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Commentary

Inulin, the gut microbiome and the deeper breath of asthma patients – Novel pathways in asthma treatment

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Modern westernized lifestyles have changed human health attitudes and conditions in many ways. Comparison of the gut microbiota of uncontacted indigenous tribes such as the Amazonian Yanomami with those of westernized subjects underline this observation, by vividly depicting that these changes affect even basic physiological conditions [1]. The phylogenetic co-evolution of man and microbes led to a diverse and beneficial symbiotic microbiota at the mucosal surfaces of the host. The Yanomami with their primitive close-to-nature lifestyle represent an ancestral, up to now conserved, manifestation of this multi-variant microbial community. In contrast, the microbiota of westernized subjects significantly lacks this diversity. Many factors shape the diverse gut microbiome of the indigenes, including dietary habits. Taking a closer look at the nutrient spectrum of semi-nomadic hunter-gatherers like the Yanomami, high-fiber dietary fruits, roots and vegetables built the basic body of daily nutrition. Plants, such as manioc, plantains and sweet potatoes harbor high amounts of inulin, a fructose oligosaccharide, and are cultured by the Yanomami and frequently consumed in their daily diets [2]. In comparison to the Yanomami food spectrum, the modern diet is characterized by a low content of high-fiber foods. The decreased intake of high-fiber products and the coincident increase of autoimmune and allergic diseases in industrial societies, gave rise to the hypothesis that there might be a causative relationship between these observations [3]. Based on the assumption that homeostasis of the gut is most relevant to provide immune tolerance, depletion and disturbance of gut microbial communities may lead to immune deviation that favors chronic inflammatory conditions in the gut and throughout the whole body. A number of recent studies support this “diet–microbiota–gut–immune axis” [4]. Inulin acts as a potent stimulus for the growth of the beneficial genus Bifidobacterium in the gut microbiota, while maintaining potential pathogens such as Salmonella and Clostridia at low levels [5]. Various gut bacteria, including Bifidobacterium, degrade inulin to butyrate and other short fatty acids that provide an array of health benefits [6]. These fermentation products are able to act as histone deactetylase (HDAC) inhibitors and bind to G-protein coupled receptors (GPCR) situated at the outer surface of epithelial cells. GPCR are shown to be involved in the activation of regulatory T cells (Treg), as well as in the maintenance of epithelial integrity and gut homeostasis. Lack of this metabolic sensing may result in a suppression of Treg subsets and a loss of control of T helper cell 2 populations that drive allergic diseases [7].

As we cannot turn our dietary habits from Space Age to Stone Age, new sophisticated strategies must be employed which respect this evidence, in order to develop better, well-adapted treatments of chronic inflammatory diseases. This postulation is consequently addressed in the short-term trial conducted by McLoughlin et al. and published in *EBioMedicine* [8]. In a 7-day treatment of asthma patients with the prebiotic soluble fiber inulin, they aimed to assess benefits on clinical asthma parameters, impacts on the composition of the gut microbiota and on biomarkers that demonstrate inulin degradation and immune modification.

The placebo-controlled study reveals several remarkable results [8]. Firstly, it is striking that eosinophils in sputum, a basic hallmark of allergic asthma, were found to be significantly diminished upon inulin supplementation. From the patients' perspective it is even more relevant that control of asthma was improved by inulin treatment. Interestingly, allergic patients, with a high proportion of sputum eosinophils, and especially those reported to have poorly controlled asthma, were shown to have a noticeable benefit from fiber supplementation. Inhibition of HDAC9 following inulin supplementation suggests a mechanistic pathway that may be important in this context.

Secondly, the study reveals that short-term consumption of a soluble fiber alone, is able to modify the gut microbiota significantly, while simultaneous consumption of inulin-degrading bacteria did not improve this outcome. At a first glance, this result seems surprising. However, it is known that the gut microbiota harbors a number of bacterial strains that immediately can switch on metabolic pathways to utilize inulin as a carbon source and thereby stimulate bacterial growth of other species [9]. This metabolic capacity of the microbial gut community appears to be more adaptive than a de-novo colonization by digested probiotic strains. As a consequence, the authors expected to detect an increase in short chain fatty acids (SCFA), a product of this metabolic bacterial activity, in the plasma of inulin-treated subjects, but failed to verify this

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assumption. In plasma, free fatty acids are subject to a fast metabolic turnover and timing of sample collection may not have been suitable.

This study is a first step towards new holistic approaches to improve clinical parameters, control of asthma and, possibly, other chronic inflammatory diseases. But it is still questionable if short-term intervention with high-fiber dietary components is efficient enough to reveal sustainable results. In future trials, long-term and preventive study designs are needed to prove the potential, as well the limitations, of fiber supplementation in allergic diseases. A look back at ancient and primitive lifestyles might inspire us to develop further innovative strategies to combat chronic inflammatory diseases.

Disclosure

The authors declared no conflicts of interest.

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