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Clinicopathological Study of Angiogenesis in Gastric Cancer

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Short Review

Many models of multistage tumorigenesis have been proposed to explain the conversion of a normal cell into a neoplastic one. In addition to all genetic and epigenetic changes, angiogenesis is necessary for the growth and expansion of tumors [1]. Besides, no neoplastic lesion could not exceed the size of 2 mm if not supported by a rich vascular network [2]. Angiogenesis is a basic requirement for nutrition and oxygenation of tumor cells. It is necessary for the cellular proliferation and metastatic spread of solid neoplasm including gastric carcinoma [3].

Angiogenesis evolves through a complex cross talking process of pro-angiogenic and anti-angiogenic signals that are generated from cancer, endothelial and stromal cells [4]. Among molecules implicated in angiogenesis, the effectors vascular endothelial growth factor A (VEGF-A), through its specific receptors (VEGFR-1 and VEGFR-2), regulate physiological as well as pathological angiogenesis. VEGF, through these receptors, is not only a paracrine stimulator of angiogenesis but an autocrine one, as well. The effects of VEGF on tumour growth include stimulation of neovascularization, increased vessel permeability, increased intra-tumoral pressure and inhibition of maturation of dendritic cells from haemopoietic progenitors, altering the host immune response [5-11].

The demonstration of angiogenesis could be difficult, and for many years, the only method was represented by the counting of blood vessels in the tumor area, well known as MicroVessel Density (MVD), performed on specimens stained for an endothelial marker, such as CD34 and CD105. Recently, several studies have indicated that CD105 is a more specific and sensitive endothelial cell marker, to count the intratumor MVD than other commonly used pan endothelial antibodies in cancers of the cervix, colon, endometrium, and breast [12-22].

Angiogenesis has been proposed as a prognostic marker in a variety of human malignancies-including colon, lung, breast, renal, glioblastoma, the female genital tract, prostate, melanoma, and other cancer. Several previous studies showed expression of VEGF-A in tumor cells of gastric carcinomas and correlations of VEGF-A with the micro vessel density (MVD). However, there are contradictory results as far as it concerns the prognostic value of VEGF-A, its receptors and MVD. However, in the case of gastric cancer, vessels in different tumor subtypes have been counted based on immunostaining with different antibodies marking endothelial cells. Then, prognostic values determined using different cut-off values. The results from the various studies showed a significant correlation with patient survival [23-25] vs. None [1]. Moreover, VEGF was widely used in cases with GC with contradictory results.

Therefore, in the present study we analyzed 145 cases of gastric adenocarcinomas, selected from the archive of the Department of Pathology of the University of Ioannina, for 1) the immunohistochemical expression of VEGF-A, VEGFR-1 and VEGFR-2 proteins and 2) the MVD with the immunohistochemical markers CD34 and CD105 (MVD-CD34 and MVD-CD105) to gain further insight on the pathogenesis of this tumor. Moreover, the results were correlated to clinicopathological parameters and clinical outcome of the patients. The program SPSS for Windows Release 17 was used for statistical analysis.

Expression of VEGF-A, VEGFR-1 and VEGFR-2 proteins in tumor cells was detected in 123/145 (84.8%), 127/144 (88.2%) and 105/143 (73.4%) cases, respectively. The MVD-CD34 and the MVD-CD105 were 64.99 and 23.56, respectively. Positive correlations were found between VEGF-A and VEGFR-1 ($p = 0.002$), VEGF-A and VEGFR-2 ($p = 0.046$), VEGF-A and MVD-CD105 ($p = 0.024$), MVD-CD105 and MVD-CD34 ($p < 0.001$), as well as VEGFR-1 and VEGFR-2 ($p < 0.001$).

Analysis of protein expressions and MVD of the tumor with clinicopathological parameters showed that, VEGF-A expression was correlated with the clinical stage ($p = 0.007$), VEGFR-1 expression with the histological grade and histological type of the tumor ($p = 0.037$ and $p = 0.002$, respectively), VEGFR-2 expression with the vascular invasion ($p = 0.045$). In addition, survival curve for VEGR-2 showed that high expression of VEGFR-2 was correlated with worse prognosis, suggesting that VEGFR-2 may be an independent predictor factor of unfavourable clinical outcome.

The results of the present study suggest an important role of angiogenesis in the pathogenesis of gastric carcinoma. In accordance with numerous others studies showed that a main source of VEGF is the cancer cells. As far as it concerns the expression levels of the two receptors, VEGFR-1 and VEGFR-2, they are also found to be expressed in tumor cells of gastric carcinomas, confirming the results of previous studies [26-32]. The two receptors of VEGF have been also found to be expressed in stromatic vessels of the tumor [33]. Expression of pro-angiogenic proteins VEGF-A, VEGFR-1 and VEGFR-2 by tumor cells is a common event. VEGF-A produced

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by tumour cell may act as paracrine and autocrine growth factor in gastric adenocarcinoma by promoting angiogenesis and tumor cell proliferation through its receptors. In addition, it was found a positive correlation between the two receptors of VEGF, VEGFR-1 and VEGFR-2. The last finding may support a possible mechanism of heterodimerization between the two receptors. Under certain circumstances, VEGFR-1 may heterodimerize with VEGFR-2 leading to transactivation of VEGFR-2 [9], positively regulate angiogenesis. In contrast, when VEGFR-1 is activated by a ligand that only causes receptor homodimerization and results in no cross-talk with VEGFR-2, VEGFR-1 is not capable of promoting biological responses such as cell migration, cell proliferation and intercellular calcium release. Thus, the ability of VEGFR-1 to propagate a productive signal and to stimulate biological responses either negative or positive is limited to its ability to heterodimerize with VEGFR-2 [9-11]. Moreover, protein expression of VEGFR-2 is independent predictor factors of unfavorable clinical outcome in gastric carcinomas.

Correlation of VEGF with the MVD in gastric cancer is a common finding in the literature. The present study also found a significant correlation between VEGF expression of tumor cells and MVD-CD105 of the tumor, confirming that tumor cells are the main source of VEGF in gastric carcinomas and showing that neoangiogenesis is a common phenomenon in VEGF-positive tumors. Our results are in agreement with Nikiteas, et al., as high expression of VEGF is accompanied by high expression of CD105 [34,35].

In our study, VEGF was also correlated with the stage of the disease which is in accordance with previous studies [24], but it was not proved to be a prognostic marker for gastric cancer, like in other studies [1]. Furthermore, we do not find any correlation of VEGF expression and vessel invasion, such an absence of correlation was also observed by Fondevila, et al. [36], while others disagree with this finding [37,38].

There are not many studies that correlate the VEGFRs with survival or other clinicopathological parameters in gastric cancer. In the present study, VEGF was correlated with the first receptor, but not the second one, which has been described again [28]. Moreover, VEGFR-1 was correlated with the grade of the tumor, which is not met again in another study, while VEGFR-2 with MVD-CD34, vessel invasion and survival.

In accordance with Ding S, et al. [35], the MVD-CD34 is almost always higher that MVD-CD105. This is reasonable, as anti-CD34 mAbs stains old as well as newly formed vessels, while anti-CD105 mAb, specifically reacts with proliferating endothelial cells in tissue undergoing active angiogenesis, including tumor tissues, whereas it would stain no or weakly with blood vessels within normal tissues, thus suggesting the hypothesis that the anti-CD105 mAb could be a more specific marker in evaluation of tumor angiogenesis. It was also found a significant positive correlation between the micro vessel counts obtained with the two mAbs CD34 and CD105.

Recent acquisitions in the field of diagnosis and treatment induced the improvement of prognosis in patients with superficial gastric cancer, but in advanced stages of the disease, the rate of mortality was not significantly changed. The rate of mortality is mainly due to the tumour spread by both lymphatic and blood vessel route, and finally leads to systemic metastases. Today, in the era of launch of clinical application of antiangiogenic therapies, any clinical research that improves our understanding on angiogenesis in specific tumor types is highly warranted. Based on first positive clinical results it is now believed that rational combining of cytotoxic and antiangiogenic therapies can yield maximal therapeutic benefit in a range of malignancies.

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