Review Article

Study on the effect of spleen deficiency on the pathogenesis of psoriasis based on intestinal microbiome

Tingting Di[1], Yan Wang[1], Jingxia Zhao[1], Xiaoyao Guo[2], Zhaoxia Chen[1], Chunyan Zhai[2], Ping Li[1]

[1]Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing Institute of Traditional Chinese Medicine, Beijing 100010, China; [2]Capital Medical University, Beijing 100069, China

Contributions: (I) Conception and design: P Li; (II) Administrative support: J Zhao; (III) Provision of study materials or patients: Z Chen; (IV) Collection and assembly of data: T Di, Y Wang, C Zhai; (V) Data analysis and interpretation: X Guo; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ping Li. Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing Institute of Traditional Chinese Medicine, Beijing 100010, China. Email: Liping411@126.com.

Abstract: Psoriasis is a chronic inflammatory skin disease. In recent years, studies have found that intestinal microecology has undergone significant changes in psoriasis. Due to the regulatory effect of intestinal microecology on the immune system, disordered intestinal microecology plays an important role in the occurrence and development of psoriasis. Traditional Chinese medicine believes that spleen deficiency is an important basis of intestinal microecological disorder. The process and symptoms of psoriasis with spleen deficiency are more prolonged and difficult to recover, which are easy to recurrence. Improving the spleen deficiency can adjust the quantity and variety of intestinal flora and its metabolites, so as to alleviate the symptoms and improve the prognosis of psoriasis.

Keywords: Inflammation; intestinal microbiome; psoriasis; spleen deficiency

Received: 13 August 2019; Accepted: 04 September 2019; Published: 30 September 2019.
doi: 10.21037/lcm.2019.09.02
View this article at: http://dx.doi.org/10.21037/lcm.2019.09.02

Psoriasis is an immune-mediated chronic inflammatory skin disease. According to the global report on psoriasis by the World Health Organization, this disease affects approximately 100 million individuals worldwide (1). Under the induction of various genetic and environmental factors, patients can cause recurrent and well-defined erythema and scale, which can seriously develop into life-threatening systemic erythroderma and arthritis. These symptoms not only reduce the quality of life, but also bring heavy financial burden to patients. The histological characteristics of psoriasis include keratinocytes excessive proliferation, parakeratosis, infiltration of inflammatory subsets such as neutrophils, dendritic cells and T lymphocytes. These characteristics reflect the differentiation of keratinocytes and the abnormal activation of the immune system.

Psoriasis and intestinal microecology

Gut-skin axis

Intestinal microecology is an important immunomodulatory environment for human body. The metabolic function of intestinal flora provides nutrition for the body and enhances the immune function of human body to resist the invasion of pathogenic bacteria. Many studies have found that the composition of intestinal flora and metabolites play an important role in immune and inflammatory response (2). These symbiotic bacteria can not only regulate intestinal immune function, but also affect the immune function of distant organs by stimulating the development of intestinal mucosa lymphoid tissue and regulating the activity of immune cells (3).

The "gut-skin axis" is based on the close correlation between the similar pathological structure of two kinds of tissues and the symptoms of clinical diseases (4): (I) both intestinal and skin tissues are rich in blood supply and dense innervation. As a complex epidemic-free and neuroendocrine organ, it is involved in the regulation of the overall immune and endocrine system. (II) As important organs in contact with the external environment, both of them have a large number of microbial communities. (III) Most of the patients with clinical intestinal dysfunction were accompanied by inflammatory rash. (IV) Dietetic changes and gastrointestinal diseases could affect the skin structure. The overall fur state and experimental dermatosis were significantly improved after probiotics feeding. (V) Specific dermatitis also indicates the occurrence of some gastrointestinal diseases.

Psoriasis is usually accompanied by inflammation of other organ systems, especially with gastrointestinal inflammation. 7–11% of inflammatory bowel disease (IBD) patients were diagnosed with psoriasis at the same time (5). Some common genetic and environmental factors and immune pathways are involved in the pathogenesis of these two diseases. For example, Th17 cells and their cytokines play a major role in the occurrence and development of psoriasis, and also participate in the pathophysiological process of IBD (6).

Changes of intestinal microbiota in patients with psoriasis

In addition to the skin inflammation symptoms of erythema and scales, there are also changes in intestinal tissue structure and intestinal microecology in patients with psoriasis. The intestinal mucosal permeability in patients with progressive psoriasis vulgaris was higher than that in normal subjects and patients after skin lesion regression, which was correlated with the severity of the disease (7). Comparing psoriasis patients with normal controls, it was found that there were significant changes in intestinal microflora of psoriasis patients (8). The quantity and variety of beneficial symbiotic bacteria in psoriasis decreased, including *Bifidobacterium*, *lactic acid bacteria*, *prausnitzii*, *fecal bacteria* and so on. However, the abundance of *Salmonella*, *Escherichia coli*, *HP*, *campylobacter*, *mycobacteria*, *Alcaligenes* and other pathogenic bacteria increased. Among them, the abundance of *actinomycetes* decreased in patients with psoriasis, and the proportion of *actinomycetes* was negatively correlated with the severity of the disease (9), while the ratio of *Firmicute/Bacteroidetes* increased, which was positively correlated with PASI score. The decrease of beneficial intestinal bacteria such as *methamidophos*, *prausnitzii* and *fecal head bacteria* in the intestinal flora of psoriasis leads to the weakening of the regulation of intestinal immune response, which further affects the distal organ system (10).

The role of intestinal microecological imbalance in the pathogenesis of psoriasis

In recent years, it has been found that intestinal microflora plays an important role in the pathogenesis of psoriasis. The changes of the bacteria quantity and variety in the intestines of psoriasis directly affect the skin inflammation. In the imiquimod-induced psoriasis model, mice treated with broad-spectrum antibiotics or metronidazole showed milder skin inflammation than mice without intervention (11). After treatment, the abundance of *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and *Parabacteroides distasonis* increased significantly in intestine and skin. With the deepening of the study of intestinal microecology, the effect of intestinal microecology on psoriasis has been gradually clarified.

Invasion of bacteria and metabolites

Intestinal bacteria can enter the circulatory system through disordered intestinal barriers and directly target distant organs including the skin and joints to induce inflammation (12). There is some evidence that supports bacterial translocation in the context of psoriasis. It has been reported that bacterial intestinal DNA fragments can be found in the peripheral blood of psoriasis patients (13). In addition to the translocation and invasion of intestinal bacteria, bacterial metabolites also enter the circulatory system, affecting the homeostasis of the skin environment. Intestinal microflora has a huge ability to synthesize molecules, which is good or bad, can enter the blood circulation, and affect the skin and other distant parts. For example, free phenols and p-cresol produced by Clostridium difficult are metabolites of aromatic amino acids produced by intestinal bacteria, and p-cresol is a biomarker of intestinal disorders. Recent evidence suggests that free phenol and p-cresol in mice fed foods rich in l-tyrosine are able to enter the bloodstream and accumulate preferably in the skin (14). *In vitro* data showed that p-cresol and phenol decreased the expression of keratin 10 in keratinocytes cultured *in vitro*, thus affecting the differentiation and barrier function of epidermis.

Activation of the immune system

The intestinal microbiota metabolites have the potential of immune modification, which can change the balance between immune tolerance and inflammation by affecting the differentiation of T cells into regulatory T or Th17 lines. Effector T cells are usually anabolic and dependent on glycolysis as their source of adenosine triphosphate (ATP). However, memory and resting T cells are thought to be catabolic, using fatty acids and amino acids to produce ATP through oxidative phosphorylation in addition to glucose. The main transcription factors of adipogenesis pathway and glycolysis pathway are adenosine monophosphate activated kinase and rapamycin, respectively. Both act as energy sensors and are regulated by the availability of nutrients in the intestinal environment, which can be regulated by intestinal microflora.

Lipopolysaccharide (LPS), also known as endotoxin, is the product released after the death and lysis of Gram-negative bacteria. When the intestinal microecology is destroyed, the content of Gram-negative bacteria increases significantly in human body, which develops to the disorder of LPS metabolism, leading to the activation of dendritic cells and the proliferation of keratinocytes, thus causing or promoting the occurrence and development of psoriasis (15). It was found that probiotics could reduce the LPS concentration *in vivo* (16). *Astragalus polysaccharides*, an effective component of Astragalus membranaceus, can promote the growth of intestinal beneficial bacteria, adjust the intestinal flora imbalance and reduce the LPS content (17).

Reduced synthesis of short chain fatty acids

Recent results suggest that Intestinal symbiotic flora and its metabolites are regulated by the proliferation, differentiation and function of Treg cells, which plays an important role in maintaining the stability of the host immune system. Short chain fatty acids (SCFAs), the products of intestinal flora, play an important role in promoting the Treg maturation and inhibiting the T lymphocytes inflammatory response (18). It was found that SCFAs could enhance the histone H3 lysine 27 (H3K27) acetylation level of CNS1 and CNS3 enhancers in Foxp3, thus enhancing the effect of Fopx3. Moreover, SCFAs also enhance the function of DC to induce the differentiation of Treg cells by inhibiting histone acetylase. In addition, SCFAs can regulate Treg cells by stimulating G-protein-coupled receptors including GRP43, GRP41 and GRP109a (19).

Butyrate, for example, a form of SCFA, provides energy to colon cells, reduces oxidative stress, and acts as an anti-inflammatory material by triggering regulatory T cells to participate in immune tolerance which extends beyond the gastrointestinal system. *Prausnitzii* is one of the most common microorganisms in colon and an important source of butyrate. However, the number of such microorganisms in psoriasis decreased significantly (20). Some studies have shown that *Sijunzi* decoction can promote the significant proliferation of bacteria related to SCFA production. Therefore, the use of spleen-invigorating method has a positive impact on the production of SCFA.

Neuroendocrine network

The intestinal tract has a complex neuroendocrine network, which can regulate the function of the intestinal tract, and regulate the physiological and biochemical activities of the whole body by acting on extra-intestinal tissues and organs through endocrine factors, neuropeptides and "gut-brain axis". Some neurotransmitters, neuropeptides, hormones and immune molecules in neuroendocrine immune network have also been closely related to the pathogenesis of psoriasis.

It was found that there was TLR4 on vagal afferent nerve and SCFA could significantly increase its responsiveness, which suggested that intestinal flora was involved in the regulation of "gut-brain axis" (21). For example, the imbalance of flora could significantly increase the substance P (SP) in the serum of rats (22). SP is one of the members of neurokinesis family, which plays a role in activating T cells, delaying apoptosis of neutrophils and prolonging inflammation, and can induce the expression of adhesion molecules and the production of IL-8 by endothelial cells and neutrophils. The contents of SP in the progressive and chronic plaque quiescent stage psoriasis lesions were significantly higher than that in convalescent patients and normal subjects, which played an important role in the occurrence, development and maintenance of psoriasis.

Spleen deficiency and intestinal flora

The spleen plays an important role in maintaining the stability of normal intestinal flora. Spleen deficiency is mostly caused by the diet disorder and emotional fatigue, which reflects the disorder of body function, and the main symptoms are loose, anorexia and abdominal distension (23). When the human body is in the state of spleen deficiency, gastrointestinal function will be abnormal, resulting in intestinal microecological imbalance, which has an impact

on the occurrence and development of psoriasis and other diseases related to intestinal microecology.

Studies have shown that the number of intestinal beneficial bacteria is significantly reduced with spleen deficiency and the pathogenic bacteria are relatively abundant, leading to the imbalance and disorder of intestinal flora (24). When the spleen and stomach function was abnormal, the number of intestinal beneficial anaerobes such as *Bifidobacterium* and *Lactobacillus* decreased significantly, while the content of *Enterobacter* and other pathogenic bacteria increased (25). On the other hand, the disorder of intestinal flora leads to gastrointestinal discomfort, decreased digestive function, diarrhea, abdominal distension and other TCM spleen deficiency syndrome. The balance of intestinal flora can be restored by invigorating the spleen, such as Shenling baizhu Powder can restore the number of anaerobes such as *Bifidobacterium* to normal, and can obviously inhibit the number of aerobic bacteria represented by enterococci, so as to enhance the role of normal intestinal flora (26).

From the above, it can be seen that the imbalance of intestinal flora can aggravate spleen deficiency, and can be adjusted by using traditional Chinese medicine, through the regulation of the quantity and variety of intestinal flora, SCFA, LPS, neuropeptide and so on. It is also contributes to Inhibit the pathogenesis of psoriasis.

Spleen deficiency is the basis of difficult recovery and recurrence of psoriasis

Psoriasis patients often suffer from chronic course of disease due to weak body and spleen qi deficiency, or exogenous dampness and heat, or emotional disorders and improper diet, or overwork disorders, or excessive use of cold drugs, accompanied by spleen deficiency.

Traditional Chinese medicine believes that the spleen and stomach are the postnatal foundation and the source of qi and blood. The absorption and transportation of nutrition rely on spleen transfer and dispersion. Spleen deficiency can lead to the occurrence of a variety of diseases. Since deficiency in the spleen causes failure of the usable refined essence to be transported to the lung and nourish the body, there present such symptoms as a pallid complexion, cold hand and feet, fatigue, poor appetite, loose stools and cough. The performance of spleen deficiency in psoriasis is: qi cannot fix blood into blood vessel to cause megascopic erythema; disorder of qi and blood transport cause dry skin, scale, psoriasis nail and pale erythema. In addition, the health table is not solid, easy to be affected by wind evil, so there is pruritus. Spleen deficiency result in abnormal body fluids metabolism which stopped in middle-energizer to impede qi's ascending and descending function, and make the disease difficult to heal.

Invigorating the spleen and draining dampness to improve the symptoms and prognosis of psoriasis

Many modern doctors realize the importance of spleen deficiency in the pathogenesis of psoriasis. Chushiweiling decoction has achieved good clinical results in the treatment of psoriasis patients with chronic course by using. Taken Sijunzi decoction as the main prescription, combined with drugs for clearing heat, psoriasis was treated by dehumidifying and detoxifying, nourishing yin, replenishing qi and fixing the surface. Psoriasis vulgaris with blood heat and blood dryness syndrome was ameliorated by treat with modified Xiaoyin jiedu Yin which added the product of invigorating spleen and replenishing yin. Doctor Hongxia Liu analyzed the physique of 583 psoriasis patients in Xinjiang Uygur Autonomous region. It was found that the treatment of invigorating spleen and detoxification was effective in clinic, and the condition of skin lesions and quality of life were significantly improved.

Generally speaking, it is advised to strengthen the spleen to treat psoriasis chronic course accompanied by spleen disorders. Reinforcing the health qi to eliminate pathogenic factors is the key to treatment, though invigorating the spleen and nourishing blood for reinforcing the health qi, and clearing heat and detoxification and removing toxic materials for eliminating pathogenic factors.

Summary

The imbalance of intestinal flora in patients with spleen deficiency leads to abnormal metabolism of SCFA, LPS and growth factors. On the one hand, invigorating the spleen can regulate SCFA, LPS and growth factors, on the other hand, it can maintain the ecological balance of intestinal flora. Jianpi recipe can promote the growth of intestinal beneficial bacteria in patients with spleen deficiency, adjust intestinal microecology, and restore the balance of unbalanced intestinal flora. Stable intestinal flora can increase the level of SCFA and decrease the level of LPS in patients with psoriasis and improve the clinical symptoms of psoriasis.

Acknowledgments

Beijing Key Laboratory of Clinic and Basic Research with Traditional Chinese Medicine on Psoriasis provided experimental research platform.

Funding: This study was supported by the National Natural Science Foundation of China [No. 81573974], Special subject of scientific research of National Clinical Research Base National Administration of traditional Chinese Medicine [JDZX2015190]. Beijing Excellent Talents Individual Project [No. 2017000021469G299].

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. WHO. Global Report on Psoriasis 2016, 1–44. Available online: www.who.int/about/licensing/%0A (www.who.int/about/licensing/%0Acopyright_form/en/index.html)%00.
2. Belkaid Y, Harrison OJ. Homeostatic Immunity and the Microbiota. Immunity 2017;46:562-76.
3. Ma Y, Xu X, Li M, et al. Gut microbiota promote the inflammatory response in the pathogenesis of systemic lupus erythematosus. Mol Med 2019;25:35.
4. O'Neill CA, Monteleone G, McLaughlin JT, et al. The gut-skin axis in health and disease: A paradigm with therapeutic implications. Bioessays 2016;38:1167-76.
5. Egeberg A, Mallbris L, Warren RB, et al. Association between psoriasis and inflammatory bowel disease: a Danish nationwide cohort study. Br J Dermatol 2016;175:487-92.
6. Whitlock SM, Enos CW, Armstrong AW, et al. Management of psoriasis in patients with inflammatory bowel disease: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol 2018;78:383-94.
7. Sikora M, Chrabąszcz M, Maciejewski C, et al. Intestinal barrier integrity in patients with plaque psoriasis. J Dermatol 2018;45:1468-70.
8. Shapiro J, Cohen NA, Shalev V, et al. Psoriatic patients have a distinct structural and functional fecal microbiota compared with controls. J Dermatol 2019;46:595-603.
9. Thio HB. The Microbiome in Psoriasis and Psoriatic Arthritis: The Skin Perspective. J Rheumatol Suppl 2018;94:30-1.
10. Salem I, Ramser A, Isham N, et al. The gut microbiome as a major regulator of the gut-skin axis. Front. Microbiol 2018;9:1459.
11. Stehlikova Z, Kostovcikova K, Kverka M, et al. Crucial Role of Microbiota in Experimental Psoriasis Revealed by a Gnotobiotic Mouse Model. Front Microbiol 2019;10:236.
12. Mu Q, Kirby J, Reilly CM, et al. Leaky gut as a danger signal for autoimmune diseases. Front. Immunol 2017;8:598.
13. Munz OH, Sela S, Baker BS, et al. Evidence for the presence of bacteria in the blood of psoriasis patients. Arch Dermatol Res 2010;302:495-8.
14. Miyazaki K, Masuoka N, Kano M, et al. Bifidobacterium fermented milk and galacto-oligosaccharides lead to improved skin health by decreasing phenols production by gut microbiota. Benef Microbes 2014;5:121-8.
15. Kell DB, Pretorius E. No effects without causes: the iron dysregulation and dormant microbes hypothesis for chronic, inflammatory diseases. Biol Rev 2018;93:1518-57.
16. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. Nutr Res Rev 2018;31:35-51.
17. Hiippala K, Jouhten H, Ronkainen A, et al. The potential of gut commensals in reinforcing intestinal barrier function and alleviating inflammation. Nutrients 2018;10:E988.
18. Xiong N, Hu S. Regulation of intestinal IgA responses. Cell Mol Life Sci 2015;72:2645-55.
19. Krejner A, Bruhs A, Mrowietz U, et al. Decreased expression of G-protein-coupled receptors GPR43 and GPR109a in psoriatic skin can be restored by topical application of sodium butyrate. Arch Dermatol Res 2018;310:751-8.
20. Eppinga H, Sperna Weiland CJ, Thio HB, et al. Similar Depletion of Protective Faecalibacterium prausnitzii in Psoriasis and Inflammatory Bowel Disease, but not in Hidradenitis Suppurativa. J Crohns Colitis 2016;10:1067-75.
21. Holzer P, Farzi A. Neuropeptides and the microbiota-gut-brain axis. Adv Exp Med Biol 2014;817:195-219.
22. Biaggini K, Barbey C, Borrel V, et al. The pathogenic potential of Pseudomonas fluorescens MFN1032 on enterocytes can be modulated by serotonin, substance P

and epinephrine. Arch Microbiol 2015;197:983-90.
23. Olivera-Toro A, Fossion R, Li L, et al. Changes in heart rate variability in patients with Spleen-Qi deficiency syndrome. J Acupunct Meridian Stud 2019;12:111-21.
24. Qiu JJ, Liu Z, Zhao P, et al. Gut microbial diversity analysis using Illumina sequencing for functional dyspepsia with liver depression-spleen deficiency syndrome and the interventional Xiaoyaosan in a rat model. World J Gastroenterol 2017;23:810-6.
25. Ewaschuk JB, Dieleman LA. Probiotics and prebiotics in chronic inflammatory bowel diseases. World J Gastroenterol 2006;12:5941-50.
26. Zhang G, Zhang Q, Sun X, et al. Clinical Observation of Addition and Subtraction Therapy of Shenling Baizhu San to Antibiotic-associated Diarrhea with Spleen-stomach Deficiency and Cold Syndrome. Chinese Journal of Experimental Traditional Medical Formulae 2019;10:13422.

doi: 10.21037/lcm.2019.09.02
Cite this article as: Di T, Wang Y, Zhao J, Guo X, Chen Z, Zhai C, Li P. Study on the effect of spleen deficiency on the pathogenesis of psoriasis based on intestinal microbiome. Longhua Chin Med 2019;2:14.

