

## ADAM and EMMPRIN: a promising couple for more prognostic precision in patients with gastric cancer

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Gastric cancer is still a highly problematic tumor entity. Even in early stages, individual clinical prognosis can be rather poor, and limited response to neo-adjuvant and adjuvant therapeutics still remains to be a considerable problem. For these and other instances, powerful molecular markers able to more precisely predict the individual risk for tumor recurrence and metastasis for the individual, as well as the probability to respond to certain types of therapeutics are still desperately needed.

Already more than a decade ago, different research groups including our own have implicated tumor-associated proteases and especially the urokinase-type plasminogen activator (u-PA) system as promising candidates for the development of independent prognostic markers in gastric cancer (1-4), and since then, more and more highly interesting proteinases, their molecular actions and interactions and their potential for diagnostic and therapeutic purposes have been defined. EMMPRIN (Extracellular Matrix Metalloproteinase Inducer) has been shown to be highly expressed especially by tumor cells, but also in the stroma (5) in several cancer entities, and has been demonstrated to support several aspects of tumor progression and metastasis by, for example, promoting the degradation of extracellular matrix components, at least in part by inducing matrix metalloproteinases and also the uPA-system (6-10). Recent reports suggest that a significant increase of EMMPRIN-expression in tumor cells might at least in part be due to epidermal growth factor receptor-related signaling (11), and interestingly, ADAM17, a member of the A Disintegrin and Metalloproteinase

(ADAM)-family, has been shown to regulate activity of epidermal growth factor receptor, at least in part due to its ability to regulate cleavage and activity of cell membrane-anchored receptor ligands.

Based on this background, in the recent issue of *Annals of Surgery* (11), SHOU and colleagues conducted a highly interesting retrospective study at 436 out of 1,200 consecutive gastric cancer patients who underwent gastrectomy between 1998 and 2004. At resected gastric cancer - and corresponding normal tissue samples established on tissue microarrays, they immunohistochemically investigated the expression of ADAM17 and EMMPRIN and their association with clinical prognostic parameters. A high expression of ADAM17 was found in around 36% of resected tumor tissue specimens in contrast to corresponding normal tissues, whereas a similarly high percentage of around 37% of the tumors revealed a high expression of EMMPRIN. There was a highly significant correlation between the expression of ADAM17 and EMMPRIN in the gastric cancer tissues investigated ( $P < 0.01$ ). A high expression of ADAM17 as well as of EMMPRIN was significantly associated with advanced tumor stages, especially invasion of lymph nodes and distant metastasis. Also, a high expression of ADAM17 and also EMMPRIN was significantly associated with poorer overall survival. Both ADAM17 and also EMMPRIN revealed to be independent prognostic parameters in a multivariate Cox proportional hazard analysis which considered all relevant clinical prognostic parameters known for gastric cancer to date.

An especially important result from my point of view is that stage II gastric cancer patients with low ADAM17 expression showed significantly longer mean survival than stage I patients with high expression of ADAM17. This result could become of special importance since this suggests that ADAM17, after appropriate future validation, could become a biomarker that can discriminate patients with early stage gastric cancer that, from a biological point of view, are high at risk for later tumor recurrence or progression in contrast to patients with biologically more uncritical early disease. On the other hand, stage II patients with low ADAM17 expression might be treated less aggressively than the ones with high expression. If validated in further studies, this should have clinical consequences in terms of, e.g., changing clinical follow-up protocols for such patients and/or considering more individualized therapeutic concepts in addition to curative tumor surgery, e.g., within adjuvant therapy protocols. Another interesting aspect which is discussed by the authors in their article is that ADAM17 has been suggested to be able to predict certain therapeutic outcomes. For example, as the authors mention, ADAM17 might be able to indicate patients with a high probability of resistance to therapeutic regimen directed either against EGFR or c-erbB2. This has been indicated in studies at other tumor entities such as specifically breast cancer. However, since it is known that a considerable percentage of gastric cancers express immunohistochemically easily detectable c-erbB2 (12-17), ADAM17 might also become an important biomarker to predict patients able to respond to HER2-directed therapies in gastric cancer. Suchlike speculations are based on recent studies suggesting that, for example, ADAM-inhibitors are able to inhibit the process of activation of erbB-ligands, leading to an inhibition of gefitinib-resistant HER3 signaling and enhancing the ability of compounds such as gefitinib to inhibit EGFR-initiated signaling (18). Furthermore, since, in their present paper, SHOU *et al.* found significant correlations between the expression of ADAM17 and EMMPRIN and since it has been described that two EGFR-ligands have been reported to induce EMMPRIN expression (19), the authors speculate that their data on 436 gastric cancer patients support the hypothesis that ADAM17 might enhance expression of EMMPRIN via an activation of expression of the epidermal growth factor receptor.

Certainly, as the authors also rightfully acknowledge, the present study by SHOU *et al.* which is retrospective needs to be further and independently confirmed by

large prospective clinical studies, not only confirming the independent prognostic relevance of ADAM17 and EMMPRIN expression in gastric cancer and deeper exploring their ability to predict therapy response, but also contributing to a higher level of international standardization of ADAM17 and EMMPRIN measurement and the clinically relevant definition of ADAM17 and/or EMMPRIN positivity. Nevertheless, besides previously defined tumor-associated proteinase systems such as the u-PAR/PAI1-system, ADAM17 and also EMMPRIN might be promising and prognostically relevant molecular markers for the initiation of further studies. The study also supports attempts to proceed with the development of targeted therapies against ADAM17 and/or EMMPRIN in the search for novel tools to combat gastric cancer.

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