Vascular Endothelial Growth Factors, Angiogenesis, and Survival in Human Ileal Enterochromaffin Cell Carcinoids

Background and Aims: Well-differentiated neuro-endocrine ileal carcinoids are composed of serotonin-producing enterochromaffin (EC) cells. Life expectancy is determined by metastatic spread to the liver because medical treatment options are still very limited. Selective inhibition of angiogenesis or lymphangiogenesis might prevent tumour growth and metastatic spread. We examined the role of the vascular endothelial growth factors (VEGFs) A, B, C, D, and their receptors (VEGFRs) 1, 2, 3 in angiogenesis and lymphangiogenesis of ileal EC cell carcinoids with and without liver metastases.

Methods: The expression of various VEGFs and VEGFRs was determined by quantitative real-time RT-PCR in healthy mucosa, primary tumour, lymph node metastases and liver metastases of 25 patients with ileal EC cell carcinoids. Microvessel density (MVD) was determined by CD-31 staining in primary tumours and lymphatic vessel density (LVD) by LYVE-1 staining. VEGF expression levels, MVD, LVD, and patients’ survival time were correlated using logistic regression and Kaplan-Meier survival analysis.

Results: VEGF-A was highly expressed with no difference between normal mucosa and tumours. VEGF-B and -D as well as VEGFR-1 and -2 expression levels were significantly increased in the tumours when compared to normal mucosa. Patients with liver metastasis, however, had a significantly lower expression of the factors A, B, and C
and the receptors 2 and 3. MVD in primary tumours positively correlated with the expression of VEGF ligands and their receptors, except for VEGF-D. LVD did not correlate with any VEGF ligand or receptor. Interestingly, low expression levels of VEGF-B were associated with poor survival.

Conclusion: Patients with more aggressive metastatic spreading had relatively decreased expression levels of VEGF ligands and receptors. Thus, anti-angiogenic therapy may not be a suitable target in metastatic ileal EC cell carcinoids.

Stichworte: Enterochromaffin cell; Carcinoid; Vascular endothelial growth factor; Angiogenesis

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