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Immune Cell Infiltration and Prognosis in Colorectal Cancer

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Akademisk avhandling

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Avhandlingen kommer att försvaras på engelska.

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Abstract
Background: Colorectal cancer (CRC) is globally the second most common form of cancer among women, and third in men. It is also one of the most common causes of cancer-related death in high-income countries. Surgical resection is the basis for curative therapy but still almost half of the patients die from metastatic disease. It is therefore imperative to strive on in the search for more efficient strategies to improve patient survival. The success scores for accurate prediction of patient prognosis remain discouraging and novel markers to identify high-risk patients are called for.
The tumour immune response has proven critical to prognosis in CRC. A high amount of tumour infiltrating lymphocytes have in studies been found to significantly improve patient outcome. The opposite has been seen in patients with sparsely infiltrated tumours. Findings in this area have driven forth the design of the Immunoscore system, which may be implemented in clinic as a complement to the TNM staging system. Ongoing research is also focusing on which immune evading mechanisms CRC might deploy in order to progress and metastasize.

Aim: To study immune cell infiltration in relation to prognosis in CRC. More specifically the aim has been to investigate the prognostic importance of different subsets of immune cells infiltrating the tumour, not only according to quantity but also to intratumoural subsite (tumour invasive front, tumour centre and within the tumour epithelium). The tumour immune response was also evaluated in different molecular subgroups of CRC. Another part of this thesis concerns possible molecular mechanisms involved in tumour immune escape in CRC.

Methods: CRC cases in the Colorectal Cancer in Umeå Study (CRUMS) were evaluated using immunohistochemistry, gene expression analyses as well as methylation analyses. Cytokine and chemokine expression was evaluated in CRC tumour tissues and one CRC cell line (Caco2) and derivatives using semi-quantitative real-time PCR. Methylation was analysed using methylation-specific pyrosequencing.

Results: We found high quantities of both cytotoxic T cells (CTLs) as well as of regulatory T cells (Tregs) to associate with a better patient outcome. The infiltration of CTLs within the tumour epithelium provided the strongest prognostic information, whilst Tregs withheld the strongest association to prognosis at the tumour invasive front and tumour centre. We could further show that a high Th1 lymphocyte infiltration was strongly associated with a better prognosis in patients with CRC, independently of intratumoural subsite. Another finding was that the extent of Th1 infiltration and patient outcome differed in different molecular subgroups of CRC. We also found down-regulation of TAP1, a protein involved in antigen presentation by MHC class I, to be significantly associated with low infiltration of various subtypes of immune cells. Down-regulation of TAP1 was also correlated to poor prognosis in patients with early stages of CRC. Furthermore, we found TAP1 expression to be inversely correlated with methylation at sites close to the *TAP1* promotor region.

Conclusion: Tumour infiltrating T lymphocytes have a significant positive impact on prognosis in CRC patients. Different subsets of T lymphocytes vary in their dependency on intratumoural subsite, in to what extent they exert their prognostic influence. We moreover found varying Th1 lymphocyte infiltration rates as well as prognostic impact thereof, in different molecular subgroups of CRC. Our results also show down-regulation of TAP1 to be a mechanism of tumour immune escape in CRC. Further findings suggest methylation of the *TAP1* gene to be a putative mechanism for TAP1 downregulation.

Keywords
Colorectal cancer, molecular subgroups, immune cell infiltration, immune escape, prognosis

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