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Linking Microbiota to Cancer Prognosis

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COMMENTARY

Through evolution, all living organisms on Earth are structurally and/or functionally integrated to form a unified biological system, within which all organisms are connected by an intricate network composed of complex interactions and interdependences. Under certain circumstances (e.g. symbiosis), the dependency leads to a better life for one or both of the interacting partners, while under other circumstances, the dependency may be destructive, or even lethal, to one or both partners, depending on the type of alteration as well as the speed of alteration. A gradual physiological or environmental alteration can be compensated by a gradual switch of interacting partners. This is especially true for microorganisms which are more diverse and spread more quickly and dynamically than higher organisms. Since microorganisms quickly respond to physiological conditions, including the strength of immunity, the composition of microbiota in our body is able to reflect the physiological conditions of an individual.

Under healthy conditions, symbiotic relationship between a human host and the microbiota living in the intestine provides mutual benefit to both sides, and, from our point of view, these microorganisms are considered as "probiotics". The symbiotic relationship is built on the facts that our diets are their major sources of nutrients to support their growth and that, in exchange, these microorganisms enhance the catabolic process of food through fermentation, making it easier for our body to absorb the nutrients. Such symbiotic microorganisms have been studied for many decades in animals, especially for cows and humans, because they are easily accessible. What about those living somewhere within our body?

There are microorganisms living within human body [1] or even tumor tissues [2]. Some microorganisms living in blood circulation are unculturable; and some may live inside erythrocytes [3,4]. These microorganisms deserve a close investigation.

This issue can now be solved by modern technologies, especially next-generation sequencing (NGS). By sequencing cell-free DNA (cfDNA) isolated from blood plasma, NGS and associated analytic bioinformatics approaches are making the detection of microbial inhabitants an easy task. This approach, although indirect, does provide a convenient approach.

As demonstrated by our group [5], the microbial inhabitants can be associated with the host's physiological conditions. The proof-of-concept study employed both healthy females (references) and patients with early-onset breast cancer (EOBC) of various clinical stages. The hidden microbial species were deduced from microbial sequences in plasma cfDNA and the microbiomes of patients were compared to that of healthy individuals and used to extrapolate patients' overall health conditions.

This approach is made possible by a stringent pipeline, which comprises a dual mapping process against microbial databases, selection of PE reads, contig assembly and alignment. Such multiple layers' scrutiny ensures accuracy. Besides Bowtie, BWA should also be tested as a mapping tool. To ease quantification and cross-species comparison, MCRPM (Microbial cfDNA reads per million quality PE reads) was defined and used to quantify microbial cfDNA levels in plasma. Since the processing of cfDNA fragments, starting from the release from the originating cells till ending up in blood circulation, remains largely unknown, there inevitably exists a gap between the titer of a microbe and its corresponding cfDNA level in plasma.

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Besides cancer, patients with chronic diseases, such as Alzheimer's disease and diabetes, should be examined by cfDNA sequencing. Theoretically, elevation of sugar level in blood would favor the growth of certain microbial species. How these potential microorganisms interact with the host is largely unknown and thus how these microbes contribute to disease progression is equally elusive. Cell-free DNA-mediated identification of microbial inhabitants for chronic diseases may provide valuable information for personalized treatment. Such noninvasive approach should be able to facilitate our understanding of how microbiota is linked to diseases.

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