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Meeting abstract

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Increased migration of colorectal cancer cells induced by TNF-alpha-treated stromal fibroblasts from human liver metastases

L Müller*[1], J Schumacher[1], B Temel[1], L von Seggern[2], S Tiwari[1], H Kalthoff[1] and DC Bröring[1]

Address: [1]University Hospital Schleswig-Holstein, Campus Kiel, Molecular Oncology, General and Thoracic Surgery, Kiel, Germany and [2]University Hospital Hamburg-Eppendorf, Department of Hepatobiliary Surgery and Solid Organ Transplantation, Hamburg, Germany

* Corresponding author

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Background

Inflammation plays key roles in invasion, angiogenesis and metastasis. Given the multifaceted roles of tumor-necrosis-factor-alpha (TNF-alpha) in these processes, its effects on the stromal fibroblasts that constitute the desmoplastic stroma in colorectal metastases are of interest.

Methods

Primary cultures of cancer-associated stromal fibroblasts (CAFs) were generated from human tissues harvested during hepatic resection. TNF-alpha expression in tissue was examined by immunohistochemistry. Activation of nuclear-factor-kappaB (NF-kappaB) activity was measured by gel mobility shift assay. The effect of TNF-alpha on migratory capacity and gene expression of CAFs was tested in presence/absence of parthenolide, an herbal inhibitor of NF-kappaB. Gene expression in tissues and cell cultures was examined by Northern blot analysis. Protein measurements in the cell culture supernatant were performed with cytometric capture beads.

Results

The colorectal metastases display immunoreactivity for TNF-alpha in tumor cells and leukocyte cells, whereas stromal fibroblasts are negative. To investigate transcriptional effects of TNF-alpha on CAFs, we analysed the expression of potential inflammatory target genes that are involved in tumor progression. CAFs that were exposed for 24 hours to TNF-alpha (10 ng/ml) showed a dramatic increased expression of interleukin-6 (IL-6), monocyte-chemotactic protein-1 (MCP-1) and intercellular cell adhesion molecule-1 (ICAM-1). Increasing concentrations of parthenolide (1, 5, 10 microM) dose-dependently inhibited the activation of NF-kappaB by TNF-alpha exposure for 30 min, as well as the TNF-alpha effect on IL-6 and MCP-1 mRNA and protein expression. Exposure of CAFs with TNF-alpha significantly increased the chemotaxis of HT29 colon carcinoma cells towards these cells in a coculture migration chamber system. This migratory effect activated by paracrine TNF-alpha was inhibited by co-incubation with parthenolide.

Conclusion

CAFs are an important target for inflammatory signaling mediated by TNF-alpha/NF-kappaB in the context of tumor-stroma interaction and may play an important role in metastasis progression. Our results suggest that the inhibition of NF-kappaB activation may be an interesting strategy in antitumor therapy targeting hepatic colorectal carcinoma metastatis.