Will the Stroma-derived Factor-1 α (CXCL12)/CXCR4 Pathway Become a Major Concern for Advanced Colorectal Cancer?

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The chemokine stroma-derived factor (SDF-1 α /CXCL12) is a homeostatic chemokine. The major function of this chemokine is to regulate hematopoietic cell trafficking and secondary lymphoid tissue architecture [1]. SDF-1 α is also widely expressed in various organs. Including the heart, liver, brain, kidney, skeletal muscle, and lymphoid organs, and it plays multiple roles in tumor pathogenesis. SDF-1 α has been demonstrated to promote tumor growth, enhance tumor angiogenesis, participate in tumor metastasis, and contribute to immunosuppressive networks within the tumor microenvironment. SDF-1 α expression is reported in ovarian cancer, breast cancer [2], colorectal cancer, pancreatic cancer, prostate cancer, thyroid cancer, and many other human tumors.

SDF-1 α can increase the invasiveness and the migration of cancer cells, and its levels are correlated with node involvement and long-term survival in patients with breast cancer. SDF-1 may, therefore, have potential value in assessing clinical outcomes of patients with breast cancer [3]. Although colorectal cancer (CRC) tissues contain SDF-1 α -positive stromal cells, immunohistochemistry clearly demonstrated that the cancerous cells in more than 50% of the CRC samples examined had much stronger expression of SDF-1 α than their neighboring normal colonic epithelial cells. Accordingly, as with CXCR4 overexpression, the SDF-1 α /CXCR4 pathway appears to play important roles in the progression of CRC [4].

In this study, the authors merely measured the SDF-1 α expression level in the normal colonic mucosa and in colorectal

cancer tissue. If this study had included the SDF-1 α specific receptor CXCR4 expression level, the authors would have obtained better results. Nevertheless, the results are quite impressive. SDF-1 α expression was highly correlated with pericolic lymph-node metastasis, distant metastasis, tumor-node-metastasis stage and lymphovascular invasion. Strong SDF-1 α expression was inversely related with patients' survival, suggesting suggest SDF-1 α could be a prognostic factor. Further study evaluating the distinctive value of SDF-1 α expression in clinical practice may be warranted.

According to the literature, it is evident that manipulation of this pathway represents a new strategy for cancer treatment. CXCR4 antagonists, such as Plerixafor (AMD3100) and T140 analogues (TN14003/BKT140), and blocking antibodies toward CXCR4 or SDF-1 α are being investigated in various cancer settings. In an *in vitro* study using a colorectal cancer cell line, results indicate that a CXCR4-antagonistic therapy might prevent tumor cell dissemination and metastasis in CRC patients, consequently improving survival [5]. Of course, we need to bear in mind that although targeting CXCR4/CXCL12 is an attractive option in treating human tumors, it is certain that to gain effective, reliable, and consistent clinical efficacy, a definitive combinatorial therapeutic regimen should be found.

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