker podoplanin plays an important role in both cancer invasion and lymphangiogenesis.

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