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Commentary

Targeting gut microbiome, is it always a therapeutic option?

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Obstructive sleep apnea (OSA), the most common form of sleep-disordered breathing, involves disrupted breathing due to episodic upper airway collapse. OSA has become a public health problem since it affects a billion people worldwide [1] and is associated with cardiovascular and cancer comorbidities, increasing both morbidity and mortality [2]. Chronic intermittent hypoxia (CIH) is the principal feature of OSA, which mimics the recurring episodic oxygen fluctuations that characterize sleep apnea and causes sympathetic nervous system hyperactivity and systemic hypertension mediated by oxidative stress, inflammation and endothelial dysfunction [2].

The mammalian gut is a complex ecosystem where trillions of microorganisms live. They constitute a finely tuned network that is necessary for the optimal regulation of host immunity, metabolism and circadian rhythms. Perturbation of the ecosystem balance, known as dysbiosis, has been linked to chronic diseases, such as metabolic syndrome, depression and cognitive dysfunction, as well as cardiovascular disease [3]. Accumulating evidence indicates that both short-term partial sleep deprivation and OSA compromise the diversity and abundance of human gut microbiome, increase gut permeability which then contributes to the development of insulin resistance [3,4].

As OSA and CIH are associated with the alteration of gut microbiome, microbiome-based therapies are tested for the management of these disorders. For instance, O'Connor et al. [5] have recently published an article that evaluates the effect of gut microbiota modulation by prebiotic administration in a hypertension associated-CIH experimental model in rats. The authors reported that CIH results in the development of adverse cardiorespiratory consequences, including hypertension, cardiac autonomic imbalance and higher risk of apnea. Moreover, they describe a reduction of fecal SCFA concentrations and lactobacilli species without modifying the functionality of the gut microbiota in CIH-exposed rats. Although prebiotic treatment modulated the microbiome composition, diversity and functions, it did not prevent CIH-associated hypertension in this rat model or affect apnea index during normoxia, only demonstrating a modest effect on brainstem neurochemistry. This work suggests that gut microbiota dysbiosis, at least in a relatively mild model of CIH, are not mandatory for the development of this condition. These findings have important implications because there are numerous gaps that need to be filled in the concept linking OSA to hypertension through the gut microbiome, particularly in humans. When considering the gut microbiome, most of the studies rely on 16S amplicon sequencing, which limits the analysis to genus level. However, recent analyses indicate that many taxonomic associations might emerge only at levels subordinate to species [6]. Moreover, amplicon technologies hamper the taxonomic scope to bacteria and archaea, thereby missing data signals on eukaryotic and viral members. O'Connor et al. avoids these limitations by using whole-genome shotgun metagenomic sequencing which provides readouts on the microbiome gene and functional repertoires and allows to identify microorganisms with the same functionality that involve different mechanisms. In fact, gut microbiota may exert an effect on the CIH through several pathways. Moreover, it is well described that bacterial communities with different taxonomy can exert similar functions [6]. And on the other hand, not all commensal microorganisms have the same effects on the host, some significantly influence host immunity to improve the outcome of the disease, whereas others could even aggravate it. Shotgun metagenomic sequencing has also revealed that known factors can only account for a shockingly small fraction of the total microbiome variation, at least without microbiome state stratification [7]. Microbiome modification studies have further enhanced our understanding of the microbiome functionality, both with regard to its inherent interaction structure and to cause-effect associations with external factors. Additionally, it is becoming evident that the microbiome mediates, stratifies, and probably personalizes host-level responses to therapy.

The authors have revealed the importance of a personalized medicine, so future studies should focus on identifying microbial species with particular metabolic phenotypes, thus providing specific therapeutic targets.

In summary, a deeper understanding of the microbiome allows us to identify when it can be used as a therapeutic target and to choose the best appropriate way to intervene. In this regard, more and larger-scale longitudinal and interventional studies are expected, as well

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as the application of updated methodological techniques, including multi-omic technologies. The integrative multidimensional study of microbiome alterations will thereby make truly advance in the research on the human gut microbiome, moving from association to modulation.

Declaration of Interests

The authors declare no conflicts of interest.

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