A potential pathway may guide new therapies for inflammatory bowel disease and other inflammatory diseases

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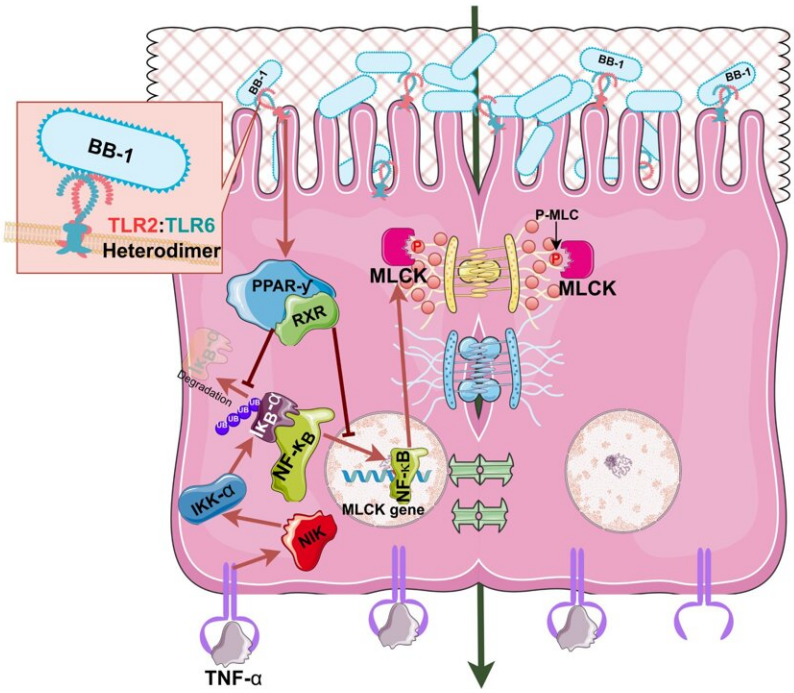

TNF-α–induced increase in intestinal epithelial TJ permeability is mediated by the activation of NF-kB p50/p65. The activated NF-kB translocates to the nucleus, binds to the cis-kB binding site on the myosin light chain kinase (MLCK) promoter region, and activates the MLCK gene transcription and protein synthesis process. The increase in MLCK protein level and activity [phosphorylated myosin light chain (P-MLC)] results in MLCK-induced opening of the TJ barrier. BB1 treatment activates the toll-like receptor (TLR)-2/TLR-6 signaling pathway, leading to the activation of peroxisome proliferator-activated receptor γ (PPAR- γ). The PPAR- γ activation results in inhibition of TNF-

α–induced IKK [inhibitor of nuclear factor-κB (IκB) kinase]-α activation, which, in turn, leads to the inhibition of NF-kB activation, MLCK gene activation, and MLCK-induced opening of the TJ barrier. RXR, retinoid X receptor. Credit: The American Journal of Pathology

There is a critical unmet need to help tighten and maintain a healthy intestinal barrier and treat a leaky gut. Researchers have now found that a unique strain of probiotic bacteria, Bifidobacterium bifidum BB1, enhances intestinal barrier function and protects against penetration of bacteria and various harmful agents in the intestine.

The findings, detailed in an article in *The American Journal of Pathology* can help advance the development of novel, targeted, naturally occurring probiotic therapy for patients with inflammatory bowel disease (IBD) and other inflammatory diseases, such as fatty liver disease or alcoholic liver disease, that are associated with a leaky or disordered intestinal barrier.

Lead investigator Thomas Y. Ma, MD, Ph.D., Penn State College of Medicine, Hershey Medical Center, explains, "There is a critical need to develop nontoxic, patient-friendly, naturally occurring products such as probiotics for treatment of IBD and other inflammatory diseases associated with leaky gut. Our studies suggest that BB1 is such a precision probiotic strain; it has the unique biological activity to produce maximal intestinal barrier enhancement and also protect against the activation of inflammation."

Patients with active IBD have elevated proinflammatory cytokines, including tumor necrosis factor (TNF)-α and IL1β. TNF-α levels are markedly elevated in intestinal tissue, serum, and stool of patients with IBD and at elevated levels produce an increase in intestinal tight junction

permeability.

TNF-α plays a central role in promoting intestinal inflammation in patients with IBD, and anti–TNF-α antibodies are highly effective in the treatment of the active disease. Previous studies from the laboratory at Penn State College of Medicine have shown that BB1 caused a marked enhancement of the intestinal epithelial barrier function and protects against the development of dextran sulfate sodium–induced intestinal inflammation.

Dr. Ma adds, "Our results show that BB1 prevented the TNF-α increase in intestinal tight junction permeability via a toll-like receptor (TLR)-2 signal transduction pathway inhibition of NF-kB p50/p65 activation and MLCK gene. We also found that a protein called PPAR-γ was a critical intestinal cell mediator that regulated the intestinal barrier protection. Treatment of patients with active ulcerative colitis with a PPAR-γ agonist, rosiglitazone, significantly reduced the ulcerative colitis disease activity index score and resulted in an improved quality of life."

Dr. Ma concludes, "These studies unravel novel intracellular mechanisms of BB1, a unique probiotic bacterial strain, demonstrating the promise of promoting health and treating inflammatory diseases including inflammatory bowel disease by maintaining a healthy intestinal barrier and protecting against leaky gut or intestinal barrier disruption."

IBD, which includes Crohn's disease and ulcerative colitis, is characterized by inflammation affecting the gastrointestinal tract. The defective intestinal epithelial tight junction barrier is an important pathogenic factor contributing to the development of IBD.

Patients with IBD have a defective intestinal tight junction barrier, characterized by increased intestinal permeability and increased luminal antigen penetration. Intestinal epithelial cells cover the entire intestinal

mucosal surface and serve as a physical and functional barrier against the intestinal permeation of noxious luminal substances, including bacterial antigens, toxins, digestive enzymes, and food by-products.

More information: Raz Abdulqadir et al, Bifidobacterium bifidum Strain BB1 Inhibits Tumor Necrosis Factor-α–Induced Increase in Intestinal Epithelial Tight Junction Permeability via Toll-Like Receptor-2/Toll-Like Receptor-6 Receptor Complex–Dependent Stimulation of Peroxisome Proliferator-Activated Receptor γ and Suppression of NF-κB p65, *The American Journal of Pathology* (2024). DOI: 10.1016/j.ajpath.2024.05.012