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The intestinal microbiota, a leaky gut, and abnormal immunity in kidney disease

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Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are associated with systemic inflammation and acquired immunodeficiency, which promote cardiovascular disease, body wasting, and infections as leading causes of death. This phenomenon persists despite dialysis-related triggers of immune deregulation having been largely eliminated. Here we propose a potential immunoregulatory role of the intestinal microbiota in CKD/ESRD. We discuss how the metabolic alterations of uremia favor pathogen overgrowth (dysbiosis) in the gut and an increased translocation of living bacteria and bacterial components. This process has the potential to activate innate immunity and systemic inflammation. Persistent innate immune activation involves the induction of immunoregulatory mediators that suppress innate and adaptive immunity, similar to the concept of 'endotoxin tolerance' or 'immune paralysis' in advanced sepsis or chronic infections. Renal science has largely neglected the gut as a source of triggers for CKD/ESRD-related immune derangements and complications and lags behind on the evolving microbiota research. Interdisciplinary research activities at all levels are needed to unravel the pathogenic role of the intestinal microbiota in kidney disease and to evaluate if therapeutic interventions that manipulate the microbiota, such as pre- or probiotics, have a therapeutic potential to correct CKD/ESRD-related immune deregulation and to prevent the associated complications.

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The term microbiota describes the 10^{13} bacterial cells from 200 to 500 different bacterial species that colonize the outer and inner surfaces of the human body. The intestinal microbiota coevolves with the host for a mutually beneficial coexistence. The bacteria estimate the stable, intestinal nutrient environment, in return providing the host with energy-rich metabolites and vitamins. Moreover, the microbiota induces and maintains immune homeostasis and protects against infection with pathogens.[1] The human microbiome just started to be thoroughly characterized owing to the development and continuous improvement of deep sequencing technology as well as national and international funding initiatives (Human Microbiome Project and Metagenomics of the Human Intestinal Tract).[2] In addition, studies using germfree and gnotobiotic animal models complement genomic approaches for a deeper understanding of the functions of human gut microbiota and provide a more mechanistic view on host–microbiome interactions. For example, germfree mice display severe immune abnormalities, which relate to an incomplete education of the immune system.[3] From the time of the postnatal colonization of the gut, the intestinal microbiota obviously becomes an important element in priming the physiological structure of lymphoid tissues by driving the functional interactions of all elements of the adaptive immune system.[1] This applies not only to the mucosa-associated lymphoid tissue of the Peyer's patches but also to the extraintestinal lymphoid tissues. This implies some leakiness of the intestinal barrier that anatomically separates the intestinal microbiota's biotope from the host.[4] The physiology of enteric absorption of nutrients also seems to involve a certain passage of bacterial components beyond the intestinal barrier as an element of physiological shaping of the immune system and immune responses.[5] Recent studies now document that this process also contributes to the manifestations of noncommunicable diseases like autoimmune diseases, chronic heart, or liver disease.[6–9]

In this review we discuss the potential roles of the intestinal microbiota in the context of kidney disease. The intestinal microbiota's contribution in urea breakdown or uremic toxin production has been summarized elsewhere.[10] Here, we discuss the potential role of the microbiota on systemic inflammation, protein wasting, accelerated

atherogenesis, and immunosuppression as major determinants of mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD).

THE INTESTINAL MICROBIOTA, A 'SYMBIOTIC ORGAN'

Along its entire length, the orogastric/gastrointestinal tube is colonized with bacteria. In healthy individuals, the phyla Bacteroidetes and Firmicutes contribute >90% of all species, including abundant bacterial genera such as *Bacteroides* spp., *Alistipes* spp., *Prevotella* spp., *Porphyromonas* spp., *Clostridium* spp., *Dorea* spp., *Faecalibacterium* spp., *Eubacterium* spp., *Ruminococcus* spp., and *Lactobacillus* spp. Other less abundant phyla represent the Actinobacteria (that is, *Bifidobacterium* spp. and *Collinsella* spp.), Proteobacteria (that is, *Enterobacteriaceae*, *Sutterella* spp., and *Helicobacter* spp.), Verrucomicrobia (that is, *Akkermansia* spp.), and methanogenic Archaea.[2] Density and relative species composition varies considerably between the different regions of the gastrointestinal tract. The vast majority of bacterial species has a strict anaerobic metabolism; however, some species (that is, the *Enterobacteriaceae*) are facultative anaerobic. Thus, following the decreasing oxygen tension, bacterial density increases from the stomach (10^2–10^4/ml) toward the ileum (10^6–10^8/ml), reaching its maximum in the colon ($>10^{12}$ cells/ml).

Bacterial colonization in the ileum is kept in check by antimicrobial peptides, expressed by paneth cells in small intestinal crypts. This lowers the density of microbial competitors to ensure resorption of readily available nutrient components by the enterocytes. Persistent dietary components like plant-derived polysaccharides or resistant starches reach the colon where they are degraded by the concerted action of the resident microbial food web. A large number of degraders (that is, Bacteroides) express secreted glycan-degrading enzymes freeing mono- and oligosaccharides from complex dietary glycans, starches, or mucin, which are thereafter metabolized in primary fermentation reactions. Products of the primary fermentors include hydrogen and CO_2 as well as short-chain fatty acids acetate, butyrate, propionate, and lactate as well as ethanol. Short-chain fatty acids serve as energy source of colonocytes but other bacteria use them as substrate for secondary fermentation reactions. The last link of the chain constitutes hydrogen-consuming sulfate-reducing bacteria as well as methanogens competing for the available hydrogen. Hydrogen is a thermodynamic inhibitor of the primary fermentations; thus, hydrogen consumption plays an important role for the colonic ecosystem. Thus, stability of this ecosystem is maintained by functional diversity, which is mostly driven by oxygen tension and nutrient availability.

Despite the beneficial functions of its intestinal microbiota, the host has to keep bacteria outside the body to prevent infection. The 10^{12} bacterial cells/ml within the colonic lumen are merely separated by a single-layered, highly absorptive epithelium that still prevents bacterial translocation.[4] This is guaranteed by the protective mucus layer, defensins, and antibacterial lectins shielding the epithelium from direct contact with the bacteria as well as the innate (that is, sensing of microbial patterns by innate immune cells in the lamina propria) and adaptive arms (that is, immunoglobulin A–secreting plasma B cells) of the mucosal immune system.[5,11,12] It is still incompletely understood how the mucosal immune system remains largely ignorant toward the autochthonous flora while triggering a subacute response, which maintains the symbiotic equilibrium. However, a disrupted tolerance triggers an overshooting inflammatory response against the microbiota, which can lead to overt pathology and chronic intestinal inflammation, for example, in inflammatory bowel diseases. Experimental studies suggest a defective mucosal barrier (for example, introduced by muc2, Nod2, or interleukin-10 deficiency) or microbiota abnormalities, that is, dysbiosis, to cause inflammatory bowel diseases. In addition, gnotobiotic mouse models revealed that different members of the microbiota induce different types of immune responses. A mixture of anaerobic *Clostridium* spp. has been demonstrated to induce FoxP3$^+$ regulatory T cells. Another, yet uncultivated member of the Clostridia, the segmented filamentous bacteria, promotes T helper type 17 cell differentiation.[13]

Certain members of the normal microbiota harbor a particular pathogenic potential and can cause disease under certain conditions. For this reason, they are termed pathobionts.[14] Examples for pathobionts are *Helicobacter hepaticus*, *Bacteroides*, and *Prevotella* spp., as well as γ-Proteobacteria that drive experimental colitis. Dysbiosis can be promoted by the inflammation itself, making it difficult to discern cause and consequence of the disease.[15,16] Furthermore, the host genotype and environmental factors such as antibiotics can induce dysbiosis.[17,18]

POTENTIAL IMPACT OF CKD/ESRD ON THE INTESTINAL MICROBIOTA AND BARRIER

Various extraintestinal noncommunicable diseases are associated with dysbiosis because they affect intestinal immunity in a way that it can no longer maintain the physiological control of the microbiota.[5,7,11,14] Therefore, it is reasonable to assume that the metabolic and hemodynamic alterations of CKD/ESRD also alter the composition and function of the intestinal microbiota (Figure 1). Evolving data now confirm this concept. For example, Vaziri *et al.*[19] characterized the intestinal microbiota of uremic versus nonuremic patients and rats and found uremia to be associated with an increase in intestinal pathobionts. How could CKD affect the gut flora? The potential factors are: metabolic acidosis, retention of uremic toxins, volume overload with intestinal wall congestion, and frequent use of antibiotics and oral iron that promotes pathogen overgrowth. Also, intestinal ischemia induces dysbiosis that may be supported by renin–angiotensin–aldosterone system blockade and/or vascular calcifications. The polymer phosphate binder sevelamer also binds intestinal bacterial products. Furthermore, diet changes