*Mini review*

# Promising probiotics for the treatment of nephrotoxicity induced during immune-checkpoint therapy against cancers

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**Abstract:** The immune-related adverse events resulting from the therapy of immune checkpoint inhibitors could cause kidney injury. Inflammatory reprogramming of regulatory T helper (Treg) cells or type 17 T helper (Th17) cells might be involved in the pathogenesis of nephropathy. Accumulating evidence confirms a connection between the diversity of gut microbiota and kidney diseases, suggesting that successful modification of gut microbiota could attenuate kidney injury. In other words, certain gut microbiota could contribute to the protection of kidneys via the gut-kidney axis. It has been shown that the dysbiosis of gut microbiota might affect the gut-kidney axis, leading to nephrotoxicity. On the contrary, altered levels of D-amino acids, ROS, and SCFAs through the adjustment of gut microbiota might be relevant to the reduction of nephrotoxicity. Here, we have discussed and suggested the beneficial roles of gut microbiota in the prevention of the kidney injury induced during immune-checkpoint therapy.

**Keywords:** immune-related adverse events; immune checkpoint inhibitors; gut-kidney axis; gut-immune axis; short-chain fatty acids; D-amino acids; reactive oxygen species

**Abbreviations:** ATP: adenosine triphosphate; CTLA-4: cytotoxic T lymphocyte-associated protein 4; CKD: chronic kidney disease; DNA: deoxyribonucleic acid; FMT: fecal microbiota transplantation; GVHD: graft-versus-host disease; HDAC: histone deacetylase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; ROS: reactive oxygen species; SOD: superoxide dismutase; Th1: type 1 T helper; Th17: type 17 T helper; Treg: regulatory T

# 1. Introduction

The immune checkpoint inhibitors targeting programmed cell death protein-1 (PD-1) or its ligand (PD-L1) are among the most effective immunotherapy agents, which are now given to increasing numbers of patients with advanced cancers. Consequently, a considerable number of immune-related adverse events have been reported, predicting that such events will become important [1]. The immune-related adverse events which may result from the therapy of immune checkpoint inhibitors could affect various organs, including the kidneys [2]. Now, the number of immune-related adverse events have grown noticeably, and it has become a major focus of current investigation. The most common kidney side effect associated with immune-related nephrotoxicity is acute kidney injury, which is usually caused by acute tubule-interstitial nephritis, with severity ranging from mild to life-threatening; it is also imitating the acute T-cell-mediated kidney injury of graft-versus-host disease (GVHD) in hematopoietic stem cell transplantation [3]. In addition, it has been reported that the use of the immune checkpoint inhibitors in patients with a preexisting autoimmune disease might be related to the increased occurrence of overall adverse events [4]. Recently, probiotics and/or prebiotics were shown to attenuate the severity of the disease condition within acute kidney injury [5], GVHD [6] and autoimmune disease [7], suggesting that gut microbiota might have considerable protective effects on the host against the above-mentioned immunological disorders. In addition, the uses of probiotics and/or prebiotics have shown potential positive effects, even against the production of uremic toxins in kidneys, with minimal risk of hyperkalemia and/or cachexia [8]. An increasing number of studies are also suggesting the effects of gut microbiota on the alleviation of acute kidney injury. In fact, plant-based diets and prebiotic, probiotic and symbiotic supplementation may lead to favorable alterations in the gut microbiota [9], suggesting that probiotics and/or prebiotics have potential benefits for the primary prevention of immune-related adverse events. Therefore, probiotics may therefore be a promising strategy to reduce the severity of acute kidney injury [5].

# 2. Treg cells and Th17 cells may be involved in the pathogenesis of immune-related adverse events

PD-1-blocking antibody therapy may rapidly result in the depletion of circulating PD-1 positive T regulatory (Treg) cells [10], which plays an important role in the effective anti-tumor responses in the tumor microenvironment [11]. Treg cells can facilitate immune-avoidance by tumor cells via diminishing anti-tumor immunity [12]. Similarly, the role of PD-L1 is overriding in type 1 T helper (Th1) and type 17 T helper (Th17) cell immunity [13]. Functional T cells, including the subsets of Th17 cells and Treg cells, play significant roles in determining the inflammatory microenvironment [14]. Therefore, anti-PD-1 therapies often trigger T cell-mediated adverse events that mimic Th17-mediated inflammatory diseases [15]. The reprogramming of immune cells might be a feature of GVHD, which is associated with the differentiation of CD4 positive Th1 cells into Th17 cells, along with the dysfunction of Treg cells [16]. In addition, Th17 cells are more prevalent in immune-related enterocolitis than Th1 cells [17]. Arthritis, after combined CTLA-4 and PD-1 inhibitor therapy, has favorably enhanced Th17 and transient Th1 or Th17 cell signatures [18]. Treg cells and/or Th17 cells are important in the immunopathology of lupus nephritis [19]. A high ratio of Th17/Treg cells was observed in lupus nephritis [20]. A potential role of the Th17 cells was also indicated in renal inflammation in glomerulonephritis [21]. In the setting of inflammatory responses with pathogenic

Th17 cells, mesenchymal stem cells may suppress the differentiation of Th17 cells and the related inflammation in the kidneys [22]. In addition, it has been suggested that an imbalance of Th17/Treg cells seems to be an immunological basis of nephritic syndrome [23]. Accordingly, inflammatory reprogramming of Treg cells and/or Th17 cells might be a feature of the nephropathy in immunotherapy-induced immune-related adverse events [24].

## 3. Gut microbiota could contribute to the protection of kidneys

Accumulating evidence confirms a connection between the diversity of gut microbiota and host diseases. In other words, the potential of gut microbiota has been recognized as a contributing factor in the development of various diseases, including obesity, diabetes, kidney disease and hypertension [25,26]. Gut microbiota can affect the systemic levels of reactive oxygen species (ROS) that play vital roles in inflammatory diseases [27]. Generally, living cells reluctantly release ROS for indispensable ATP synthesis, which may cause DNA damage in cells [28]. However, some important physiological roles of ROS include the regulation of enzymes involved in autophagy, whose signaling could affect the balance of Th17/Treg cells [29]. ROS are defined as oxygen-hugging active molecules capable of reacting with various host molecules or organs, which also result from inflammatory reactions [30]. Gut microbiota may manage the production of ROS, which eventually protect some organs against oxidative stress [31]. Therefore, understanding the redox regulation of physiological processes seems to be important for developing a therapeutic approach with the modification of gut microbiota. The pathogenic connection between the gut microbiome and kidney diseases is termed the gut–kidney axis [32], which is often implicated in IgA nephropathy and/or in chronic kidney disease (CKD) (Figure 1). In the cases of both diseases, an apparent reduction of the tight junction proteins may be possibly be attributed to the production of uremic toxins [33,34]. In addition, gut bacteria could activate a Th17/Th1 T-cell response, which may increase the production of inflammatory cytokines, triggering inflammation and/or immune response in the kidneys [35]. In fact, changes in the composition of the gut microbiota can promote an inflammatory status that is relevant to the pathogenesis of nephropathy [36]. For example, patients with renal failure have a low abundance of the genus *Lactobacillus*, whereas the proportion of the family *Enterobacteriaceae* are increased in the patients [37].

A beneficial role of gut microbiota in the progression of kidney diseases has been suggested. For example, probiotics such as *Akkermansia* and *Lactobacillus* could alleviate renal metabolism in CKD through the gut-kidney axis [38]. The reversal of gut dysbiosis using fecal microbiota transplantation (FMT) may be a promising therapy for CKD [39]. Successful modification or remodeling of the composition of gut microbiota could attenuate kidney inflammation [40]. In the development and/or prevention of diabetic nephropathy, the microbiota in the gut-kidney axis might play a key role [36], suggesting potential efficacy of the gut microbiota in the nephrotoxicity induced during immune-checkpoint therapy. For example, *Salvia miltiorrhiza* could alleviate the renal metabolism caused by cyclosporine-induced chronic nephrotoxicity through the gut-kidney axis [38] (Figure 1).
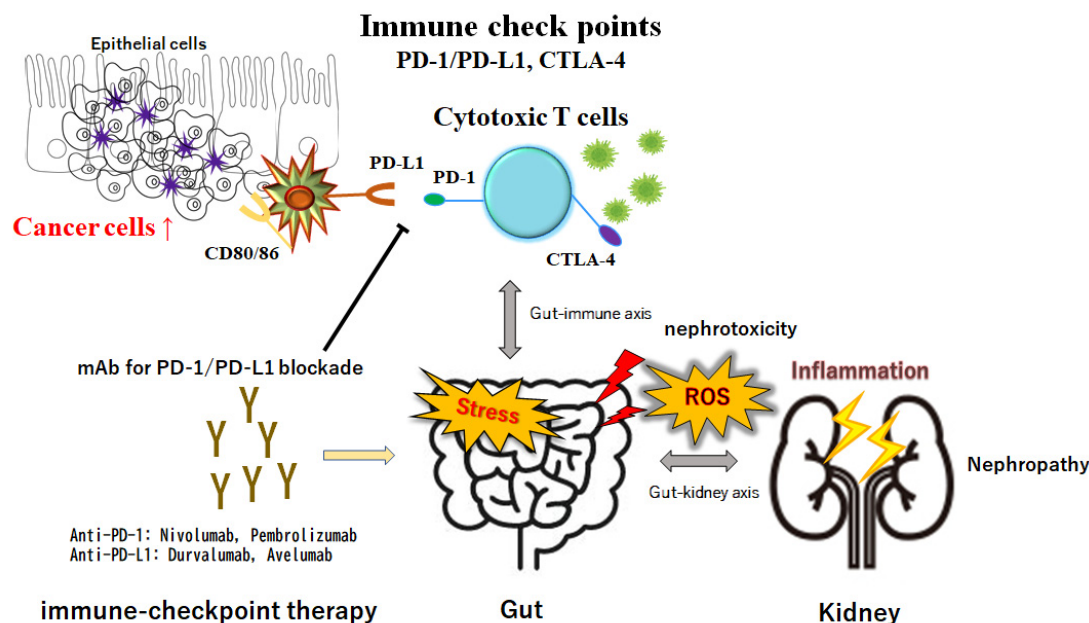
**Figure 1.** Hypothetical schematic image of the gut-kidney axis and the gut-immune axis involved in the nephrotoxicity induced during immune-checkpoint therapy. The indicated antibodies are provided as examples, and are in no particular order. The arrowheads mean stimulation, whereas the hammerhead represents inhibition. Note that some critical pathways, such as inflammation activation and/or epigenetics pathways, have been omitted for clarity. Abbreviations: ROS, reactive oxygen species; SCFAs, short-chain fatty acids; CTLA-4, cytotoxic T lymphocyte-associated protein 4; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand 1.

## 4. Favorable roles of gut-kidney axis for the protection of kidneys

As a vital regulator of gut microbiota, the role of the linkage between nutrition and the gut microbiota in conserving the host health has been widely discussed [41]. Therefore, researchers have increasingly turned their attention to gut microbiota and its derived metabolites as a potential target for various therapeutics [42]. In clinical practice, the most largely used gut microbiota-targeted therapies are probiotics and prebiotics. Probiotics are alive bacteria that have health benefits when administered [43]. Prebiotics can promote the growth and/or activity of beneficial bacteria [43]. Synbiotics denote a mixture comprising probiotic and prebiotics, and they also present a health benefit. Also, the use of substances produced through metabolism of the gut microbes has also shown an encouraging effect on the host as postbiotics [44]. The gut microbiota may produce various D-amino acids that are beneficial for the protection of kidneys. For example, D-Ala inhibits ROS production and/or improves the potential of mitochondria [45]. Some *Enterobacteriaceae*, including *Escherichia coli* and/or *Klebsiella oxytoca*, could generate D-Ala in the gut, which might ameliorate kidney injury in mice, suggesting that D-Ala could be a promising therapeutic target [45]. In addition, it has been demonstrated the protective effects of gut-derived D-serine on kidney injury as another potential therapeutic target [46]. Several studies highlighted the relationship among the gut microbiota and oxidative stresses in various diseases [47]. ROS might be strictly controlled by the various signaling

processes for appropriate gut immunity [48]. Some microbial products could upregulate the activity of superoxide dismutase, which results in a lower level of systemic ROS [49]. Nephrotoxicity rapidly weakens kidney function due to exposure to ROS, leading to inflammatory responses [50], which could be affected by alterations in the redox conditions of the gut. Carbohydrates are fermented to generate short-chain fatty acids (SCFAs), which are fatty acids with fewer than six carbon atoms, and they may work as an inhibitor for histone deacetylase (HDAC) [51]. HDAC inhibitors can attenuate acute kidney injury-mediated damage in the animal models of kidney diseases [52]. In addition, certain levels of SCFAs produced by healthy gut microbiota have been shown to possess anti-inflammatory properties with the regulation of T cell proliferation [53]. Furthermore, it has been shown that SCFAs can improve kidney function through the modulation of the inflammatory process via the expression levels of the enzymes involved in chromatin epigenetic modification [54]. In other words, SCFAs can improve kidney function after an injury, most likely via the epigenetic modification occurring as a result of a dual relationship between gut and kidneys [54]. Altering the composition of the gut microbiota has been shown to systematically alleviate the immunopathology of the CTLA-4 blockade in a Treg-dependent manner in mice [55]. The gut microbiota might also impact host cell metabolism [55]. Consequently, levels of D-amino acids, ROS and SCFAs that have been altered via the modification of gut microbiota could be relevant to the reduction of nephrotoxicity and/or the protection of kidneys. Recent relevant research showing promising effects of probiotics, prebiotics and FMT against kidney injury, including nephropathy, are shown in Table 1.

**Table 1.** Relevant researches showing promising effects of probiotics, prebiotics and fecal microbiota transplantation (FMT) against kidney injury.

| Method | Reference No. |
| --- | --- |
| Probiotics | 5,36,42,43,44 |
| Prebiotics | 42,43,44 |
| FMT | 36,39 |

## 5. Next perspectives

It has been shown that cisplatin causes the dysbiosis of gut microbiota, which might change the microbiota-derived metabolites and affect the gut–kidney axis, leading to nephrotoxicity [56]. Therefore, potential mechanisms for kidney protection should include several changes in the structure of commensal bacteria, such as increasing butyrate-producing bacteria, decreasing pathogenic bacteria and modulating the levels of microbiota-dependent metabolites, such as those affected by SCFAs, endotoxins and uremic toxins. As for immune-related adverse events, the gut-immune axis might affect the pathogenesis of the events. As an interesting example, it has been shown that high salt-intake may induce Th17 cells via the gut-immune axis, affecting autoimmunity and/or cardiovascular disease [57]. In a dose-dependent manner, sodium chloride was shown to be a driving factor for autoimmune diseases, including rheumatoid arthritis, through the induction of pathogenic Th17 cells [58]. Furthermore, it has been reported that a diet rich in sodium chloride may affect gut microbiota and increase intestinal Th17 cells, indicating the harmful effects of salt consumption on the gut-immune axis in multiple sclerosis [59]. Prospective clinical trials will be mandatory to investigate the effects of gut microbiota as a potential supportive therapeutic intervention against the nephropathy in human immune-related adverse events. In the end, the application of microorganisms could transmit

antibiotic-resistance actors to the other microorganisms in the gut, which could result in important infections to the host [60]. Therefore, more studies should also be compulsory for identifying promising strategies to evade antibiotic resistance spread to pathogens in the gut.

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## Conflict of interest

The authors declare no conflict of interest.

## Author contributions

Conceptualization, SY and SM; original draft preparation and editing, KT, HS, YI, AT and SM; visualization, SY and SM; supervision, SM. Each author (SY, KT, HS, YI, AT, SM) has participated sufficiently in the work of drafting the article and/or revising the article for the important rational content. All authors gave final approval of the version to be submitted.

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