

TIMP-1: a Strong Player in Colorectal Cancer

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In this issue of the *J Gastrointest Liver Dis*, Ionescu et al evaluate, in a pilot study, the potential prognostic impact of a panel of six genes (*CDH1*, *SMAD3*, *TGFβ1*, *ICAM-1*, *TIMP-1* and *MUC12*) in colorectal cancer (CRC) patients [1]. These genes have been studied by RT-qPCR in normal and CRC tumor tissues, and the relative gene expression values have been correlated with clinical, histological and pathological parameters. The authors found that the tissue inhibitor of matrix metalloproteinase type-1 (TIMP-1) and SMAD3 showed a statistically significant correlation. They suggest that TIMP-1 and SMAD3 might have a potential prognostic impact in CRC. This is an important observation for several reasons.

Colorectal cancer is the second most common newly diagnosed cancer and the second most common cause of cancer death in the Western world and Central-Eastern Europe with an enormous health and economic burden. Despite the significant advances in diagnosis and treatment, more than half of CRC patients are still diagnosed only in advanced stages. Although different clinico-pathological prognostic factors have been revealed and the impact in predicting survival of classical tumor staging (as reflected in Dukes or TNM classification) has been widely acknowledged, it would be very

useful for clinicians to have additional preoperative prognostic indicators available, in order to better identify patients who really require adjuvant or neoadjuvant treatment. Thus, there is a need for additional tumor-associated antigens at the time of clinical presentation, eligible as prognostic markers in CRC [2-4].

Proteolytic enzymes are important in the breakdown and reconstitution of basement membrane and extracellular matrix components (ECM) in tissue remodelling, wound repair, inflammatory responses, angiogenesis, destructive diseases, as well as CRC invasion and metastasis [5, 6]. Matrix metalloproteinases (MMPs) consist of a family of zinc-dependent endopeptidases implicated in the degradation and remodelling of ECM components. Their activity is crucial in CRC growth and the multistep processes of invasion, metastasis and angiogenesis. MMPs are controlled by endogenous tissue specific inhibitors, called tissue inhibitors of metalloproteinases (TIMPs). The imbalance between MMPs and TIMPs is an essential step in the development of CRC and is of critical impact in early events of tumor progression. TIMPs might display a dual influence on CRC progression and metastasis: on the one hand they directly regulate and inhibit MMPs and on the other hand they inhibit the apoptosis of tumor cells, influence angiogenesis and finally, facilitate tumor growth and metastasis [7-9]. Four TIMPs have been characterized in humans (TIMP-1, -2, -3 and TIMP-4). TIMP-1 inhibits angiogenesis either directly or indirectly via restraining MMP-9-mediated release of vascular endothelial growth factor (VEGF) from matrix [10].

Several studies have demonstrated an increased expression of MMPs and TIMPs in CRC. It has also been shown that high preoperative serum or plasma MMPs and TIMP-1 antigen levels are strongly predictive factors for a poor prognosis in patients with CRC and their assessment might be useful for the identification of patients with a higher risk for cancer recurrence. We and others have also proposed that MMPs and TIMP-1 might play a part not only in CRC invasion and initiation of metastasis but also in colorectal carcinogenesis from colorectal adenomas [11-15].

Strong evidence supports the concept of the use of MMPs as targets for cancer therapy. Several therapeutic MMP inhibitors (MMPIs) have been developed to target MMPs and were tested in phase III clinical trials in humans. In contrast to their promising effect in preclinical models, most of these

agents unfortunately failed in clinical trials. The use of broad-spectrum MMPs may lead to undesired adverse events because of the wide range of MMPs that are inhibited [16, 17]. The development of a new generation of selective inhibitors highly specific for certain MMPs with improved pharmacokinetic properties is a major challenge for the near future. Their use in combination with classical chemotherapeutic strategies might have the potential to become supplementary oncological treatment modalities [18-22].

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