**Global microbial signatures for colorectal cancer established**

**Colorectal cancer is characterised by consistent changes in our gut bacteria across continents, cultures, and diets**

Trento, 1st April 2019 – Cancers have long been known to arise due to environmental exposures such as unhealthy diet or smoking. Lately, the microbes living in and on our body have entered the stage as key players: while stomach cancer can be caused by a single bacterial species, *Helicobacter pylori*, the role that gut microbes play in the development of colorectal cancer – the third most common cancer worldwide – is less clear. To determine their influence, association studies aim to map how the microbes colonizing the gut of colorectal cancer patients are different from those that inhabit healthy subjects.

Researchers from EMBL, the University of Trento, and their international collaborators have now analysed multiple existing microbiome association studies of colorectal cancer together with newly generated data. Their meta-analyses establish disease-specific microbiome changes which are globally robust – consistent across seven countries on three continents – despite differences in environment, diet and life style.

Georg Zeller from the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany: “We used a rigorous machine learning analysis to identify microbial signatures for colorectal cancer. We validated these signatures in early cancer stages and in multiple studies, so they can serve as the basis for future non-invasive cancer screening.”

Nicola Segata from the University of Trento in Italy: “We not only established a panel of gut microbes associated with colorectal cancer across populations, but also found signatures in microbial metabolism that have similar predictive power. These will enable new research aiming at understanding how gut microbes may contribute causally to cancer development.”

The study led by EMBL scientists focuses on a process in which certain gut bacteria turn bile acids that are part of our digestive juices into metabolites that can be carcinogenic. The related study from the University of Trento shows how certain classes of bacteria degrade choline, an essential nutrient contained in meat and other foods, and turn it into a potentially dangerous metabolite. This metabolite has previously been shown to increase cardiovascular disease risk, and can now also be linked to colorectal cancer.

One of the challenges of metagenomic studies, which are based on genetic material from microbes in environmental samples such as stool, is to link genetic fragments to the various microbial organisms they belong to. The goal of this so-called taxonomic profiling task is to identify and quantify the bacterial species present in the sample.
“Despite different approaches in taxonomic profiling and statistical analysis, our studies reached very similar conclusions,” says EMBL group leader Peer Bork, “which makes this one of the most promising cases for microbiome-based diagnostics so far.”

“On the road to fully characterize the human gut microbiome for association studies”

In the panel of reproducible microbial markers associated with colorectal cancer that were established, there are both previously linked bacteria, such as Fusobacterium nucleatum, and novel microbial species and genes. “In the analysis of metagenomic data, the key role is played by the computational analysis. We needed to develop algorithms to identify microbes at very high resolution and precision,” says Segata who led the study at University of Trento. “The gene that degrades choline in a potentially dangerous metabolite is a good example. This gene is frequently carried in the gut microbiome by a bacterial species that does not have a name and that we discovered in another work earlier this year.”

In this other work published in journal Cell, Segata and his group identified - via metagenomics - several hundred microbial species that are prevalent in the gut microbiome but remained so far unexplored using standard experimental tools. “Continuing this effort toward fully uncover the diversity of the gut microbiome may lead to find additional associations of microbiome members with other human diseases.”

Further expanding cohort sizes and population diversity

The studies also found that the number and size of the cohorts included in the meta-analysis were key for establishing the strong association between the gut microbiome and colorectal cancer. “The gut microbiome is heavily dependent on factors such as diet, lifestyle, and environment,” continues Segata, “and considering geographically and culturally diverse populations is thus needed to obtain microbial signatures that are indeed globally associated with colorectal cancer.” This also means that including more metagenomic samples from underrepresented populations and approaching the sample size of some current human genetic studies can further improve the association and better drive future microbiome-based diagnostic and therapeutic strategies for colorectal cancer.