A complex triad determining metabolic health: diet, host, and microbiome interaction

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Dietary strategies can contribute to prevention, development, and progression of various diseases. In this context, much attention has been attributed to the health benefits of the traditional Mediterranean diet, a dietary pattern rich in unsaturated fats and fibers, as it consists of high levels of intake of fresh fruit, vegetables, legumes, and olive oil (1). Robust epidemiologic data support an inverse relation between adherence to the Mediterranean diet and overall mortality as well as the development of obesity, metabolic and inflammatory diseases, and even cancer (2–4). Interestingly, all of these pathologies are associated with an impaired intestinal barrier function, dysbiosis, and endotoxemia (4). Therefore, growing interest emerges regarding the complex interaction between dietary patterns, microbial composition, and intestinal homeostasis. Among others, short-chain fatty acids (SCFAs) are credited with mediation of the beneficial effect of the Mediterranean diet. These short carboxylic acids are produced by anaerobic fermentation of dietary fibers by commensal bacteria and have barrier-protective and immunomodulatory properties (Figure 1A) (5).

In this issue of the American Journal of Clinical Nutrition, Seethaler et al. (6) elucidate a causal relation by which the SCFA-rich Mediterranean diet exerts protective effects on intestinal barrier integrity. In their study, 260 women with intestinal barrier impairment due to a pathogenic BRCA1 or BRCA2 mutation were randomly allocated to a control (n = 136) or an intervention (n = 124) group, in which a biweekly training resulted in increased adherence to the Mediterranean diet and higher intake of typical Mediterranean food groups and components. Strikingly, this resulted in significantly lower levels of intestinal permeability biomarkers, namely, lipopolysaccharide binding protein (LBP) in plasma and fecal zonulin, as well as in higher amounts of fecal SCFA, particularly butyrate and propionate.

Moreover, the use of a model-based causal mediation analysis enabled the authors to distinguish between SCFA-mediated effects and non-SCFA-mediated effects on intestinal permeability. The model revealed that butyrate and propionate completely mediated the effect of insoluble fibers and legumes on LBP and, to a minor extent, on fecal zonulin and other food groups. This indicates that although SCFAs protect the intestinal barrier integrity, other nutritional factors may also play an important role and must be considered in prospective studies. For instance, vitamins, polyphenols, and secondary bile acids have been suggested to regulate differentiation of intestinal epithelial cells and have immunoregulatory properties (4).

However, as a large interindividual variability in both groups was observed, participants were divided in responders and nonresponders. Using a machine learning–based random forest classification (RFC), the authors assigned a strong predictive effect for baseline propionate and butyrate on individual responsiveness to the Mediterranean diet intervention. On the basis of these results, the authors propose fecal butyrate measurement as a screening parameter to identify patients who would particularly benefit from a dietary intervention in terms of a personalized nutrition-based approach.

Collectively, this study uses sophisticated mathematical models and machine learning algorithms to identify SCFAs as key mediators of the beneficial effect of Mediterranean diet food components on intestinal barrier function and as a potential biomarker for a personalized nutritional therapy. Nonetheless, restricting the study population to women with the BRCA mutation may limit external validity. Future studies will be needed to confirm these results and to generalize them to broader patient collectives, as sex differences and distinct pathophysiologic processes could differentially influence intestinal integrity (7). If it holds true, these findings would be a promising approach to nutritional therapy for patients with common diseases in Western societies, such as obesity, cardiovascular and inflammatory diseases, chronic liver pathologies, and cancer.

The mechanisms by which SCFAs and other dietary components exert protective effects on the intestinal barrier are not yet fully understood, demanding further mechanistic studies. A direct stabilizing effect on hypoxia inducible factor 1α as well as butyrate-mediated upregulation of tight junction genes via activation of STAT3 and SP1 signaling pathways has been...
Dietary patterns influence the microbial composition and intestinal barrier function. Dietary fibers, abundant in the Mediterranean diet, are processed by commensal bacteria to short-chain fatty acids (SCFAs), which have a protective effect on intestinal integrity and immunoregulatory functions (A). Western-style diet and/or genetic predisposition leads to dysbiosis, intestinal barrier disruption, translocation of microbial components, endotoxemia, and systemic inflammation, which in turn promote metabolic diseases (B). HIF-1α, hypoxia inducible factor 1α. SCFAs may induce the production of antimicrobial peptides by intestinal epithelial cells (8).

Diet, microbiota, and intestinal stroma cells form an extraordinarily complex triad. Elucidating the relevant interactions in this context remains challenging. Recently, sophisticated taxonomic and functional profiling from stool metagenomes revealed that the protective association of the Mediterranean diet with cardiovascular disease risk is in fact modulated by the microbial composition (9). As the association was particularly strong in those with microbiomes depleted of *Prevotella copri*, it is tempting to ascribe a special role to this bacterium. Other studies linked a higher frequency of *Faecalibacterium prausnitzii* and *Roseburia* and lower frequency of *Ruminococcus gnavus, Collinsella aerofaciens*, and *Ruminococcus torques* to improved health under the Mediterranean diet (10, 11). However, epidemiologic studies of human microbiome profiles are purely observational by design, and the results can only show a correlative relation.

The matter becomes even more complex, once we consider how the triad of diet, microbiota, and intestinal environment regulates local and systemic immune responses. Resident innate immune cells are equipped with pattern recognition receptors to sense microbial-derived components (1). In homeostasis, their anti-inflammatory signature maintains the intestinal barrier. In addition, microbiome-metabolized food components have immunoregulatory functions as well. Butyrate, for instance, possesses anti-inflammatory properties by inhibiting NF-κB signaling and inflammatory cytokine production (1). Thus, diet, microbiota, and the intestinal immune system are constantly and dynamically shaping each other to form a finely tuned anti-inflammatory environment. Unhealthy lifestyle disrupts this homeostatic equilibrium, resulting in dysbiosis, impaired barrier function, endotoxemia, immune dysregulation, and disease (Figure 1B). Although the health-promoting effect of the Mediterranean diet is apparent from numerous epidemiologic studies, the exact mechanisms are incompletely understood. The current work from Seethaler et al. (6), using clinical samples and machine learning approaches, provides interesting avenues toward “precision nutritional interventions.” However, the complexity of the topic will require an astute combination of broad epidemiologic approaches and reductionist experiments to fully understand the underlying causalities, in order to head toward a personalized medicine.

Figure 1 was created with BioRender.

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