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The Search for a Novel Diagnostic Marker or Therapeutic Target for Gastrointestinal Cancer

Hepatocellular and gastric carcinomas are among the most frequent gastrointestinal tract cancers, and have an exceedingly poor prognosis. Decreasing the high incidence and mortality of hepatogastrointestinal cancers will require earlier diagnosis of these cancers, as well as a wider range of therapeutic alternatives. In this study, the identification of new markers or therapeutic targets that may be able to improve the diagnosis and treatment of hepatocellular and gastric carcinomas was approached from two different directions.

For the identification of novel genes relevant for gastrointestinal tumour biology, differential display was used to compare non-tumour tissues and HCC. A novel candidate gene that was up-regulated in HCC was identified as GSDML, a novel member of the cancer-associated GSDMDC protein family. GSDML is expressed in both tumour and non-lesional tissues, but the expression profile of GSDML splicing variants may be altered, and a larger tissue- and/or tumour-specific analysis of the expression of the GSDML gene and transcripts, as well as more information about the actual protein sequence and structure is required before its role in tumour biology can be clarified.

Using a different approach, the putative role of multifunctional membrane proteases during the development and progression of gastrointestinal cancers was evaluated. NEP, APN, DPIV, ACE, ADAM9, ADAM12, and ADAM15 are ectopeptidases known to be important for tumour growth and dissemination, which was here also observed for liver and gastric carcinomas. Further investigations, based on the immunohistochemical results described here for HCC, have shown that the expression patterns of NEP and APN can be applied as diagnostic markers for HCC, and in combination, have proved useful in diagnostic pathology to differentiate HCCs from non-HCCs metastatic to the liver (Röcken et al 2005). Additionally, the low expression of ACE in focal nodular hyperplasia can assist diagnosis of these lesions (Gräntzdörffer et al 2004). All the investigated ectopeptidases were up-regulated in gastric cancer, and expressed in intestinal metaplasia and lymph node metastases. Gastric cancer cell proliferation was retarded by inhibition of NEP, APN, and ACE. Inhibitors of these ectopeptidases are already established for treatment of, for example, hypertension, and may well provide future therapeutic options for the treatment of gastric cancer. The ADAMs also influence gastric cancer cell proliferation. However, although the ADAMs are up-regulated in gastric cancers, their expression pattern is not tumour-specific enough to be practical for diagnosis, or as therapeutic targets. Since the investigated ADAMs are almost ubiquitously expressed, the GPCR stimulation of ADAMs-mediated growth factor shedding and subsequent EGFR transactivation (Wallasch et al 2004) makes the regulation of GPCR ligands by the ectopeptidases increasingly interesting.

Ang II is generated by ACE-mediated cleavage of Ang I, and its GPCRs, AT1 and AT2 are involved in EGFR transactivation. ACE and AT1 have previously been shown to be biologically significant for the development and progression of gastric cancer. The association of ACE with the development of early gastric cancer (Ebert et al 2005) may reflect the upregulation of ACE in inflammatory conditions of gastritis and ulcers observed here, and the subsequent increase of proinflammatory Ang II. Indeed, ACE expression is regulated by cytokines, possibly also in the lymph nodes. ACE and AT1 are strongly associated with tumour staging and lymph node metastasis, functions not usually associated with the local angiotensin II system (Röcken et al 2005). Here, it has been shown that the involvement of the local angiotensin II system in metastasis and invasion is not limited to the generally accepted promotion of angiogenesis, but the expression of ACE, AT1, and AT2 by the tumour cells directly facilitates invasion, and thereby lymphatic metastasis. This invasion can be attenuated by ACE inhibitors, and AT1 and AT2 antagonists, and inhibitors of local Ang II system components might prove to be useful for the treatment of gastric cancer, particularly by preventing or reducing nodal spread in high risk patient groups.