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Can Circulating Microbiome be Used as Biomarkers?

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Editorial

The circulating cell-free DNA (circDNA) is present in meager quantities in the plasma of human beings including healthy individuals. The mechanism of DNA release into the circulation is not completely known. The circDNA can be released either passively or actively. The release of DNA into the circulation from the dead cells, due to apoptosis or necrosis, is referred as the passive mechanism, which could be the primary source of circDNA [1]. The release of DNA by the living cells is known as the active mechanism. For instance, certain tumor cells can spontaneously release DNA fragments into the circulation. Higher levels of circDNA have been reported in various diseases, including cancer and cardiovascular diseases [1,2]. Recent literature suggests that the non-host DNA also circulates in the blood. For example, Spisák et al., have shown evidence that the plant-derived DNA fragments from the food can enter into the bloodstream through an unknown mechanism and being circulated [3]. Similarly, the presence of DNA from viruses, bacteria, and fungi have been detected in the circulation [4].

Human microbiomics is a promising area of research, and an enormous amount of scientific data has been generated in the last decade. From the first week of the birth, a human child is colonized with microorganisms in various parts of the body altogether referred as the "human microbiota". The total genomes of the human microbiota represent the "human microbiome". The human microbiomes have been extensively studied through the "Human Microbiome Project" followed by the Integrative Human Microbiome Project. Blood has initially been considered as sterile, and microbes could be detected in the circulation only in sepsis condition. In recent years, the presence of bacterial DNA in the circulation have been reported even in healthy individuals [5]. Blood is circulating throughout the human body and therefore, have access to the microorganisms or the microbial products, including DNA, associated with every part of the body [4].

Païssé et al., studied the circulating (circ-) microbiome from 30 healthy volunteers and reported that, at the phylum level, the circ-microbiome was predominated by Proteobacteria (>80%) followed Actinobacteria, Firmicutes, and Bacteroidetes [6]. Similarly, Whittle et al., have reported the circ-microbiome from healthy individuals and asthmatic subjects through DNA-level and RNA-level analyses [7]. Though no significant difference was observed between healthy and asthmatic subjects, the phylum level distribution was similar to the previous report by Païssé et al., [6]. When compared, the circ-microbiome composition was more similar to the oral and skin microbiomes than with the gut microbiome. Therefore, it was suggested that the circulating microbiome is more likely to originate from the oral cavity and skin have reported the circ-microbiome of severe acute pancreatitis (SAP) patients [7,8]. When compared to healthy controls, the blood and neutrophil-associated microbiomes were significantly altered in the SAP patients. The levels of Bacteroidetes and Firmicutes were increased while the level of the Actinobacteria was decreased in the SAP patients.

The method of microbiome profiling also plays a significant role in characterizing the circ-microbiome. Earlier, we compared the circ-microbiome composition determined by the 16S rRNA gene analysis and the whole-metagenome shotgun sequencing analysis in six samples [9,10]. We observed strikingly dissimilar compositions of circ-microbiome in two different strategies. The differences could be primarily attributed to the possibility of bias introduced during the PCR amplification of 16S rRNA genes. Though the 16S rRNA gene primers are designed based on the consensus sequences, no primer sequences have 100 % consensus. Therefore, the PCR-based profiling may miss some key members of the microbial communities. However, several studies have employed the 16S rRNA gene sequencing-based analysis only. The whole-metagenome shotgun sequencing may provide us with the true composition of the microbial communities without any amplification bias.

Through a massive whole-metagenome shotgun sequencing effort, Kowarsky et al., have identified hundreds of new bacterial and viral signatures in the circ-microbiome [3]. Some of the sequences were not reported earlier as the members of the human microbiota. Also, they have reported the presence of more than 3,000 novel contigs without any similarities with existing sequences in the databases. The novel contigs represented entirely novel taxa, and thus, the diversity of the human microbiota is significantly higher than it was previously realized. Overall, there is a possibility for the existence of a core circ-microbiome in humans, which can be altered in the infectious and non-infectious disease conditions. More systematic studies and meta-data analyses are needed to understand the circ-microbiome before it can be developed as a biomarker for various diseases.

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