Engineering 18 (2022) 17–20

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Views & Comments

Treating Chronic Diseases by Regulating the Gut Microbiota

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Chronic diseases comprise a wide range of abnormal conditions and illnesses that impair patients' physical and/or mental functioning, and last for a long time. Largely a contemporary plague, chronic diseases are responsible for the observed morbidity and mortality in developed countries as well as in some developing countries [1,2]. These disabling and deadly diseases range from cardiovascular and cerebrovascular diseases and metabolic disorders such as obesity, diabetes, and metabolic syndrome, to degenerative neurological disorders such as Parkinson's disease and Alzheimer's disease. They are characterized by multifactorial pathogenesis with associated specific symptoms, whose progression may be somehow delayed or alleviated through medical treatment and/or lifestyle changes. The biochemical abnormalities associated with these diseases, such as high blood glucose in diabetes mellitus, high blood cholesterol in cardiovascular diseases, and high liver fat content in fatty liver diseases, represent the biological phenotype connected with clinical manifestation (symptoms or signs). Although genetic background, unhealthy lifestyle, food, and environmental factors have been reported to play a role in the pathogenesis of chronic diseases, the underlying root causes of most of these chronic diseases remain elusive.

Lately, an increasing number of studies have shown that the gut microbiota and its metabolites play important roles in the onset and development of chronic diseases. In fact, more than 2000 years ago, Hippocrates, known as the father of western medicine, stated that "all diseases begin in the gut." Chong Wang, a Chinese scholar in the Eastern Han Dynasty (almost 2000 years ago), also proposed a close relationship between the gut and human longevity (i.e., a clean gut is helpful to live happy and long). Traditional Chinese medicine has a simple concept in which the entrance of toxic substances from the feces into circulation causes various diseases. On the other hand, fecal microbiota transplantation has been introduced as an effective therapy for some intractable diseases.

The particular roles of gut microbes and their molecular mechanisms in the physiological and pathological processes of chronic diseases have not been thoroughly characterized. In recent decades, however, the rapid development and application of high-throughput sequencing technology have revealed that myriad microorganisms are present in different ecosystems within the human body (i.e., the human microbiota). The human intestine harbors trillions of microbial cells, on the same order as the number of human cells [3], with at least two orders of magnitude more genes in the collective genomes of the gut microbiota (i.e., the gut microbiome, also known as the "second human genome") than in the human genome [4]. The gut microbiota encompasses bacteria, archaea, eukaryotes, and viruses/phages; of these, bacteria are in the vast majority. The composition of the gut microbiota is dictated by the host's genetics and by the physiological environment of the gut, which is largely influenced by food [5]. The term "superorganism" was coined by the laureate of the Nobel Prize in Physiology or Medicine, Joshua Lederberg, to emphasize the coevolution of microbiota with its host [6].

Alterations in gut microbial composition (i.e., gut dysbiosis) have been associated with a wide array of chronic diseases in humans. More specifically, a harmful profile of the gut microbiota composition can be considered to be part of the root cause of chronic diseases that include obesity and diabetes [7], cardiovascular diseases [8], Parkinson's disease [9], and Alzheimer's disease [10]. The gut microbiota can produce various small-molecule metabolites, such as short-chain fatty acids (SCFAs), trimethylamine (TMA), and secondary bile acids, which may enter the blood circulation to exert systemic beneficial or deleterious effects on health [11]. SCFAs—mainly acetate, propionate, and butyrate—are the major products of the microbial fermentation of nondigestible carbohydrates. Various investigations have demonstrated the effects of SCFAs on metabolic diseases, indicating that SCFAs might be causally linked to diabetes, atherosclerosis, and hypertension, among others [12–16]. SCFAs can bind to different cellular receptors and may function as signaling molecules that modulate host metabolism; for example, by controlling the appetite via the gut–brain axis [17–21]. Microbial metabolite TMA, derived from nutrients such as choline and carnitine, can be oxidized by hepatic enzymes to generate TMA *N*-oxide (TMAO) [22]. Although there are some arguments about its contribution (or biomarker significance) in atherosclerosis progression [23–25], plasma TMAO level is acknowledged to be a new independent risk factor for atherosclerosis, aside from plasma cholesterol level and chronic inflammation. The potential mechanisms of TMAO include

https://doi.org/10.1016/j.eng.2021.08.015

the inhibition of reverse cholesterol transport [26], enhancement of macrophage foam cell formation [27], promotion of hyperglycemia [28], induction of vascular inflammation [29], and increase of platelet hyperreactivity [30]. Bile acid metabolism, which is associated with cholesterol metabolism, is modulated by the gut microbiota. Primary bile acids synthesized in the liver are released into the small intestine to facilitate the digestion and absorption of lipids and fat-soluble vitamins. A small portion of primary bile acids that escape reabsorption are transformed into a diverse set of secondary bile acids by the gut microbiota in the distal small intestine and colon [31]. Some bile acids are recognized to function as endocrine-like signaling molecules that regulate host physiological processes by binding to various host receptors, such as farnesoid X receptor (FXR) and Takeda G-protein coupled receptor 5 (TGR5) [32,33]. These receptors are involved in signaling pathways that regulate lipid and glucose metabolism and energy expenditure [33–36]. Therefore, delineation of the mechanisms underlying the effects of gut microbiota-derived metabolites makes the gut microbiome "druggable"—that is, it provides novel therapeutic potential to treat chronic diseases by manipulating the gut microbiota [37]. Thus, medicinal agents with desirable effects on bacterial metabolites may be able to treat chronic diseases by regulating the gut microbiota.

Berberine, the major active pharmacological component in herbal *Coptis chinensis* and *Berberis vulgaris*, has exhibited clinical effectiveness in the treatment of hyperlipidemia and metabolic syndrome [38–42] by targeting host cholesterol and glucose metabolic pathways in major energy metabolism organs such as the liver and muscle. However, orally administered berberine is poorly absorbed and mainly accumulates in the gut content [43]. Modulation of the gut microbiota has been revealed to be an important mechanism underlying the beneficial effects of berberine. Berberine is known for its ability to modify the composition of the gut microbiota, not only selectively inhibiting harmful bacteria, but also enhancing the abundance of beneficial bacteria such as the genera *Bifidobacterium, Lactobacillus*, and *Akkermansia* [44]. Berberine treatment has been shown to result in increased SCFAs levels by remodeling the gut microbiota and enriching some SCFA-producing bacteria in high-fat diet (HFD)-fed rats; the berberine-promoted SCFA butyrate has also been shown to play a role in lowering plasma cholesterol and glucose levels [45,46]. Oral administration of berberine attenuated choline-induced atherosclerosis by inhibiting TMA and TMAO production via manipulating the gut microbiota composition and microbiome functionality, which was confirmed by the transplantation of TMA-producing bacteria in mice [47]. Berberine also increased the levels of conjugated bile acids in serum and feces, and inhibited bile salt hydrolase activity in the gut microbiota; furthermore, the intestinal FXR signaling pathway was shown to be involved in berberine's lipid-lowering effect [48]. These findings provide new and critical molecular mechanistic insights into the causal relationship between the gut microbiome and the anti-atherosclerosis and anti-metabolic-syndrome efficacy of berberine.

Intriguingly, the gut microbiota influences the therapeutic effects of berberine from another perspective. The gut microbiota may convert berberine into its intestine-absorbable derivative dihydroberberine by means of bacterial nitroreductase; the derivative is then oxidized back into berberine in intestinal cells and enters the circulation to increase the plasma drug concentration of berberine [49]. Moreover, the lipid-lowering effect of berberine may be bidirectionally regulated through this transformation. In comparison with healthy individuals, patients with hyperlipidemia have elevated fecal nitroreductase activity, and therefore have a higher blood level of berberine to exert its therapeutic efficacy [50]. Furthermore, the gut microbial reduction of berberine into dihydroberberine was found to promote the production of tetrahydrobiopterin, a coenzyme of tyrosine hydroxylase, which is the rate-limiting enzyme responsible for the hydroxylation of tyrosine to generate levodopa (*L*-dopa) [51]. Thus, oral administration of berberine accelerates the production of *L*-dopa by gut microbes and improves the brain's dopa/dopamine levels to ameliorate Parkinson's disease. The brain-function-improving effect of berberine as an agonist of tyrosine hydroxylase was verified by transplantation of the bacteria containing the enzyme [51]. Another antidepressant compound of Chinese herbal medicine, albiflorin, is similarly difficult to absorb and cannot be detected in the brain after oral administration. However, it has been demonstrated that the gut microbiota can transform albiflorin into benzoic acid, a key metabolite that may cross the blood–brain barrier and exert antidepressant efficacy in inhibiting *D*-amino acid oxidase in the brain [52]. These findings are good examples of the molecular and chemical mechanisms of the gut–brain axis, and shed light on improving brain function by modulating the gut microbiota in the treatment of central nervous system diseases.

In fact, a number of natural products isolated from Chinese herbs have been demonstrated by independent clinical groups to have clinical efficacy; nevertheless, their modes of action remain unclear, which presents a major challenge to traditional Chinese medicine. One of the main difficulties in learning their mechanisms is the low oral bioavailability of many botanical products or compounds (e.g., polysaccharides, alkaloids, flavones, and saponins). Thus, the question remains: How can a drug at very low blood concentrations execute its therapeutic effect in treating diseases? The gut microbiota might provide a scientific explanation for such phenomena, by establishing a convergence between the substances in medicinal herbs and their bioactivities in the human body. Poorly absorbed substances accumulate in the intestine and interact with the gut flora, in which biotransformation and desirable fermentation take place. Thus far, the gut microbiota has been linked with a number of chronic diseases. Furthermore, an increasing number of discoveries are being reported of the causative—not just associative—roles of the gut microbiota and its metabolites in chronic diseases. These discoveries are providing novel therapeutic potential for treating chronic diseases by manipulating the gut microbiota. Medicinal agents that are active in manipulating the composition of the gut microbiota and its derived metabolites—especially those derived from herbal medicines—hold great promise for the treatment of chronic diseases.

In addition, some drugs can either enter the circulation to act with their host targets or remain in the intestine to interact with the gut microbiome. For example, berberine treats metabolic disorders through a mode of action termed a "drug cloud" [53], which addresses both clinical manifestation (e.g., increased blood cholesterol and glucose level) and the root causes (e.g., gut microbiota dysbiosis and chronic inflammation). More specifically, berberine acts on the low-density lipoprotein (LDL) receptor, insulin receptor, and adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathways in the host organs to address the symptoms and signs of disorders, while simultaneously acting on the gut microbiota to address the root causes of disorders. In this way, berberine treats both the symptoms and the root causes of diseases. Some widely used drugs for metabolic or cardiovascular diseases, such as metformin (which acts on the host AMPK pathway) and statins (which act on the host LDL receptor pathway), have also been found to alter the composition of the intestinal microbiota and its metabolites to provide beneficial effects [36,54–57]. The mechanisms of these drugs' regulatory effects on the gut microbiota represent only a tip of the iceberg, and will provide further insights in treating chronic diseases by addressing not just the symptoms, but also the root causes, with an emphasis on the importance of integrating prevention with treatment by modulating the gut microbiome.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (81621064) and the Chinese Academy of Medical Science (CAMS) Innovation Fund for Medical Sciences (2021-1-I2M-009).

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