Inflammatory microenvironment and immune cell signatures in colorectal cancer: relationship with sidedness, prognosis, and anthropometric factors

Jonna Berntsson
Division of Oncology and Pathology, Department of Clinical Sciences, Lund

Main supervisor: Karin Jirström
Co-supervisors: Jakob Eberhard, Anna H Larsson

Background

Colorectal cancer (CRC) is the third most common cancer worldwide and the third leading cause of cancer-related mortality. Increasing evidence indicates that CRC should be considered a heterogeneous disease, with proximal and distal tumours showing multiple differences in clinicopathological features, treatment response, and prognosis.

The immune system may in different contexts promote or inhibit tumour growth, and different immune cell subsets have been found to correlate with improved or impaired prognosis in CRC. However, previous studies on tumour-infiltrating immune cells and their association with prognosis have not focused on sidedness. The major aim of the thesis is to investigate the prognostic impact of different immune cell signatures in CRC, with particular reference to anatomical subsite of the primary tumour. Furthermore, a characterization of immune cell signatures in relation to anthropometric and lifestyle factors will be performed.

Material and methods

The study cohort consists of all 626 cases of CRC in the prospective, population-based cohort Malmö Diet and Cancer Study from 1991 up until December 31, 2008, of which tumours from 557 cases were available for tissue microarray construction. Immunohistochemistry was applied to assess the density of tumour-infiltrating immune cells.
**Preliminary results**

Paper I demonstrates that dense infiltration of CD20⁺ B cells is an independent favourable prognostic factor in CRC, further emphasising an important role of the humoral immune system in cancer.

Paper II provides a first demonstration of high infiltration of cytotoxic T cells being an independent prognostic factor in right-sided colon cancer, but not in left-sided colon cancer or rectal cancer. Furthermore, reanalysis of the data from paper I demonstrates that the prognostic impact of B cells is only evident in right-sided tumours.

Paper III (submitted) shows, for the first time, that high immune cell-specific PD-L1 expression is an independent factor of prolonged overall survival in tumours of the right colon and left colon, but not in rectal cancer.

**Significance**

These results demonstrate that the prognostic impact of tumour-infiltrating immune cells in CRC differs by primary tumour location, further indicating that sidedness might be an important factor to take into consideration in therapeutic decisions, including eligibility for immunotherapy.

**Published papers**
