The role of the gut microbiota in human cancer

Chapter 11

Impact

Preamble

The present thesis aimed to investigate how **chemotherapy** and **cancer cachexia** interact with the **gut microbiota**, which comprises the bacterial communities residing in the digestive tract. Interactions between the gut microbiota and the two different chemotherapies, 5-Fluorouracil (5-FU)-based chemotherapy, as well as Adriamycin, Cyclophosphamide, Docetaxel (AC-D)), were investigated among patients with colorectal cancer (CRC) and breast cancer.

Although we did not detect consistent effects of capecitabine (a 5-FU-based chemotherapy) on the gut microbiota in CRC patients, this treatment seemed to interact with metabolites produced by gut bacteria (the so-called short-chain fatty acids (SCFA) and branched-chain fatty acids (BCFA)). Furthermore, we observed 5-FU-induced gut microbiota shifts in an experimental model and explored that these shifts could be counteracted by supplementing the gut microbiota with prebiotics, thereby stimulating the growth of potentially beneficial bacteria.
In addition, it was shown that chemotherapy with AC-D in breast cancer patients had a major impact on various gut bacteria.
The role of the gut microbiota in cancer cachexia was examined across four different cancer types (pancreatic cancer, breast cancer, lung cancer, ovarian cancer). Here, we found that the abundance of specific gut bacteria and fecal SCFA levels were different in cachectic cancer patients, as compared to non-cachectic cancer patients and cancer-free controls. The results from our own studies were complemented by two reviews, summarizing the current literature concerning the gut microbiota and chemotherapy or cancer cachexia respectively.

These data strongly suggest that the gut microbiota should not be neglected when treating human cancer. Since this is a relatively new concept which has not yet been implemented in clinical practice, these results are expected to have a considerable impact in different domains.

1. Scientific impact: from *"too high risk"* to *"promising"*

For the scientific community, the work presented in this thesis contains a highly important message: it encourages further research in this field.

We showed not only that clinical gut microbiota research with longitudinal fecal sampling is feasible in cancer patients, but also provided first indications that the gut microbiota and its metabolites are associated with chemotherapy treatment and the development and manifestation of cancer cachexia. Furthermore, this thesis provided insights into lessons learned from our studies and practical recommendations for future research.

These first results are essential for the progress of gut microbiota research in the cancer setting since they provide a scientific basis to justify further research. In the first years after starting our research line, our research proposals were regularly rated as *"too high risk"* by most funding agencies and evaluating commissions. This means that the risk of not finding a significant relationship was estimated as too high to fund the research. Nevertheless, we believed in our ideas, and could proceed due to the help of some early supporters. The results of these early explorative studies are presented in this thesis and will hopefully not only simplify the acquisition of future research funding but will also inspire other researchers to investigate the gut microbiota in the context of human cancer.

Two important milestones of our research team, which were considerably facilitated by the outcomes and knowledge obtained in the context of this thesis, were the provision of funding from the *Dutch Research Council* (NWO) as well as from the *Top Consortium for Knowledge and Innovation* (TKI) *Agri&Food*.
The recently initiated NWO-funded **OPTIMA study** (NCT05655780) aims to explore different biomarkers (amongst others gut microbiota parameters) during irinotecan-based chemotherapy for metastatic CRC. The experiences, results, and collaborations that we already gathered in the context of 5-FU-based chemotherapies formed the basis for the design of this new study, which also has the ultimate aim to implement targeted gut microbiota modulation. This closely corresponds, with the TKI-funded **Oncobiotics study**, investigating the effect and feasibility of a prebiotic intervention during 5-FU-based chemotherapy, as a direct follow-up of the results presented in this thesis. Together, these two studies will form the scientific basis for the implementation of gut microbiota-modulating interventions in patients with metastatic CRC.

These two follow-up studies illustrate that the results presented in this thesis have contributed significantly to a paradigm shift: currently, gut microbiota modulation in cancer patients is no longer considered to be of ***"too high risk"***, but to be ***"promising"***. And this paradigm shift opens new opportunities to develop from standardized anti-cancer therapies to gut microbiota-based personalized medicine.

However, gut microbiota research in the cancer setting is still in its infancy. Consequently, the connection of different research groups working on this same topic is of high relevance, to stimulate the exchange of different perspectives and complementary techniques. Therefore, we established external collaborations with (amongst others) *Wageningen University* (the Netherlands), the *University of North Carolina at Chapel Hill* (United States), as well as the *University of California, San Francisco* (United States) and aim to further expand our collaborative network in the near future. The publication of the current results in peer-reviewed journals will support this process, by attracting the attention of other researchers for this work.

2. Societal impact: from bed to bench and back

In 2022, almost 50,000 people in the Netherlands suffered from CRC and approximately 67,000 patients from breast cancer (1, 2). Many have been or will be treated with chemotherapy and will potentially be confronted with a suboptimal tumor response and/or chemotherapy toxicity. For instance, for 5-FU-based chemotherapies, a pooled analysis of 16 trials reported that only 34.2% of patients with advanced CRC showed response to capecitabine and 34.6% to 5-FU (3). Furthermore, it is well known that a proportion of patients experiences toxicity during 5-FU-based treatment, for instance in the form of the hand-foot syndrome (swollen and red hand/feet), diarrhea, nausea, or fatigue (4).
In addition, the presence of cancer cachexia can also negatively affect chemotherapy efficacy and toxicity (5). Altogether, this has a strong negative impact on the patients' quality of life and prognosis.

These clinical challenges from the ***"bedside"*** were the underlying motivation to conduct the studies described in this thesis (***"the bench"***).
Currently, cancer patients mainly receive standardized chemotherapy regimens. However, each patient enters the therapy with an individual gut microbiota profile, comparable to a fingerprint. Therefore, it is not surprising that tumor response and the experience of toxicity varies significantly between individuals. By using new knowledge on interactions between gut bacteria and chemotherapies, it would be possible to optimize the current treatment through implementation of microbiota-based personalized medicine.
For example, if a chemotherapy would work better in the presence or absence of specific gut bacteria, these bacteria could be stimulated or inhibited before and during the treatment by means of targeted microbiota-modulating interventions. This would considerably improve the patient's quality of life since patients would not be exposed to a toxic therapy without considerable therapeutic effect. Simultaneously, gut bacteria with anti-inflammatory properties or their metabolites could help to reduce chemotherapy- or cachexia-induced inflammation in cancer patients, with a potential positive effect on toxicity.

All patients who participate in our studies, do this without any personal benefit but with the purpose to help future patients in the same situation. Therefore, one of our main points of attention is the rapid **translation of research results back to clinical practice**, so that patients can benefit from scientific results as soon as possible. To achieve this, we collaborate with *Danone Nutricia Research*, a manufacturer of medical nutrition including prebiotics. This collaboration enables us to choose the best suitable prebiotic mixture for gut microbiota modulation in our target populations and to incorporate it into a consumable product. On the other hand, our research results also help them to develop new markets.
Of course, the collaboration between academic and private partners is not without controversies and requires critical reflection to ensure that research results are not influenced by economic interests. According to our experiences this can best be tackled by adhering to the principles of scientific integrity and by being aware of and communicate openly about potential competing interests. In this way, the partnership with industrial partners can help tremendously to make sure that the society can benefit from scientific advances and that evidence-based products become available on the market.

3. Key players involved and ways to target them

To make sure that relevant scientific results are not lost somewhere between bench and bedside, science communication is of high relevance. The results presented in this thesis are of potential interest for different target groups. To ensure that all of them are approached, different communication tools are used.

Scientific community: Our results have been presented on scientific conferences, including the *International Human Microbiome Consortium* (IHMC) Congress as well as on several editions of the Scientific Spring Meeting of the *Nederlandse Vereniging voor Medische Microbiologie* (NVMM) & *Koninklijke Nederlandse Vereniging voor Microbiologie* (KNVM). In addition, the results were published in peer-reviewed scientific journals and communicated on several internal meetings and research symposia. We also used *LinkedIn*® to share important research-related news with our professional network.

Clinicians: Clinicians represent another highly relevant target group of our research, since they are the connection between "bench" and "bedside". Therefore, we intentionally also published our work in journals with a clinical scope (e.g. *Clinical & Experimental Medicine* or *Clinical Colorectal Cancer*). Furthermore, the results were also presented on clinical symposia, such as the *Mammacongres Harderwijk* and a symposium on Nutrition & Cancer at the *Catalan Institute of Oncology* in Barcelona. In addition, an open and regular communication with all participating centers is actively maintained and centers are informed about the study progress by means of newsletters.

Students: As discussed in detail in Chapter 9, the training and education of next-generation scientists and clinicians is of great importance to further advance the research field and guarantee a continuity of high-quality research. Therefore, a total of thirteen students (medical as well as biomedical) was supervised and trained in our team. Hereby, critical scientific thinking, independent and careful laboratory work, as well as a broad interest in microbiota-related questions was stimulated. Furthermore, I was involved in tutoring, the supervision of laboratory practicals, as well as the revision of a tutor instruction. In the future, I aim to continue and further expand my educational tasks, for instance by participating in planning groups or giving lectures about gut microbiota research.

Patients and the society: To fulfil our ambition to give the results "back" to the patients, several communication tools to reach the broader public were applied. First of all, our articles were published *Open Access*, so that interested patients or family members have the opportunity to inform themselves about the study results. Furthermore, we recently implemented the possibility to subscribe to a patient newsletter concerning recent advances in our research line. We also involved patient organizations and patient representatives in the design of new studies, for instance the already mentioned OPTIMA study. For the future, a website containing information about our research activities is already planned. Finally, I will give a workshop on the gut microbiota at a public educational institution for adults (*Volkshochschule Aachen*) in March 2024.

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