Does Dysbiosis in Intestinal Microbiome Plays a Role in Children with Relapsing Idiopathic Nephrotic Syndrome?

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Idiopathic nephrotic syndrome (INS) is a clinical condition occurring predominantly in children. It is characterized by massive proteinuria, hypoalbuminemia, hyperlipidemia, and edema. This renal condition is classified into 3 groups: idiopathic (INS, 90% of cases), secondary (10%), and congenital (<1%). There are 2 histologic variants: minimal-change disease (85%) and focal segmental glomerulosclerosis (10%). The etiology of INS has been attributed to the impaired function of T cells [1], but the precise mechanism is unknown. A potential mechanism is the development of T-cell dysregulation in which cytokines act as a modifier of podocyte ultrastructure [1]. Numerous studies have failed to identify the cytokine responsible for the development of proteinuria in INS. The condition is most likely the result of a complex interaction between several cytokines and cells [2].

In 2009, Hashimura et al. [3] described a 5-year-old child with immunodysregulation polyendocrinopathy enteropathy x-linked syndrome syndrome who developed minimal change nephrotic syndrome. This patient got a mutation of forkhead box P3, which resulted in a decrease in regulatory T cells (Treg), suggesting a pathogenic role of Treg in INS. Several studies have demonstrated that the dysfunction of Treg might play a role in the pathogenesis of INS [3–4]. It is unclear how Treg af-

fect podocyte function and lead to the development of proteinuria in INS. A recent review proposes two potential mechanisms [5]. Treg may reduce the oxidative effect of circulating cells during the early immune response, which is toxic to podocytes. An alternative mechanism might involve Treg suppression of CD80 overexpression on podocytes, which is reported to be pathogenic in INS.

Under normal physiological conditions, the gut microbiota is an ecosystem with several vital functions important to host health including food digestion, development of the host immune system and intestinal epithelial barrier, and protection against pathogens. Disruption of this equilibrium can result in dysbiosis and increase risk of disease. Gut dysbiosis is an altered composition of intestinal microbial populations and is thought to provide continuous immunological stimulation leading to immune response anomalies in numerous immune-mediated inflammatory diseases [6].

Treg cells are induced by short chain fatty acids produced by gut microbiota. Children with allergies have decreased function of colonic Treg due to aberrant microbiota (dysbiosis). Although dysbiosis of gut microbiota has been reported in chronic kidney disease [7], no studies have considered the presence of dysbiosis of gut microbiota and INS.

In this issue of the journal, Tsuji et al. [8], propose that that dysbiosis involving decreased butyric acid-producing gut microbiota results in the defective induction and differentiation of peripherally induced Treg, resulting in INS relapse. They obtained stool samples from patients with INR on relapse (R) to study their microbiome using 16S rRNA metagenomic analysis, and fecal butyric acid was measured using high-performance liquid chromatography. The authors also performed flow-cytometric analysis of Treg and CD4-positive cells in peripheral blood. The children with INR on relapse were compared to a non-relapse group (NR) and healthy controls (HC).

The metagenomic analysis of gut microbiota showed that the proportion of butyric acid-producing bacteria was significantly lower in R than HC but no different be-

tween NR and HC. The fecal organic acid analysis showed lower butyric acid quantities in R than HC with no significant differences between R and NR. Circulating Treg as a proportion of CD4-positive cells were decreased in both R and NR groups.

This study showed that children with relapsing INS have gut microbiota dysbiosis, characterized by a decreased proportion of butyric acid-producing bacteria and lower fecal butyric acid quantities. They also have a reduced circulatory Treg. The role of these differences in the development of a relapse is not clear, since both R and NR groups have similar changes. Limitations of the study include a small sample size and lack of measurements of the plasma butyric acid levels. Future studies with a larger sample size are needed to verify the significance of these interesting findings.

References

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