OC20 - **Puzzling out gut microbiota composition in sporadic and hereditary colorectal cancer**

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Colorectal cancer (CRC) is the fourth most common cause of cancer-related death and the third most common cancer in the world1. CRC development follows a specific series of mutations that is translated into a specific morphological sequence, starting with the formation of adenomas and ending in the malignant carcinoma2. Depending on the origin of the mutations, CRCs are classified as "sporadic" or "hereditary". Cancers derived from mutations that appear during life and that affect individual cells and their descendants are called sporadic and account for most of the CRCs3. In approximately 5% of cases, CRC occurs in the context of Mendelian syndromes. In all CRC syndromes, variations in the clinical phenotype have been observed even among subjects with the same germline mutation, suggesting the influence of additional factors5. In the last years, human microbiota got a foothold in the list of the risk factors responsible for the onset and evolution of CRC. The microbiota is defined as the community of microorganisms that are located in and on our body. Alterations in the normal flora of the gut (dysbiosis) are linked to many types of cancer, and it is plausible that development of CRC can be driven by a previous dysbiotic stage6. During the last years, the application of next-generation DNA sequencing allowed to improve our knowledge about the human gut microbiome of sporadic CRC cases, but the gut microbiota oh hereditary CRC remains under-investigated7. This project aims at identifying specific microbial associations that can be used as biomarkers during neoplastic progression in sporadic and hereditary CRC. Taking advantage of culture-free molecular techniques (16S rRNA Illumina sequencing), we analyzed the faecal bacterial community of sporadic and hereditary CRC patients with Lynch syndrome. The Illumina sequencing data were computationally processed and bioinformatic analysis was performed using QIIME1 and QIIME2 tools8,9. We identified putative microbial biomarkers associated with stage-specific progression of sporadic CRC. Firmicutes and Actinobacteria phyla, as well as members of the Lachnospiraceae family, were associated with preneoplastic lesions. Oppositely, Alcaligeneaceae and Enterobacteriaceae families of the Proteobacteria phylum were found to be correlated with adenocarcinomas, with Sutterella and Escherichia/Shigella being the most representative genera10. Gut microbiota analysis of Lynch patients showed that Faecalibacterium prausnitzii was the most prevealent species associated with hereditary CRC, compared to healthy people. These findings can represent an important step towards the development of more effective diagnostic strategies.

References

1. WHO. World Cancer Report 2014. 2014. http://publications.iarc.fr/Non-Series-Publications/World-Cancer-Reports/World-Cancer-Report-2014

2. Fearon ER. Molecular genetics of colorectal cancer. Annu Rev Pathol. 6:479-507. 2011.
3. Fearon ER, Vogelstein B. *A genetic model for colorectal tumorigenesis*. Cell. 61:759-767. 1990.
4. Fleming M, Ravula S, Tatishchev SF, Wang HL. *Colorectal carcinoma: Pathologic aspects*. J Gastrointest Oncol. 3:153-73. 2012.
5. Valle L. *Genetic predisposition to colorectal cancer: where we stand and future perspectives*. World J Gastroenterol. 20:9828-9849. 2014.
6. Gagnière J, Raisch J, Veziant J, Barnich N, Bonnet R, Buc E, Bringer MA, Pezet D, Bonnet M. *Gut microbiota imbalance and colorectal cancer*. World J Gastroenterol. 22:501-518. 2016.
7. Dejea CM, Fathi P, Craig JM, Boleij A, Taddese R, Geis AL, Wu X, DeStefano Shields CE, Hechenbleikner EM, Huso DL, Anders RA, Giardiello FM, Wick EC, Wang H, Wu S, Pardoll DM, Housseau F, Sears CL. *Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria.* Science. 359:592-597. 2018.
8. Caporaso JG, Lauber CL, Walters WA, Berg-Lyons D, Huntley J, Fierer N, Owens SM, Betley J, Fraser L, Bauer M, Gormley N, Gilbert JA, Smith G, Knight R. *Ultra-high-throughput microbial community analysis on the Illumina HiSeq and MiSeq platforms*. ISME J. 6(8):1621-1624. 2012.
9. Caporaso JG, Kuczynski J, Stombaugh J, Bittinger K, Bushman FD, Costello EK, Fierer N, Peña AG, Goodrich JK, Gordon JI, Huttley GA, Kelley ST, Knights D, Koenig JE, Ley RE, Lozupone CA, McDonald D, Muegge BD, Pirrung M, Reeder J, Sevinsky JR, Turnbaugh PJ, Walters WA, Widmann J, Yatsunenko T, Zaneveld J, Knight R. *QIIME allows analysis of high-throughput community sequencing data*. Nat Methods. 7(5):335-6. 2010.
10. Mori G, Rampelli S, Orena BS, Rengucci C, De Maio G, Barbieri G, Passardi A, Casadei Gardini A, Frassineti GL, Gaiarsa S, Albertini AM, Ranzani GN, Calistri D, Pasca MR. *Shifts of Faecal Microbiota During Sporadic Colorectal Carcinogenesis*. Sci Rep. 8:10329. 2018.