Intestine as a Source of Inflammation in Chronic Kidney Disease: Effect of Indoxyl Sulfate

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Chronic kidney disease (CKD) is associated with a persistent systemic inflammation and oxidative stress conditions driving to the pathogenesis of many CKD-associated complications (Cachofeiro et al. 2008; Stenvinkel, 2006). This syndrome is attributed to the progressive retention of a large number of compounds which, under normal conditions, are excreted by healthy kidneys. These compounds are called uremic toxins because of their harmful effects in various physiological functions in CKD patients (Vanholder et al., 2001). Indoxyl Sulfate (IS), a protein bound uremic toxin, which, therefore, is poorly eliminated by dialysis. It results from the metabolism of dietary tryptophan. Intestine has a primary role in IS production: tryptophan is metabolized into indole by intestinal bacteria and after intestinal absorption, is further converted into IS in the liver (Niwa, 2010). IS is a nephro-vascular toxin that causes nephrotoxicity, especially on tubular cells, inhibits proliferation of endothelial cells and it is an inducer of free radicals (Niwa & Ise, 1994). Moreover, it has been reported that IS enhances inflammatory response and reactive oxygen species (ROS) in LPS-stimulated macrophages thus supporting its role in immune and inflammatory response (Adesso et al., 2013).

Evidences highlighted the gastrointestinal tract as a major source of chronic inflammation in CKD (Vaziri et al., 2015). Gut bacterial DNA fragments have been detected in the blood of both pre-dialysis CKD and chronic hemodialysis patients (Shi et al., 2014). The intestinal epithelium has an important role by forming a physical and biochemical barrier to commensal and pathogenic microorganism. Furthermore intestinal epithelial cells (IECs) maintain a fundamental immunoregulatory function that influences the development and homeostasis of mucosal immune cells. It has been reported that IS reduction ameliorated CKD-induced intestinal epithelial barrier disruption and inflammation (Vaziri et al., 2013) but the molecular mechanism/s and the modulation of IS-induced effects on IECs remain poorly studied. The aim of this study was to evaluate the effect of IS (1000-125 μM) on oxidative stress, inflammation and barrier function in IEC-6 cells. Our results indicated that IS treatment increased ROS release, reduced Nuclear factor (erythroid-derived 2)-like 2 nuclear translocation and the cytoprotective heme oxygenase 1, NAD(P)H quinone dehydrogenase 1 and superoxide dismutase expression. Moreover IS increased tumor necrosis factor-α levels in IEC-6. In order to evaluate the effect of IS on IEC-6 migration, the wound healing assay was also performed. IS reduced IEC-6 migration and induced actin cytoskeleton rearrangement in the cells. Preliminary in vivo experiments also indicated a pro-inflammatory effect of IS at intestinal level. Our results highlight that IS induces oxidative stress, inflammation and impairs barrier function in IECs. These findings let to hypothesize a significant contribution of IS to CKD-associated intestinal alterations and support the identification of IS as a potential pharmacological target in CKD.

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