Enhanced activity of meprin-?, a pro-migratory and pro-angiogenic protease, in colorectal cancer.

Meprin-? is a metalloprotease overexpressed in cancer cells, leading to the accumulation of this protease in a subset of colorectal tumors. The impact of increased meprin-? levels on tumor progression is not known. We investigated the effect of this protease on cell migration and angiogenesis in vitro and studied the expression of meprin-? mRNA, protein and proteolytic activity in primary tumors at progressive stages and in liver metastases of patients with colorectal cancer, as well as inhibitory activity towards meprin-? in sera of cancer patient as compared to healthy controls. We found that the hepatocyte growth factor (HGF)-induced migratory response of meprin-transfected epithelial cells was increased compared to wild-type cells in the presence of plasminogen, and that the angiogenic response in organ-cultured rat aortic explants was enhanced in the presence of exogenous human meprin-?. In patients, meprin-? mRNA was expressed in colonic adenomas, primary tumors UICC (International Union Against Cancer) stage I, II, III and IV, as well as in liver metastases. In contrast, the corresponding protein accumulated only in primary tumors and liver metastases, but not in adenomas. However, liver metastases lacked meprin-? activity despite increased expression of the corresponding protein, which correlated with inefficient zymogen.
activation. Sera from cancer patients exhibited reduced meprin-β inhibition compared to healthy controls. In conclusion, meprin-β activity is regulated differently in primary tumors and metastases, leading to high proteolytic activity in primary tumors and low activity in liver metastases. By virtue of its pro-migratory and pro-angiogenic activity, meprin-β may promote tumor progression in colorectal cancer.