Colorectal Cancer – Evaluation of MMP as a prognostic marker and a model for peritoneal response

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs Universitet kommer offentligen försvaras i Stora aulan, Centralkliniken, Sahlgrenska Universitetssjukhuset/Östra, Diagnosvägen 11, Göteborg, fredagen den 14 juni 2019, klockan 09:00.

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I. **Jonsson A**, Hjalmarsson C, Falk P, Ivarsson ML. Levels of matrix metalloproteinases differs in plasma and serum – aspects regarding analysis of biological markers in cancer. Br J Cancer. 2016 Sep 6;115(6):703-706.

II. **Jonsson A**, Hjalmarsson C, Falk P, Ivarsson ML. Stability of matrix metalloproteinase-9 as biological marker in colorectal cancer. Med Oncol. 2018 Mar 9;35(4):50

III. **Jonsson A**, Falk P, Angenete E, Hjalmarsson C, Ivarsson ML. Plasma MMP-1 expression as a prognostic factor in colorectal cancer. Submitted 2019.

IV. Falk P, **Jonsson A**, Swartling T, Ivarsson ML. Colorectal Cancer Cells Adhere to Traumatized Peritoneal Tissue in Clusters, An Experimental Study. J Inves Surg. 2018 Aug 31(4):349-356.

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Colorectal Cancer – Evaluation of MMP as a prognostic marker and a model for peritoneal response

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Abstract

Background: There are about 6600 patients diagnosed with colorectal cancer in Sweden each year. Survival rates vary with cancer stage at diagnosis. The main treatment is surgery together with, in some cases, oncological treatment. Matrix metalloproteinases (MMP) are deeply involved in the growth and spread of colorectal cancer tumours. The aim of this thesis was to validate the methodology of sample storing and the measurement of MMP concentrations and evaluating the prognostic value of MMP in colorectal cancer survival. Furthermore, an experimental model for studying human peritoneal surface, *ex vivo*, was validated. **Methods***: Study I* – Blood samples were obtained from 65 patients and analysed for MMP in citrated plasma and serum. *Study II* – Plasma, tumour biopsies and healthy intestinal biopsies were investigated before and after long-term cryopreservation to assess MMP level stability. In *Study III* a cohort of 272 patients were followed for 10 years after colorectal cancer surgery and the association between cancer-specific survival and plasma MMP concentration was analysed. *Study IV* - An *ex vivo* model of human peritoneum as well as a model for cultured mesothelial cells were developed. The models were subjected to trauma before introduction of cancer cells and followed by microscopy. **Results**: MMP have higher concentrations in serum compared to plasma and the variation in concentration is greater in serum samples. MMP concentration in plasma remains at the same level even after a long time in cryopreservation, while tissue extract concentrations appear to increase during storage. A high plasma concentration of MMP-1 in patients with non-disseminated disease was linked to worse cancer-specific survival after colorectal cancer surgery. The mesothelial cell model as well as the peritoneal model remained viable for long periods of time, and introduced cancer cells seemed to adhere to the edges of the traumatised area. **Conclusion**: Plasma samples are superior to serum samples when measuring MMP concentrations in circulating blood. Plasma samples could be stored for a long time at -80°C without MMP degradation. MMP-1 concentration in plasma in patients treated for colorectal cancer could have a prognostic value regarding cancer survival. Peritoneal models may be used to study colorectal cancer cell invasion and spread.

Keywords: Colorectal neoplasms; matrix metalloproteinases; colorectal surgery; survival; prognosis; peritoneum; peritoneal neoplasms.

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