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Review

The impact of gut microbiota on kidney function and pathogenesis

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ABSTRACT

Chronic kidney diseases (CKDs) are a global health problem. Besides diverse leading reasons in initiation and progression of CKDs, it is evident that they might largely originate from changes in the gut microbial community (microbiota). Mounting evidence indicates that a bidirectional relationship exists between host and microbiome in humans and animals with CKDs. Changes in the microbiota composition and structure (dysbiosis) produce excessive amounts of uremic toxins (e.g. indoxyl sulfate, p-cresyl sulfate and trimethylamine-N-oxide) but less reno-protective metabolites that are implicated in oxidative stress, uremia, inflammation, deterioration of kidney function, kidney diseases progression, a higher prevalence of cardiovascular risk, and mortality in patients with CKD. The present review focuses on the pathogenic association between gut microbiota and kidney diseases like CKD, IgA nephropathy, and kidney stone disease. Certainly, novel insights into the impact of the gut microbiota in kidney diseases can be helpful to develop therapeutic strategies in order to avoid and/or treat aforementioned conditions.

Contents

1. Introduction

Chronic kidney diseases (CDKs) are considered a major health problem and defined as progressive glomerular, tubular and interstitial damage, abnormalities in kidney structure, and gradual kidney function impairment over time [1]. High blood pressure, reduction in erythropoietin synthesis, and increased levels of metabolic acidosis end products can be seen in patients with CKDs.

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Besides different causative factors in initiation and progression of CKDs, it is recognized that the local and systemic consequences of kidney injury may originate from modifications in the gut microbial community (microbiota) and their metabolites [2].

As a super-organism, human body hosts a huge number of bacteria (about 10^{14}) that perform structural and histological functions and play significant roles in the regulation of host health maintenance and homeostasis [3,4],Fig. 1. As the "second human genome" or metagenome, microbiota encodes 3.3 million unique genes that are 150-fold more than the human genome [4]. Therefore, microbiome is able to perform a variety of metabolic functions that humans are not capable of carrying out or are only able to do in a limited capacity. For example, microbes produce enzymes to eliminate oxaloacetate and non-digestible carbohydrate's calories; moreover, they make short-chain fatty acids (SCFAs) that have protective effects for the host [5]. SCFAs (acetate, propionate, and butyrate) are created by microbial fermentation of starches and fibers in the colon and moderately metabolized by gut epithelial cells, and then go into circulation to exert their systemic effects through the G protein–coupled receptors (e.g., GPR41 and GPR43) [6]. A variety of host functions including energy metabolism, regulation of immune responses [7], gut motility, and blood pressure can be affected by the SCFAs [7]. Moreover, through the protection of kidney tubular cells against oxidative stress and biogenesis of mitochondria, SCFAs reduce kidney damage [8]. It is also reported that treatment with SCFAs (e.g., acetate) can decrease ischemia-reperfusion (I/R) kidney injury, inflammation, reactive oxygen species (ROS), and infiltration of immune and apoptotic cells in the injured kidney in mice [9]. Moreover, acetate treatment was associated with an increase in proliferation of kidney epithelial cells and modulation of DNA methylation status [9].

Increasing evidence indicates that changes in the microbiota composition and structure, known as dysbiosis, can affect human health and disease. Therefore, it seems rational that altering the balance of the gut microbiota can also affect kidney physiology and pathology. Deficiency of kidney function can be derived from the retention of bacterial-produced uremic toxins (e.g., indoxyl sulfate (IS), p-cresyl sulfate (PCS), and trimethylamine-N-oxide (TMAO)). Moreover, CKD is associated with oxidative stress, endotoxemia, inflammation and a higher prevalence of cardiovascular comorbidities [10,11] where gut dysbiosis is the primary source of these events. The present article aimed to investigate the association between human microbiota and kidney diseases and to understand how changes in the composition of gut microbiota rigorously affect the kidney function. Furthermore, novel insight on how to balance gut microbiota by probiotics to interfere with the mechanisms leading to kidney disease development are put forward. The pathogenic association between gut microbiota and kidney diseases like uremia, IgA nephropathy, kidney stone disease, and hypertension is illustrated in Fig. 2.

2. Dysbiosis and chronic kidney disease

Recently, the prevalence of CKD in the general population is increasing [1]. In the last decade, rapid changes in the environment and modern lifestyle contribute to increase the development of diabetes and hypertension, the leading causes of CKD in all developed and many developing countries [12,13]. However, they do not fully account for the increased prevalence of CKD. Evidence indicates that the consequences of kidney injury may be also originated from alterations in the gut microbial population that increases the levels of inflammation, uremic toxins, and blood pressure [8], Fig. 2.

2.1. Endotoxin as a cause of inflammation in CKD

In CKD, the microbial dysbiosis can be contributed in immune dysregulation and inflammation [14]. Gut microbial dysbiosis is associated with alteration in gut inflammation and decreased gut barrier [15,16] that result in the activation of the nuclear factor-kappa B (NF-κB) pathway, dysregulated immune response, and chronic production of pro-inflammatory cytokines; leading to systemic inflammation [15,17]. Translocation of endotoxin (e.g., lipopolysaccharides; LPSs) derived from gut bacteria can stimulate immune system cells especially macrophages and endothelial cells to be more activated and secreted a wide variety of pro-inflammatory cytokines [16], Fig. 2. Evidence demonstrates that subclinical endotoxemia has various negative effects on

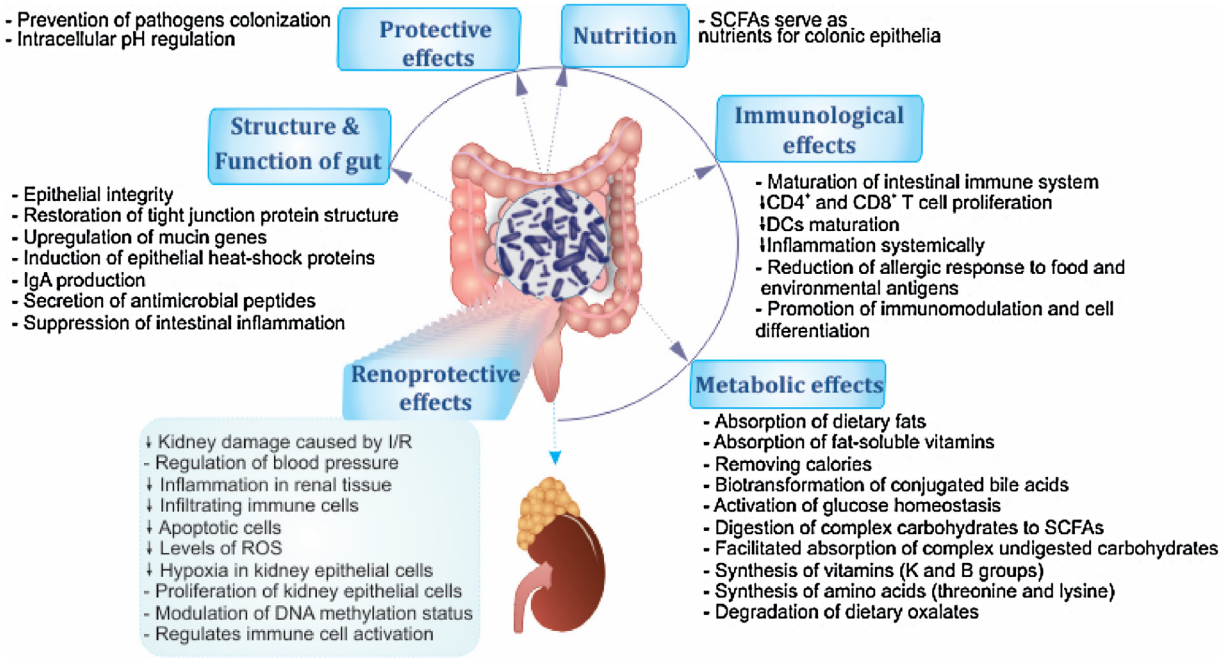

Fig. 1. Beneficial effects of gut microbiota on human health [8,9,81,90].