IMMUNOHISTOCHEMICAL EXPRESSION OF VASCULAR ENDOTHELIAL GROWTH FACTOR AND PLATELET ENDOTHELIAL CELL ADHESION MOLECULE IN SALIVARY GLAND CARCINOMAS

THESIS

Submitted to the Faculty of Oral and Dental Medicine, Cairo University, in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Basic Dental Science (Oral Pathology)

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2007

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ABSTRACT

Angiogensis is highly ordered generation of new blood vessel from pre-existing vasculature**.** VEGF is prototypical pro-angiogenic major endothelial-specific stimulatory molecule. It is regarded as the most potent candidate for the induction of tumor angiogenesis. Several reports have shown that tumor angiogenesis reflected in microvessel density (MVD) may have an important biological and prognostic implication in a broad variety of tumors**.** MVD has been correlated significantly with clinical stage, histologic grade, tumor recurrence and metastatises**.** In addition, until now, there have been relatively few studies linking the up-regulation of VEGF with MVD and severity of the disease in salivary gland carcinomas.

Key works:

(Vascular Endothelial Growth Factor- Salivary Gland Carcinomas- Angiogenesis- Immunohistochemical- Platelet Endo Thelial Cell Adhesion Molecule)

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List of Abbreviation.

MVD	Micro vessel density
VEGF	Vascular endothelial growth factor
VPF	Vascular permeability factor
VEGFR	Vascular endothelial growth factor receptors
PDEGF	Platelet derived endothelial growth factor
TGF-α	Transforming growth factor-alpha
TAF	Tumor angiogenic factors
VPF	Vascular permeability factor
PIGF	Placenta growth factor
KD	Kilo Dalton
Mr	Molecular weight
Flt.l	Fms-Like tyrosin Kinase-1
FLK^{-1}/KDR	Fetal Liver Kinase-1/ Kinase insert domain containing receptor
NRP^{-1}	Neuropilin-1
HIF-1	Hypoxia inducible factor -1
FGF	Fibroblast growth factor

PECAM	Platelet endothelial cell adhesion molecule
ECAM	Endothelial cell adhesion molecule
PNLs	Polymonphous nuclear leukocytes
TIL	Tumor infiltrating lymphocytes
IP	Inositol phosphate
TAM	Tumor associated macrophages
ACC	Acinic cell carcinoma
PLGA	Polymorphous low grade adeno-carcinoma
MEC	Mucoepidermoid carcinoma
SCC	Squamous cell carcinoma
OSCC	Oral squamous cell carcinoma
ACC	Adenoid cystic carcinoma
CCC	Clear cell carcinoma
Udiff	Udifferentiated carcinoma
WHO	World Health Organization
CXPA	Carcinoma ex-pleomorphic adenoma
C.T.	Connective tissue
BV	Blood vessel
HNSCC	Head and neck squamous cell carcinoma

CIS	Carcinoma in situe.
PBS	Phosphate buffered solution
DAB	Diamino benzoic acid
h-MVD	High microvessel density
VWF	Von willebrand factor
LN	Lymph node

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	Table (12): A table showing One way analysis of variance (ANOVA) for VEGF over-expression between different groups (regarding optical density)

Aim of the Study

The aim of the present work is:

(1) To assess the immunohistochemical expression of VEGF and CD31 in salivary gland carcinomas.

(2) To study the possible correlation between VEGF expression and MVD (as measured by the CD31 immunoreactivity) in carcinomas of salivary gland.

(3) To correlate the VEGF and CD31 immunoexpression with different grades of salivary gland carcinomas.

(4) To evaluate the possible diagnostic significance of these angiogenic biomarkers and the use of morphometric analysis in the prediction of the outcome of salivary gland carcinomas.

Conclusions

1- A positive correlation was demonstrated between the anaplastic features of studied salivary gland carcinomas and enhancement of angiogenesis.

2- VEGF act as a multifunctional cytokine in salivary gland carcinomas and up-regulation of VEGF was correlated with both angiogenesis and disease severity thus VEGF play an important role as a tumor marker.

3- The abundant expression of VEGF in higher grade MEC and certain histological subtypes of ACC may promote tumor progression through the induction of angiogenesis. Thus, VEGF might contribute to the aggressive potential of these high grade tumors and may explain the behavior of salivary gland carcinomas.

4- of and the prognosis of patients with salivary gland carcinomas.

5- Angiogenesis is essential for salivary gland carcinoma growth and aggressiveness thus MVD (measured by CD31) may be useful to predict the risk for tumor progression and poor prognosis. Hence it may serve as a useful guide to therapy.

6- A significant positive correlation between the VEGF expression and intra tumoral microvessel density in salivary gland carcinomas were observed supporting the role of VEGF as a mitogenic growth factor for vascular endothelial cells.

7- The inflammatory cells infiltrating the connective tissue stroma of salivary gland carcinoma may participate in the tumor angiogenesis by secreting VEGF.

8- Morphometric image analysis system provides standardization and automation of reading and scoring of immunohistochemical preparations with accurate determination of levels of biomarker expression (VEGF and CD31).

9- A better knowledge of the mechanism involved in dysregulated expression of VEGF and biological consequence of this expression and detection of MVD may ultimately lead to the development of improved strategies for the management of salivary gland carcinomas.

Recommendation

1. The endothelial cells compartment of a tumor mass should receive much attention in the future.
2. Further work is needed to understand the angiogenic mechanism responsible for regional lymph node metastases in salivary gland carcinoma.
3. Further investigation of the biological consequences of VEGF expression in carcinoma ex-pleomorphic adenoma may yield valuable new approaching into the development and growth of this tumor.
4. It will be of particular interest to detect whether VEGF therapies differentially affect regression of new as opposed to mature existing vessels.