Update in the relationship between gut microbiota and Kawasaki disease

Abstract

Kawasaki disease (KD) is an acute febrile systemic necrotizing medium and sma ll vasculitis in children, mainly affecting children under 5 years old, and has beco me the main cause of pediatric acquired heart disease in developing countries. Th e exact etiology of this disease is still unclear. At present, researches on KD are mostly limited to susceptibility gene, infection and immunity. However, there are few studies on the correlation between intestinal flora and KD. In recent years, so me studies have found that KD is related to the imbalance of intestinal flora, and the abundance and structure of intestinal flora in children with KD change, whic h contributes to the occurrence and development of KD by affecting the release o f inflammatory factors, damaging the intestinal barrier function and activating the autoimmune system. This review aims to elucidate the relationship between gut microflora and KD, and the mechanism of action and that of probiotics.

Key words: intestinal flora, mechanism of action of Kawasaki disease, probiotics

Introduction

Kawasaki disease (KD) is a poly systemic vasculitis of unknown etiology, which mainly occurs in children.KD was first reported by Mr.Kawasaki in 1967, after which, the etiology of KD remains uncertain.Increasing evidence now suggests that the complex interplay of genetic susceptibility and microbial infection may be involved in KD pathogenesis.[1]It is thought to be a multisystem disease, dominated by coronary arteries and, if left untreated, causes coronary artery stenosis, aneurysms, and thrombosis[2].KD has occurred around the world, and its epidemiology varies by geographical location, ethnicity.Most cases have been reported in South Korea, Japan, and Taiwan.Moreover, the incidence of KD is increasing in developed countries[3].

It is widely accepted that KD is triggered by infection in genetically susceptible individuals, followed by immune system abnormalities[4].Studies have found that intestinal microflora disorders can lead to a hyperimmune response to trigger KD[5].Now we will do a review of the relationship between intestinal flora disorders and KD and the possible mechanisms, as well as the application of probiotics in the treatment and prevention of KD.

1. Intestinal flora

There are 40 trillion bacteria in the human gut, and the gut microbiota has a great impact on human physiology, immunity and nutrition.Inteintestinal imbalance, also known as flora disorder, is related to metabolic disorders, inflammatory bowel diseases, autoimmune diseases and colon cancer.Therefore, in order to maintain physical health, controlling the balance of the intestinal environment may be an effective way to maintain human health.The gut microbiota produces large amounts of metabolites, such as short-chain fatty acids, which play important roles in maintaining

host health and suppressing the onset of various diseases.

Lactobacillus colonizes the surface of intestinal mucosal epithelial cells to form physical bacterial membrane barriers in colonization areas and improve the expression level of tight junction protein expression between epithelial cells[6], thus playing an important role in maintaining intestinal barrier function.Currently, it has been shown that the etiology of Kawasaki disease is closely related to enterogenic infection, and the weakened intestinal barrier function caused by the reduced abundance of Lactobacillus genus may be one of the high risk factors for the infection of Kawasaki disease-related pathogens.Some studies have once again confirmed[7] that the intestinal flora disorder is associated with inflammatory bowel disease. The intestinal super megatromonas and butyrate bacteria decreased relative abundance, and may be associated to T cell aberrations, these intestinal microbial composition and function may be accompanied by molecular exchange between intestinal immunoactive cells and intestinal microbes, these interactions may be related to immune disorders in BD patients[8].We observed significant changes in the composition of gut microbes in BD patients, with more species of Actinobacteria and Lactobacillus in the gut flora and less in BD patients compared with normal people.[9]

2.Gut microbiota and Kawasaki disease

In recent years, [10] through high-throughput sequencing technology has identified the existence of obvious intestinal flora disorders in children with Kawasaki disease, manifested by the change of intestinal flora structure and its abundance, the change of Lactobacillus, Verrococcus and Clostridia, and the abundance of Bacteroides, Enterococcus and Parobacterium.Recent studies [11]have also revealed the Kawasaki disease children intestinal enterococcus, acinetobacter, Acinebacter, snails, lactococcus, Staphylococcus and butyrate monas relative abundance increase, at the same time produce short chain fatty acids (SCFA) microbiota reduction, promote the gut microbiota associated with KD dysbiosis, which has never been reported in previous studies.Furthermore, we observed that gut microbiota disorders is associated with systemic inflammation in children with KD.At the same time, some scholars have found that the prevalence of Clostridium [5], Shigella and Streptococcus may be related to the pathogenesis of KD.The results also suggest that the recovery of beneficial bacteria, especially common Bacillus, Bifidobacterium, and Lactobacillus may help alleviate KD symptoms.The number of streptococci in the gut flora in acute KD patients increased significantly, in contrast, the majority of children with KD are deficient in Lactobacillus, and this difference in flora composition may be related to the pathogenesis of KD [12-13].

A case – control study first showed that [14] infants with antibiotic treatment or cesarean section and compared with children without antibiotic treatment.These suggest a possible interaction between the altered gut microbiota and the occurrence of KD, confirming the association between antibiotic administration and KD pathogenesis, which may promote the development of KD by affecting the gut microbiota in infants and young children.In addition, it is the first study to report [15]that the hydroproducer Dorea is significantly reduced in children with acute KD, and in short, intestinal microbiosis exists in children with acute KD.

3.Mechanisms associated with gut microflora and Kawasaki disease

Studies have found that enterococcus, Acinetobacter, Aspirobacter, Lactococcus, Staphylococcus and butyomonas are significantly higher in children with acute KD compared with healthy children.The levels of systemic inflammatory biomarkers were significantly increased in children with acute KD, including IL2, IL-4, IL-6, IL-10, TNF-, and INF.The altered microbiota of

Enterococcus genus and Spirococcus abundance showed a positive association with IL 6, which has not previously been reported for [11] in KD.At present, studies have proved that the changes in intestinal microflora in children with KD are significantly associated with in ROR t, FOXP3, and T lymphocyte subsets[16].Increasing evidence suggests that the imbalance between helper 17 cells (Th17s) and regulatory T cells (Tregs) is related to the abnormal immune response to KD, with studies showing that Th17s and Tregs differentiation is regulated by of short-chain fatty acids (SCFA) produced by the gut microbiota. [17]

4.Probiotics and Kawasaki disease

Probiotics are living microorganisms that have beneficial effects on their hosts by restoring an unbalanced gut microbiota or maintaining a healthy gut microbiota.Bifidobacterium and Lactobacillus are the most common probiotic bacteria, and their biological and bacteriological properties have been extensively studied to determine their beneficial functions.In recent years, great progress has been made in studying the function of bifidobacterium species, which and its metabolites play an important role in promoting the health of [18].Bifidobacterium (BIF) is one of the dominant bacteria in the gut of humans and many mammals, regulating intestinal flora disorders.It was found that [19] BIF treatment effectively inhibited TNF-induced overexpression of IL-6 and IL-8.After BIF treatment, the TNF-disrupted intestinal mucosal barrier function can be effectively restored.Moreover, BIF also inhibited TNF-induced autophagy.The TNF-activated NF-B and p38MAPK signaling pathways are also blocked by BIF.In conclusion, our study demonstrates that [19] BIF plays a protective role in the T NF-induced inflammatory response in Caco-2 cells through the N F-B and p38MAPK pathways, and our study may provide experimental evidence for the treatment of Kawasaki disease.Studies have also proved that [20] oligo-fructose can improve the intestinal microbiota disorder, improve short-chain fatty acid production, and reduce coronary artery damage in Kawasaki disease in mice.

In addition, studies have found that existing treatments of [15] combined with probiotic intervention may contribute to the treatment or prognosis of KD; molecular hydrogen, as a preventive and therapeutic medical gas, can also be innovatively used to assist the treatment of Kawasaki disease.

5. Conclusion

In conclusion, the abundance and structure of intestinal flora in KD children have significant changes, and the immune disorders caused by intestinal flora disorders and their metabolites are closely related to the occurrence of Kawasaki disease.But the thorough study between the gut flora and KD pathogenesis, treatment and found the key strains affecting the overall intestinal flora function still has a long way to go, the studies have confirmed the association between [14] antibiotic administration and KD, antibiotics may affect the intestinal microbiota to promote the development of KD.Studies have also indicated that the recovery of [5] beneficial bacteria, especially common Bacillus, Bifidobacterium and lactobacillus, may help alleviate KD symptoms.It is believed that through our joint unremitting efforts, the rational application of antibiotics and probiotics may become new targets for the prevention and treatment of Kawasaki disease in the near future.

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