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SHORT COMMUNICATION

The clinical implications of platelet derived growth factor B, vascular endothelial growth factor and basic fibroblast growth factor in colorectal cancer

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Summary

Colorectal cancer (CRC) remains a major health problem worldwide. Angiogenesis is a key process for tumor growth and metastasis. The conversion of tumor cells to an angiogenic phenotype involves the change in the balance of angiogenic growth factors and angiogenesis inhibitors.

In our study we evaluated by qRT-PCR the level of expression of 3 growth factors involved in angiogenesis: platelet derived growth factor-B (PDGFb), vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (bFGF) in patients with different stages of colon cancer. Our results showed the level of VEGF increased on all tumor without difference, statistically significant according with tumor stage whereas the others the levels of bFGF and PDGF were higher, statistically significant, on tumor classified stage B compared with stage C. The early implication of these molecules in colon carcinogenesis justifies the development of new biologic individualized therapies.

Key words: colorectal cancer, qRT-PCR, PDGFb, VEGF, bFGF

Introduction

CRC is a major health problem, being the third leading cause of morbidity and mortality in Western countries. The survival of patients with CRC remains poor with only 55% of patients being alive 5 years after diagnosis, due to the delayed diagnosis as well as to the lack of well characterized markers for prognosis [1]. The treatment of patients with CRC relies on a number of clinical and pathological prognostic factors such as tumor stage, number of metastatic lymph nodes, degree of differentiation, and age at diagnosis. However, these variables provide limited help in predicting the diversity of tumor biological behavior, creating a need to identify additional prognostic factors in order to improve the management of CRC. On the other hand, the explosion of biologic therapies targeting different molecular pathways justifies the research in this area.

Angiogenesis is a critical process for tumor growth and metastasis which involves changes in the balance between different angiogenic growth factors and their inhibitors [2].

Methods

This study was conducted to determine the clinical value as prognostic or therapeutic targets in CRC of 3 growth factors PDGFb, VEGF, and bFGF) known to be involved in different steps of angiogenesis.

Approval for this study was obtained from the Institutional Ethics Committee, and all study subjects provided written informed consent.

Thirty-three patients with operated CRC at the Surgical Clinic 1 were enrolled. Sixteen patients had stage Dukes B CRC, 11 Dukes C and 6 Dukes D [3,4]. Using

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the qRT-PCR method we analyzed the level of expression of PDGFb, VEGF and bFGF on tumor samples as well as of the surrounding normal tissue and in further analysis we used the average of fold change (fc) (the ratio of the final value to the initial value) of the investigated genes. Statistical analysis was made using the SPSS (Statistical Package for the Social Sciences). Student's *t*-test was used for comparisons between disease stages (Dukes B, C, and D). A p-value < 0.05 was considered statistically significant.

Results

Our results showed increased VEGF levels in all stages (Dukes B: 1.331 fc ± 0.815 standard deviation (SD); Dukes C: 1.099 fc ± 0.508 SD; Dukes D: 1.303 ± 0.47 SD), but without significant differences (Dukes B vs. Dukes C p=0.761; Dukes B vs. Dukes D p=0.949, Dukes C vs. Dukes D p=0.854). Regarding the other evaluated molecules, the levels of bFGF and PDGFb were significantly higher in stage B vs. C tumors (p=0.049, p=0.031, respectively). The average of fc for bFGF was 0.854 ± 0.439 SD in Dukes B tumors, 0.512 ± 0.251 SD in Dukes C, and 0.397 ± 0.287 SD in Dukes D. The values for PDGFb were 1.519 fc ± 0.686 SD in Dukes B, 0.978 fc ± 0.4334 SD in Dukes C and 1.269 fc ± 0.655 SD in Dukes D.

Discussion

Previous studies have shown that VEGF is a key component in colon tumorigenesis, its high expression being correlated with poor prognosis [5]. In the last years, better understanding of tumor biology had led to the development of some biologic therapies, like bevacizumab which targets VEGF. This agent has being approved for the treatment of metastatic CRC since 2004 [6]. In our study the high level of VEGF even in tumors classified as stage B shows the early implication of this growth factor in CRC development and justifies the large numbers of studies with bevacizumab in the adjuvant treatment of colon cancer [7].

bFGF and its receptors are involved in different biological functions including cell proliferation, differentiation, migration and survival. In CRC bFGF has been reported to be upregulated, thus being considered as a potential therapeutic target [8]. In our study the higher level of bFGF in Dukes B cases compared with Dukes C and D could be explained by its early implication in colorectal carcinogenesis. This result is in concordance with the results reported by Tassi et al. in 2006, who proposed the detection of bFGF in serum as a screening method for early detection of colon premalignant lesions [9].

The role of PDGF in tumor angiogenesis had been demonstrated in several studies, its overexpression being correlated with microvascular density and poor survival in many colorectal tumors [10,11]. Regarding the implication of PDGF in colorectal carcinogenesis the results are not very clear. The higher level of PDGF in Dukes B compared with those of Dukes C or D obtained in our study is in concordance with those reported by other authors who suggest the early implication of PDGFb in colon cancer development [12].

By evaluating the levels of PDGFb, VEGF and bFGF in different stages of CRC our study brings new information regarding the molecular pathways involved in colorectal carcinogenesis. The high level of these growth factors even in Dukes B stage could be explained by their early implication in CRC development and could justify the search for development of new biologic therapies targeting these molecules.

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