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Growth factor gene polymorphisms in colorectal cancer and establishment of a novel method to study tumor cell - host cell interaction in vitro

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INTRODUCTION: In the presented thesis two major topics were covered: 1. Colorectal cancers have gained little attention in growth factor gene polymorphisms so far. No study has so far focused on the frequency of growth factor gene polymorphisms among cancer patients with an anastomotic leakage. 2. Few researchers have used primary hepatocytes to study their interaction with tumor cells and fibroblasts. FGF-2-deficient hepatocytes have so far not been used to investigate the role of FGF-2 deficiency on colorectal tumor cells.

MATERIALS AND METHODS: PCR-RFLP was used to study the frequency of EGF, TGF- β 1 and VEGF gene polymorphisms in colorectal cancer patients, healthy controls and patients with colorectal cancer which have developed postoperative anastomotic leakage.

To investigate tumor-host interaction, the FALCONTM Cell Culture Insert System were used: here Colon-26 cells were cultured spatially separated from the other cells in the lower well in inserts. H&E-staining and BrdU incorporation into DNA were used to observe how coculture with primary hepatocytes and fibroblasts influence the migration and proliferation cancer cells. EGF and VEGF concentrations in the coculture system were detected by ELISA.

RESULTS: Part 1: 1.The EGF 61*G/G genotype and G alleles are significantly associated with colorectal cancer. 2.Colorectal cancer patients with a TGF- β 1 C/C and T/C genotype are more often found in the group with an anastomotic leakage than those with a T/T genotype at position -509. 3.In the anastomotic leakage group T/T and T/C genotypes are more often found than those with a C/C genotype at position VEGF 936. **Part 2:** 1.Hepatocytes promote cancer cell migration and proliferation and produce much more EGF. 2.The addition of fibroblasts decreased the proliferation of Colon-26 cells, but did not change the migration of Colon-26 cells. 3.When Colon-26 were cocultured with other Colon-26 cells, the migration of Colon-26 and the production of VEGF was increased as compared to Colon-26 cells alone. 4.FGF-2-depletion – either by coculture with FGF-2(-/-)-hepatocytes or by inhibition of the FGFR in FGF-2(+/-)-hepatocytes significantly increased the migration ability of Colon-26 cells as compared to FGF-2(+/-)-hepatocytes. EGF concentration was also increased.

CONCLUSION: Part 1: The EGF 61*G/G genotype and the G allele were associated with colorectal cancer. TGF- β 1-509*C/C and T/C genotypes or VEGF 936*T/T and T/C genotypes are the genotypes associated with anastomotic leakage after resection for colorectal cancer. **Part 2:** Hepatocytes act as stimulator to migration and proliferation of cancer cells. Here EGF which has been found to be secreted into the cell culture supernatant by hepatocytes is likely to play a key role. Fibroblasts act mainly the suppressors of the proliferation of cancer cells. Colon-26 cells can autostimulate their migration probably by secreting soluble factors such as VEGF. FGF-2-deficient hepatocytes and FGF-2(+/-)- hepatocytes after inhibition of the FGF-Receptors can increase the migration of Colon-26 cells. Therefore, the factors responsible for stimulating the migration of cancer cells are highly likely to be functional substitutes of FGF-2. The coculture system is a useful tool to study tumor-cell-host-cells interaction in vitro.