UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 2286

Gut microbiota in colorectal cancer

The importance of *Parvimonas micra*

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Hörsal Betula, byggnad 6M, Norrlands Universitetssjukhus, fredagen den 26 april, kl. 13:00.

Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Professor, Per Hellström, Institutionen för medicinska vetenskaper, Uppsala universitet, Uppsala, Sverige.

Department of Medical Biosciences

Organization
Umeå University
Department of Medical Biosciences

Document type
Doctoral thesis

Date of publication
02 April 2024

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Title
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Abstract
Colorectal cancer (CRC) is a heterogenous disease consisting of multiple molecular subtypes, each of which has diverse treatment responses and prognoses. The importance of the gut microbiota in CRC development and progression has undergone increasing recognition in recent years, with a structural segregation in terms of microbial composition between CRC patients and healthy controls. However, many questions remain before a full understanding of the impact of the gut microbiota on CRC is reached. The overall aim of this thesis was to explore the role of gut microbes in CRC, including their potential as CRC biomarkers and associations with clinicopathological, immunological, and molecular traits of CRC. A particular focus was the CRC-associated oral pathogen *Parvimonas micra*.

To investigate faecal microbiota as a potential biomarker for CRC, we studied the presence of specific bacteria in faeces from CRC patients and controls using qPCR. We found higher levels of *P. micra* in faecal samples from CRC patients than from control patients. A test for high levels of *P. micra* was able to identify CRC with a specificity of 87.3% and a sensitivity of 60.5%. Adding the oral pathogen *Fusobacterium nucleatum*, as well as colibactin-producing bacteria and faecal haemoglobin, to the test enhanced its sensitivity.

We further aimed to explore the associations of *P. micra* and *F. nucleatum* with molecular subtypes of CRC and the tumour immune response. The levels of *P. micra* and *F. nucleatum*, as analysed by qPCR in both faeces and tumour tissue from CRC patients, were found to be positively correlated. High levels of intratumoural *P. micra* and *F. nucleatum* were associated with tumours of the microsatellite instable subtype and BRAF-mutated tumours. For *F. nucleatum*, an additional association with right-sided tumours was found. Moreover, both *P. micra* and *F. nucleatum* in tumour tissue were associated with the immune-activated consensus molecular subtype (CMS) 1 subtype of CRC. In line with this finding, we found novel associations between intratumoural *P. micra* and specific immune traits, which were evaluated by flow cytometry, and an active immune response in CRC. These results were further confirmed using transcriptomics. However, no associations with specific immune traits were found for *F. nucleatum*.

We also investigated associations between faecal and intratumoural levels of *P. micra* and *F. nucleatum* and survival in CRC patients. CRC patients with high levels of intratumoural *P. micra* and *F. nucleatum* showed reduced five-year cancer-specific survival. This association remained significant for *P. micra* in multivariable analysis. No associations with cancer-specific survival were found for levels of *P. micra* and *F. nucleatum* in faeces.

To investigate the faecal microbial landscape of CRC patients on a larger scale, we used 16S rRNA sequencing. Network analysis revealed a cluster of associated bacteria, including *P. micra* and *F. nucleatum*, as well as other CRC-related pathogens such as *Bacteroides fragilis*, *Peptostreptococcus stomatitis*, and *Porphyromonas* spp. Furthermore, beta-diversity analysis indicated a significantly different gut microbial composition depending on tumour location and microsatellite instability status. Interestingly, three of the six annotated species most strongly associated with microsatellite instable tumours were also present in the cluster: *P. micra*, *P. stomatis*, and *F. nucleatum*.

In conclusion, our results suggest P. micra as a putative candidate for a future non-invasive microbial test panel for detection of CRC. Moreover, our results indicate that intratumoural *P. micra* and *F. nucleatum* are associated with immune-active subtypes of CRC, including microsatellite instable tumours and tumours of the CMS1 subtype, as well as decreased patient survival. Furthermore, *P. micra* and *F. nucleatum* were found to be associated with a cluster of other CRC-related oral pathogens. An improved understanding of the role of the gut microbiota in tumour progression may lead to the identification of important biomarkers for CRC disease and outcome, as well as putative targets for future therapy.

Keywords
Colorectal cancer; mucosal microbiota; *Parvimonas micra*; *Fusobacterium nucleatum*; immunity; survival

Language
English

ISBN
print: 978-91-8070-299-7
PDF: 978-91-8070-300-0

ISSN
0346-6612

Number of pages
53+ 4 papers