ISSN 2220-3192 (online)

World Journal of *Pharmacology*

World J Pharmacol 2019 August 28; 8(3): 26-40



Published by Baishideng Publishing Group Inc

World Journal of Pharmacology

Contents

Irregular Volume 8 Number 3 August 28, 2019

REVIEW

26 Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases
Chandra N, Srivastava A, Kumar S

Contents

World Journal of Pharmacology

Volume 8 Number 3 August 28, 2019

ABOUT COVER

Editorial Board Member of *World Journal of Pharmacology*, Vicente Lorenzo-Zúñiga, MD, PhD, Associate Professor, Chief Doctor, Senior Scientist, Staff Physician, Endoscopy Unit, Department of Gastroenterology, Hospital Universitari Germans Trias i Pujol/CIBERehd, Badalona 08916, Spain

AIMS AND SCOPE

World Journal of Pharmacology (*World J Pharmacol*, *WJP*, online ISSN 2220-3192, DOI: 10.5497) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

The *WJP* covers topics concerning neuropsychiatric pharmacology, cerebrovascular pharmacology, geriatric pharmacology, anti-inflammatory and immunological pharmacology, antitumor pharmacology, anti-infective pharmacology, metabolic pharmacology, gastrointestinal and hepatic pharmacology, respiratory pharmacology, blood pharmacology, urinary and reproductive pharmacology, pharmacokinetics and pharmacodynamics, clinical pharmacology, and drug toxicology.

We encourage authors to submit their manuscripts to *WJP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Pharmacology is now indexed in China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Mei-Yi Liu*

Proofing Production Department Director: *Yun-Xiaojian Wu*

NAME OF JOURNAL
World Journal of Pharmacology

ISSN
ISSN 2220-3192 (online)

LAUNCH DATE
February 9, 2012

FREQUENCY
Irregular

EDITORS-IN-CHIEF
Nam Deuk Kim

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2220-3192/editorialboard.htm

EDITORIAL OFFICE
Ya-Juan Ma, Director

PUBLICATION DATE
August 28, 2019

COPYRIGHT
© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

© 2019 Baishideng Publishing Group Inc. All rights reserved. 7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
E-mail: bpgoffice@wjgnet.com https://www.wjgnet.com

World Journal of Pharmacology

Submit a Manuscript: https://www.f6publishing.com

World J Pharmacol 2019 August 28; 8(3): 26-40

DOI: 10.5497/wjp.v8.i3.26

ISSN 2220-3192 (online)

REVIEW

Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases

Niharika Chandra, Ankita Srivastava, Sunil Kumar

ORCID number: Niharika Chandra (0000-0002-0931-5231); Ankita Srivastava (0000-0002-4054-8391); Sunil Kumar (0000-0001-7632-7252).

Author contributions: Chandra N prepared the first draft of the manuscript; Srivastava A reviewed and modified the manuscript; Kumar S is the corresponding author of the manuscript who conceived the idea and approved the final draft.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Manuscript source: Invited manuscript

Received: January 22, 2019
Peer-review started: January 23, 2019
First decision: January 30, 2019
Revised: July 5, 2019
Accepted: July 16, 2019
Article in press: July 16, 2019

Niharika Chandra, Faculty of Biotechnology, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Uttar Pradesh 225003, India

Ankita Srivastava, Sunil Kumar, Faculty of Bio-Sciences, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Uttar Pradesh 225003, India

Corresponding author: Sunil Kumar, PhD, Associate Professor, Faculty of Bio-Sciences, Institute of Bio-Sciences and Technology, Shri Ramswaroop Memorial University, Lucknow-Deva Road, Uttar Pradesh 225003, India. sunil.bio@srmu.ac.in
Telephone: +91-73-79893670

Abstract

Inflammatory bowel disease (IBD) has been a worldwide health problem. It is characterized by severe intestinal inflammation due to immune responses against the gut microbes in genetically susceptible individuals. The understanding of gut microbiota for its composition and complex interaction in normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics studies. The alteration of intestinal microbiota is the key determinant in the degree of inflammation caused and the prolonged course of disease. The relationship between luminal gut bacteria and innate immunity is also of prime significance. Such developments have further led to the search of specific (including bacteria and fungi) as a causative agent of IBD. Although detailed research has been done for the role of gut microbiota in IBD, molecular mechanisms and related gene expression are still not well understood in this disease, which hampers the generation of effective therapeutic agents for IBD. This paper assessed various factors contributing to IBD, genetic dysbiosis and pathogenic influence in the gut microbiota, interactions such as microbiome-host immune system interaction and microbe-microbe interactions involved in IBD, currently available IBD therapies, followed by a detailed review on bacterial infections that might be involved in IBD, globally and specifically in India.

Key words: Ulcerative colitis; Crohn's disease; Inflammatory bowel disease; Gut microbiota; Lactic acid bacteria

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Ulcerative colitis and Crohn's disease are two clinical forms of inflammatory bowel disease (IBD) causing recurring diarrhea, abdominal bleeding, pain and inflammation. Scientific evidence clearly indicated the role of heredity in IBD, but an

Published online: August 28, 2019

P-Reviewer: Bourgoin SG, Huang X, Zhai KF
S-Editor: Cui LJ
L-Editor: Filipodia
E-Editor: Wu YXJ

accurate cause of IBD is still unclear. However, complex interactions between genes, environmental factors and the immune system could be one of the leading causes in IBD. Gut microbiome is a key link between these factors and progression of IBD. This article reviews all contributing factors and pathogenic association in IBD. Identifying such microbial causes of the onset of IBD can help researchers to develop effective treatment strategies.

Citation: Chandra N, Srivastava A, Kumar S. Bacterial biofilms in human gastrointestinal tract: An intricate balance between health and inflammatory bowel diseases. *World J Pharmacol* 2019; 8(3): 26-40
URL: https://www.wjgnet.com/2220-3192/full/v8/i3/26.htm
DOI: https://dx.doi.org/10.5497/wjp.v8.i3.26

INTRODUCTION

Inflammatory bowel disease (IBD) is a common gastrointestinal disorder whose pathophysiology is still not completely understood due to its complex and multifactorial nature. It is generally characterized by abdominal pain and recurring diarrhea. It occurs in genetically vulnerable populations or individuals due to inappropriate and intensified immune response to commensal bacteria, which leads to intestinal inflammation[1,2]. The two main clinical forms of IBD according to their location and nature of histological modifications/damage caused in the gastrointestinal wall are ulcerative colitis (UC) and Crohn's disease (CD). UC is limited to mucosal surfaces of the colon, cecum and rectum. Several microbes such as *Salmonella spp*., *Shigella spp*., *Fusobacterium spp*., and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC[1-4]. CD exhibits transmural inflammation and the mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual[5,6]. The most predominant bacterial species found in CD was *Bacteroides spp*., which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of *Listeria monocytogenes* and adherent-invasive *E. coli* (AIEC) has been determined in CD[5,6]. Both UC and CD cause diarrhea with or without bleeding and patients display a weakened tolerance to antigens present in the intestines[1]. Its occurrence is similar in both sexes (men and women), and most cases are recorded in young adults[6,7].

Depending upon the type of microbes, several unfriendly and mutuality interactions occur between the residing gut microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating. Also, formation of biofilms protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics[5,8]. The residing microbes also regulate their gene expression in response to changing microbial cell population and its concentration through a cell-cell communication known as quorum sensing[9].

UC

UC is the chronic and recurring IBD in which severe inflammation and immune responses (T helper cell and production of cytokines) are generated in the intestinal mucosa. The initiation site for ulcers is distal large intestine, and eventually the inflammation moves towards the proximal bowel. UC can severely disturb the quality of life, and if oral medicines are not effective, surgical removal of parts of ulcer affected intestines is obligatory. Several microbes such as *Shigella spp*., *Fusobacterium spp*. and adhesive *E. coli* have been found in the inflamed colon, but no causative microbial species has yet been made responsible for UC[2-4].

CD

CD exhibits transmural inflammation and epithelioid granulomas in the gut tissues with T-helper cell (Th1) responses and elevated levels of interferon gamma. The mucosal bacteria concentration in CD patients has been found to be twice as high as that of a healthy individual[5,6]. Higher levels of antibody IgG is a characteristic of CD patients. The most predominant bacterial species found was *Bacteroides spp*., which composed 80% of the total mucosal bacteria as compared to 15% in UC. Also, the role of AIEC has been determined in CD[5,6].

Rural populations are less susceptible to IBD. Environmental factors such as poor sanitation, decreased use of antibiotics, rural environment, consumption of whole unrefined food, *etc* decrease the risk of IBD. That is increased exposure to microbes or infection will lead to low susceptibility for IBD infection. Also, the mucosal immunity in intestines is changed during IBD. UC and CD patients tend to secrete more antibodies (IgG and IgA) against the commensal intestinal microflora and damage their intestinal mucosa[10,11]. Thus, the pathogenesis of IBD is partly understood, and it has also been discovered that multiple factors are associated with IBD such as genetic vulnerability, environmental factors, host-commensal/pathogenic microbe interaction and disturbed mucosal immune responses[12-14].

ENVIRONMENTAL FACTORS CONTRIBUTING TO IBD

The maximum occurrence of IBD has been reported in Northern Europe and North America, whereas it is rare amongst Asians and Africans. Incidences of IBD vary depending on race, and its prevalence increases in regions with industrialization. According to the hygiene hypothesis, the autoimmune and inflammatory responses in the body occur due to the absence or low exposure to pathogens in childhood/infancy due to rigorous sanitation practices.

The effect of smoking was guarding against UC and aggravating for CD. That is smoking may improve one's condition during UC, but CD patients may suffer with a declined quality of life. Other factors, such as domestic hygiene, prenatal events, oral contraceptives, microbial agents and refined sugar consumption require further evaluation to confirm their involvement in IBD and to describe their strength[15-17]. Another accepted factor to increase IBD inflammation and cause relapse of the disease is psychological stress. Any sort of depression, adverse life situations or chronic stress can deteriorate the course of disease[18,19]. Several clinical studies suggest that IBD is not a psychosomatic disease, but stressful life events and depression are associated with high risk of relapse and increased pathogenesis of IBD[20,21].

GENETIC SUSCEPTIBILITY IN IBD

Heterogeneous geographical distribution and occurrence of ancestral forms of IBD as well as monozygotic twin studies strongly support the genetic component of IBD. High risk in patients having family members with IBD, relatively high risk of siblings acquiring the disease and high concordance rate of monozygotic twins than dizygotic twins of being affected by IBD further strengthen the hypothesis. Therefore, genetic makeup plays an important role in both forms of IBD. Also, several susceptibility genes have been reported. Autophagy genes such as ATG16L1, IRGM and Card15/NOD-2 have been reported to be associated with CD for innate immunity responses. Other candidate genes involved in UC are HERC2, STAT3 and PTPN2[22,23]. Several other susceptible genes such as IL23R, IBD5, NKX2-3, BSN, IL12B and CCNY have been found to be associated with both UC and CD. Table 1 lists some of the genes and their respective roles in IBD. Mutations in these particular genes can lead to abnormal immune response generation in the gut mucosa and adversely affect healthy microbial population in terms of composition and concentration.

COMPLEXITY OF GUT MICROBIOTA

The complex anaerobic environment of the gut is home to several microbial communities including bacteria, archaea and fungi. This microbial diversity in the gut has been studied by the culture independent 16S rRNA studies. These studies indicate that the gut is mainly inhabited by Gram-positive *Firmicutes* and Gram-negative *Bacteroidetes*, while *Actinomycetes*, methanogens and fungi are present in lower quantities[24]. Most *Firmicutes* were identified as clostridia and are butyrate-producing bacteria. Several *Proteobacteria* and *Actinomycetes* were also identified out of which *Bifidobacteria* (subgroup of *Actinomycetes*), which has health promoting utilities was

Table 1 Susceptible chromosomal loci for inflammatory bowel disease

No.	Related disease	Gene(s)	Role(s) ininflammation	Ref.
1	UC + CD	NOD2/CARD15, CD19, CD11, IL4R	Detection of cytosolic bacterial components	[105]
2	UC + CD	IL23R, PTGER4	Generation and maintenance of Th17 cells; prostaglandins signaling	[23,106]
3	CD	IRGM, IL12B	Autophagy	[22,23]
4	CD	STAT3, ORMDL3	Development of T cell response	[22,23]
5	CD	IL3, IL4, IL5 and IL13,OCTN1, OCTN2, CSF2, SLC22A5	Mucosal barrier function, cytokines production, Regulation of inflammation	[106]
6	UC + CD	MST1, BSN, GNAI2	Regulation of expression of proinflammatory mediators	[105]

CD: Crohn's disease; UC: Ulcerative colitis; NOD2: Nucleotide-binding oligomerization domain-containing protein 2; CARD15: Caspase recruitment domain-containing protein 15; CD19: Cluster of differentiation 19; IL4R: Interleukin 4 receptor; IL23R: Interleukin 23 receptor; PTGER4: Prostaglandin E receptor 4; IRGM: Immunity related GTPase M; IL12B: Interleukin 12B; STAT3: Signal transducer and activator of transcription 3; ORMDL3: Orosomucoid like 3; OCTN1: Organic cation transporter, novel, type 1; CSF2: Colony stimulating factor 2; SLC22A5: Solute carrier family 22 member 5; MST1: Macrophage stimulating 1; BSN: Bassoon (presynaptic cytomatrix protein); GNAI2: G protein subunit alpha I2.

found to be 5% of the microbiota. Archaeal diversity consists of *Methanobrevibacter smithii* and *Methanosphaera stadtmanae*. Eukaryotic microbes in the human gut consist of *Blastocystis* sp., (uni- and multicellular protists) and several fungi belonging to *Ascomycetes* (53.5%) or *Basidiomycetes* (46.5%) with the majority belonging to the genera *Candida albicans*, *C. glabrata* (6%), *Penicillium italicum*, *P. glabrum*, *P. sacculum*, *P. verruculosum* (61.5%), *Saccharomyces cerevisiae*, *S. cariocanus* and *S. bayanus* (24.1%)[24-26].

PATHOGENIC INFLUENCE OF GUT MICROBIOTA IN IBD

Several studies aiming to distinguish residing microbes in a healthy gut and an IBD gut revealed an overall decline in bacterial diversity in IBD patients. Further, a decrease in methanogen diversity and an increase in fungal diversity were noted in the guts of IBD patients[25,26]. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities did not vary over the healthy gut tissues.

Different studies have also reported the presence of pathogenic microbes in the gastrointestinal tract of IBD patients. *Saccharomyces cerevisiae*, *Candida albicans*, *Listeria monocytogenes*, *Mycobacterium avium* subsp. paratuberculosis, *Chlamydia pneumonia* and AIEC have been reported as the potentially infectious microbes in the spread of CD. In CD, *Bacteroides, Peptostreptococcus* and *Eubacteria* are increased, whereas *Bifidobacteria* numbers are considerably reduced. Moreover, in UC the presence of facultative anaerobic bacteria is amplified. Table 2 lists the infectious agents (viral, bacterial, fungal and parasitic agents) that have been suspected in IBD etiology. *E. coli* has been reported to induce the release of cytokines in the inflamed IBD gut. AIEC, which is a facultative pathogen, has been reported to cause CD in genetically susceptible hosts[27-29]. Even though these studies have shown relation between pathogens and IBD, specific pathogenic microbes responsible for CD or UC is still contentious.

GENETIC DYSBIOSIS IN IBD

IBD may not be caused by any specific microbial infection; instead it occurs due to a change in the overall residing microbes in the gut (intestinal microbe biofilms). It may also be caused by misrecognition of normal, commensal microbes as foreign leading to immune responses and inflammation. This change in intestinal microbiota (in terms of species and their concentration) or misrecognition by the body is termed genetic dysbiosis[30,31]. This ever-changing gut microbiota can modify the expression of certain genes that are involved in various activities in the intestines. Further, it can cause inflammation and disease in genetically susceptible individuals who have mutations or polymorphism in genes involved in immune responses (as described in previous

Table 2 Suspected pathogenic microorganism in tissue of patients with inflammatory bowel disease

Bacteria	Virus	Fungi
Campylobacter spp.	Adenovirus	*Saccharomyces cerevisiae*
Escherichia coli	Cytomegalovirus	*Candida albicans*
Helicobacter spp.	Coronavirus	
Legionella spp.	Rotavirus	
Mycobacterium spp.	Measles virus	
Pseudomonas spp.	Paramyxovirus	
Shigella spp.	Epstein-Barr virus	
Yersinia spp.		Parasite
Bacteroides vulgatus		Borrelia *spp.*
Listeria monocytogenes		Treponema *spp.*
Staphylococcus spp.		
Streptococcus spp.		
Enterococcus		
Adherent-Invasive *E. coli*		
Chlamydia spp. (*Chlamydia trachomatis*)		

spp.: Species.

sections)[30,31]. Figure 1 represents how genetic dysbiosis can lead to diseases.

INTESTINAL MUCOSAL BARRIER FUNCTION IN IBD

The intestinal mucosal barrier consists of two layers of mucus (inner and outer), which are associated with antimicrobial factors. Under this mucus layer are the gut epithelial cells that are joined together by a network of connecting proteins called tight junctions. Hence, this intestinal mucosal barrier splits the luminal components (food particles, microbes, *etc.*) from the immune system components (innate and adaptive immunity) (Figure 2)[32].

MICROBIOME–HOST IMMUNE SYSTEM INTERACTION IN IBD

Under normal conditions the microbiota does not interact with the epithelial cells, other than the controlled interaction in the Peyer's patches. Under the condition of disturbed microbiota composition or genetic dysbiosis, as is the case with IBD, this mucosal barrier is interrupted, and the interaction between the microbiota and immune system components occurs, which leads to generation of a heightened immune response and inflammation as shown in Figure 2.

In IBD, the mucus layer is permeable and defective due to improper secretion of mucus components by goblet cells (decreased mucin, antimicrobial factors, glycosylation products, *etc.*). In the case of UC, the goblet cells are depleted in the epithelium, and the mucus layer formed is very thin. Also, the tight junction protein network becomes increasingly penetrable in IBD, which further increases the interaction between immune and luminal components. Such changes are a result of environmental factors and genetic dysbiosis as discussed earlier[33,34].

Various studies have shown that microorganisms that pass the mucus layer and invade the epithelial cells, activate various components of the immune system comprising innate immune responses, adaptive immune responses and autophagy[35,36]. According to Parkes, CD is linked to mutations in autophagy genes such as nucleotide oligomerization domain 2 and ATG16L1. Intracellular pathogens have also been observed to form autophagic vacuoles to prevent interaction with immune components and remain protected[37].

Microorganisms that pass through the damaged tight junctions mesh and reach the lower surface of epithelial cells are recognized by the pattern recognition molecules similar to toll-like receptors present there. This interaction then activates the innate

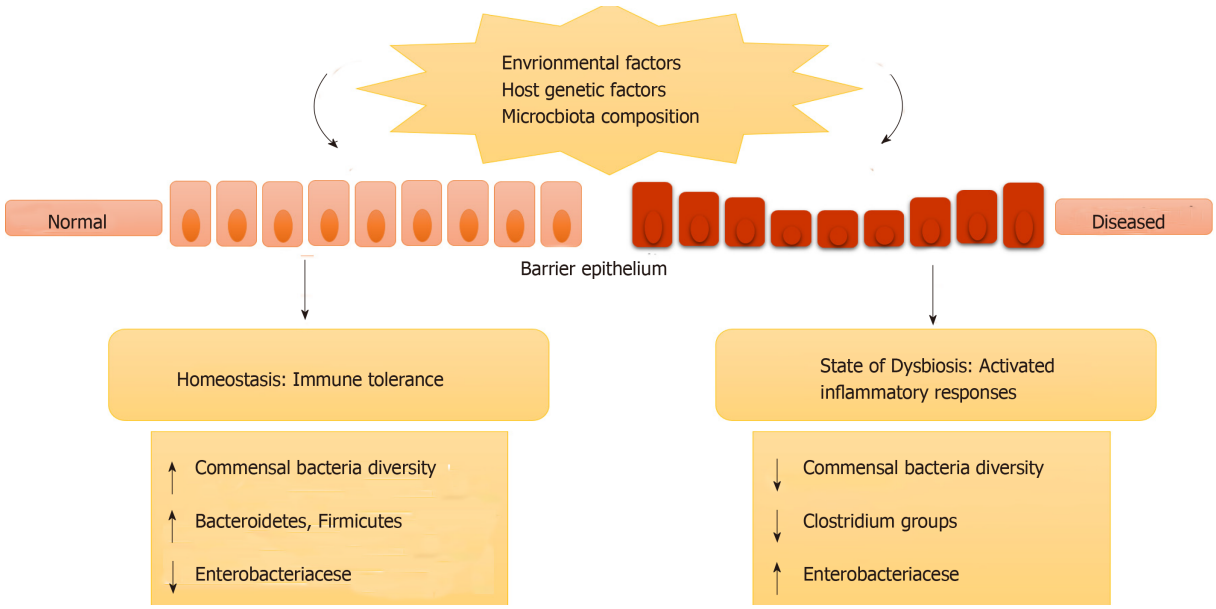


Figure 1 Pathway for genetic dysbiosis.

immune responses (including phagocytic cells, natural killer cells, dendritic cells, inflammation-related proteins, cytokines and antimicrobial peptides such as defensins and cathelicidins) and adaptive immune response including several cytokine profiles[38,39]. Fernandes *et al*[40] reported that in IBD, the expression of regulatory molecules of immune system and toll-like receptors is different from that in a healthy tissue.

MICROBE–MICROBE INTERACTIONS IN IBD

Other than interaction with the host cells, the survival and activity of gut microbiota also depends upon their interaction with the other surrounding microbes. These interactions can be unfriendly or mutualistic, which primarily depends upon the type of microbes. The three main mechanisms by which the bacteria communicate with fellow bacteria around them are: combatting, competing and cooperating (Figure 3).

Combatting

Gut bacteria combat other microbes by production of antimicrobial peptides (AMP) and specialized secretions. Bacteriocins, colicins and microcins are some AMP that inhibits other microbial invading species without harming the eukaryotic gut cells. Bacteriocins are produced by Gram-positive bacteria, and they fight against other microbes by pore formation in their cell wall. Gram-negative bacteria produce colicins and microcins, which kill other microbes by a variety of strategies such as nuclease activity, inhibition of RNA polymerase, intervention cell wall synthesis and pore formation[41,42]. These bacterial AMPs under the effect of environmental factors control surrounding microbiota composition and concentration.

Other mechanisms of combatting surrounding microbes are contact dependent growth inhibition systems and type VI secretion systems. In contact dependent growth inhibition system, the C terminal end of CdiA protein move in on the target cell and kill it by nuclease activity. Type VI secretion system cells inject toxins in Gram-negative bacteria and eukaryotic cells to combat bacterial competition and cause pathogenesis, respectively[41,42].

Competing

One of the essential parameters that governs colonization of microbes and dysbiosis in gut is the competition for carbohydrates. Other than carbohydrates, bacteria also compete for phosphorus, nitrogen, vitamins, trace elements and other vital cofactors. Bacteria encode a variety of transporters for smooth uptake of vitamins and essential cofactors[43,44]. Some bacteria interfere with the uptake of trace elements by other bacteria by secretion of some inhibitors or AMP. For instance, a study by Raffatellu *et al*[45] showed that *Salmonella typhimurium* produced lipocalin-2 to inhibit iron uptake by surrounding microbes.

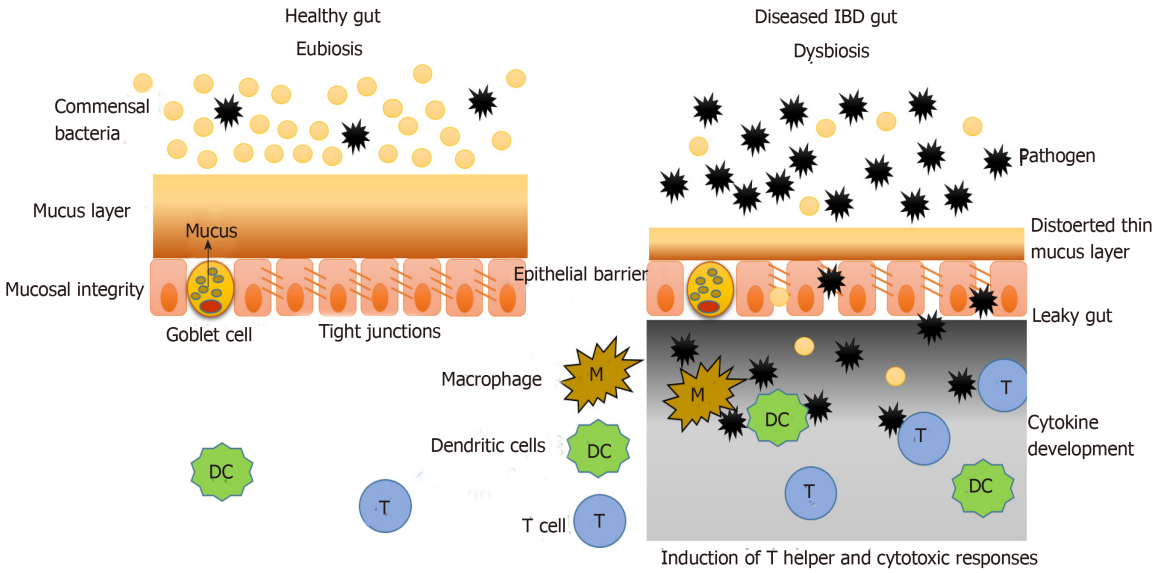


Figure 2 Mechanism of inflammatory bowel disease.

Cooperating and communicating

Even after such limiting conditions and competition for food, gut bacteria also communicate and live in cooperation and share by-products. One of the methods of such cooperation is horizontal gene transfer. Horizontal gene transfer is responsible for secretome molecules, which is the most common method to help in production of certain molecules for communal use. For instance, chelators of iron (siderophores), which help in absorption of iron from the surrounding, can be used by any bacteria in the surrounding. In this way, horizontal gene transfer of such genes and public use of these secretions helps the bacterial population to live in cooperation in the gut[46,47].

Formation of biofilms also protects the bacterial population from host immune responses and antimicrobials/antibiotics by secretion of extracellular matrix and binding bacteria together in layers. It prevents the loss of useful secretions and nutrients from a population of microbes living in cooperation with other surrounding microbes. Thick, dense and resistant biofilm formation is very common in IBD patients and is the prime cause of dysbiosis and resistance to treatments/therapies including antibiotics[5,8].

Many cooperative/group behaviors in the gut are governed by the cell-to-cell communication called quorum sensing (QS). The signaling molecules are released in the environment and regulate gene expression in the surrounding communities. QS governs several mechanisms important to survival such as biofilm formation, antibiotic production and expression and release of secretions like type VI secretion systems. Although QS has been known in *Lactobacillus* species and probiotics, its role in human gut commensal bacteria and pathogens is still not understood well. Further studies are necessary for understanding the microbial communication in both homeostasis and IBD conditions[48-50].

Quorum sensing

QS occurs by the production and release of extracellular chemical signal molecules called autoinducers by bacteria that are subsequently detected by other bacteria. When a particular threshold concentration of autoinducers is reached, the gene expression is altered in all the bacterial cells residing there. This alteration in gene expression is associated with the variations in cell population density[9]. Several physiological activities such as biofilm formation, virulence, competence, symbiosis, conjugation, antibiotic production, sporulation and motility are controlled by QS communications in bacteria. This communication through autoinducers can take place both within and amongst the bacterial species. Acylated homoserine lactones are produced as autoinducers in Gram-negative bacteria, while Gram-positive bacteria release oligopeptides for communication[9,51].

Gram-negative bacteria *V. fischeri* demonstrated LuxI/LuxR-type QS. LuxI-like proteins synthesized a particular acylated homoserine lactone signaling molecule, which is an autoinducer. When these homoserine lactone signaling molecules reach a threshold concentration, LuxR-like proteins bind to them and stimulate particular gene transcription[52]. Several other Gram-negative bacteria, including those involved

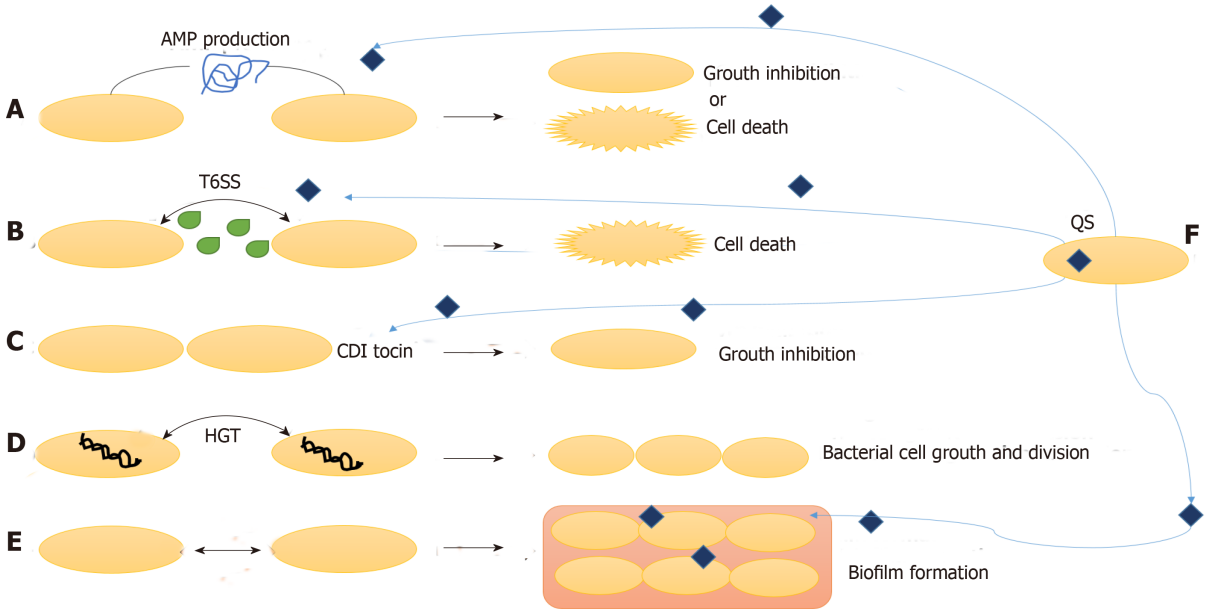


Figure 3 Various communication mechanisms used by bacteria (combatting: A-C; cooperating: D-F). A: Antimicrobial peptides; B: Type 6 secretion system; C: Contact-dependent growth inhibition systems; D: Horizontal gene transfer; E: Formation of a protective biofilm; F: Quorum sensing[39].

in pathogenesis of IBD regulate gene expression through homologous LuxI/LuxR-type circuit. For instance, in *P. aeruginosa*, LasI/LasR-RhlI/RhlR virulence system circuit regulates QS. Homoserine lactone signaling autoinducers N-(3-oxododecanoyl)-homoserine lactone and N-(butryl)-homoserine lactone are produced by the action of LasI and RhlI autoinducers. Expression on several virulence factors (lasB, lecA and aprA) in *P. aeruginosa* is controlled by this circuit[53,54].

Gram-positive bacteria also show QS mediated regulation by secreting peptides as autoinducers. An example of this is *Staphylococcus aureus* AgrC/AgrA virulence system. An RNA molecule named RNAIII regulates biofilm formation and pathogenicity in *S. aureus*. The *agr*BDCA operon regulates the levels of RNAIII. Function of RNAIII is to express several virulence factors in *S. aureus*[55,56].

In a recent study by Goliska *et al*[57], pathogenicity of enterococci (*Enterococcus faecalis*) in IBD was studied. The expression of several genes encoding the virulence factors (gelatinase, extracellular surface protein, cytolysin and hyaluronidase) was studied in IBD patients and control groups. The strains with these virulence genes were also found to have QS genes *fsrA-C* that regulates the expression of these virulence factors.

IBD THERAPIES

Any effective therapeutic strategy to treat IBD should be able to treat all its pathophysiological constituents including inflammation, dysbiosis and leaky gut. The currently available medical treatments of IBD involve three approaches: immune-based therapies, microbiota-based therapies and barrier function-based therapies. Even after these advanced approaches, some patients still require surgical removal of severely affected portions of GI tract[58].

Immune-based therapies

Immune-based therapies directly modulate the immune system to avoid further destruction of commensal microbiota and the gut tissues to relieve inflammation. Furthermore, these therapies also indirectly modulate the mucosal barrier function and the microbiota[58,59]. Immune-based therapy medication includes immunomodulators (*e.g.*, methotrexate, azathioprine), aminosalicylates, corticosteroids, integrin inhibitors and antitumor necrosis factor agents. Several other biologics are being developed to downregulate inflammatory cytokines and their receptors along with rebuilding healthy barrier function[59]. Mesalamine and other salicylates are known to modulate the intestinal microbial composition and decrease microbial adherence and biofilm formation in the gut[39,58].

Microbiota-based therapies

Microbiota-based therapies are based upon use of antibiotics, probiotics, fecal microbiota transplantation and alteration in diet.

Antibiotics: Antibiotics have been found most effective in CD and only of little use in UC, where it is sometimes used to treat children. Antibiotics such as rifaximin, metronidazole, ciprofloxacin and antimycobacterial agents are being used. These antibiotics decrease the concentration of some pathogens and increase the content of healthy microbiota including *Bifidobacteria* and *F. prausnitzii*. Indiscriminate use of antibiotics can lead to severe side effects such as reduction in microbial biodiversity in gut and developing resistance in microbes[60,61].

Probiotics: Probiotics can be defined as the living organism (specific bacterial strains together) that when ingested provides health benefits and protective regulatory activities in the body. Commonly the content of yogurts such as *Lactobacilli*, *Bifidobacteria* and *Streptococci* play the role of probiotics. Probiotics have more efficiently been used in UC and are less effective for CD patients. The most extensively used probiotics for IBD are VSL#3 and *E. Coli* Nissle 1917. VSL#3 are a combination of eight diverse bacterial strains (four strains of *Lactobacilli*, three strains of *Bifidobacteria* and one strain of *Streptococcus*). These bacteria stimulate the growth of anti-inflammatory bacteria and prevent the growth of pathogenic microbes[62,63].

The use of lactic acid bacteria, which includes *Lactobacillus*, as probiotics for treatment and prevention of IBD has been proposed in several studies. They are Gram-positive bacteria that normally reside in anaerobic conditions but are facultative aerobes[64,65]. They provide probiotic action by production of bacteriocins, hydrogen peroxide, lactic acid and by forming dense biofilms on gut epithelium, which block all the adhesion sites for attachment of pathogens[65]. *Lactobacillus* species such as *L. casei, L. acidophilus, L. plantarum, L. rhamnosus, L. fermentum, L. amylovorus and L. delbrueckii, etc* have been extensively studied for probiotic action against *H. pylori, Salmonella, E. coli, Clostridium difficile, Yersinia enterocolitica* and *Listeria monocytogenes, etc*[65,66]. The microbial interactions amongst themselves and with other commensal/pathogenic microbes in the biofilms formed in the gut are regulated by the *luxS* gene QS mechanisms. Several other proteins that are involved in biofilm formation in different *Lactobacillus* strains consist of collagen-binding protein, biofilm associated proteins, glycosyl-transferases and mucus-binding protein[66,67]. Most of the *Lactobacillus* species are bacteriocin producing. A specific class of bacteriocin, called plantaricins are produced by some species such as *L. plantarum* and *L. fermentum*. The plantaricin genes which can be identified in *Lactobacillus* are *plnA, plnB, plnC, plnD, plnEF, plnI, plnJ, plnK, plnG, plnN* and plantaricin structural genes[68,69].

Fecal microbiota transplantation: This strategy of re-establishing healthy microbiota and treating IBD involves ingestion of healthy donor stool by an ill individual. This has been extensively used with mixed and moderate results in IBD patients. Repetitive infusions are required for sustained results. Keeping in view the chance of transmitting infectious microbes, recent studies suggest the use of artificial stool with limited risk of such infections[70,71].

Alteration in diet: A balanced, high fiber, healthy diet with vegetables, fruits and grains is recommended for IBD patients. Diets with high protein content, excessive red meat and alcohol abuse are discouraged in IBD as it may aggravate or relapse the inflammation. Specific carbohydrate diets that eliminates milk, grains and sugar from the diet has been found effective in some cases of IBD showing an improvement in microbiota diversity[72,73].

Barrier function-based therapies

This therapy is evolving as the most effective and future approach for treating IBD. If the mucus layer in the gut epithelia is restored, then eventually the immune responses and inflammation can be controlled as well as microbiota diversity can flourish.

Establishing healthy microbiota and inhibition of TNFα and other inflammatory cytokines have recorded an enhanced barrier function in case of IBD. Amino acid, L-glutamine supplements and natural ingredients such as curcumin have been shown to restore tight junctions and hence can be used in treating IBD. Delayed released drugs such as phosphatidylcholine are also being examined extensively as a cure for IBD[39,74-76].

BACTERIAL INFECTION IN IBD

Prominence worldwide

A number of studies with the aim to distinguish between residing microbes in a healthy patient and an IBD patient revealed an overall decline in bacterial diversity in the gut of patients with IBD[25,26]. Clustering of microbial communities was found over inflamed gut surfaces, but the microbial communities may not vary over the healthy gut tissues. Different studies have also reported the presence of pathogenic microbes in gastrointestinal tracts of IBD patients.

Ma *et al*[77] studied the occurrence of *Campylobacter concisus* in CD patients colonic biopsy samples and concluded there may be potential involvement of *C. concisus* in IBD. In another study by Arora *et al*[78] the risk of *C. jejuni* infection in UC was established.

Similarly, the presence of several virulence factors such as hyaluronidase, cytolysin and extracellular surface protein in *Enterococcus* strains isolated from colon tissue samples of children with IBD was observed[57].

There are several studies that link *Helicobacter pylori* biofilms with gastrointestinal diseases, but it still remains debatable. Mice have developed IBD symptoms in the presence of abnormal immune response and *H. pylori* infection. No symptoms appeared in germfree conditions that establish single pathogen infection[79]. Halme *et al*[80] and Luther *et al*[81] observed contradictory results and demonstrated a protective or inverse relation of *Helicobacter* towards IBD.

Furthermore, a study by Saebo *et al*[82] concluded that infection of *Yersinia enterocolitica* was an activator for IBD. Similarly, Ruckdeschel *et al*[83] analyzed the impact of virulence factors (such as cytotoxin, invasin and adhesin) of *Y. enterocolitica* against the action of polymorphonuclear leukocytes.

As far as the role of *Listeria monocytogenes* in IBD is concerned, studies revealed uncertain outcomes. *L. monocytogenes* was found proliferating at a higher rate in the colon of patients with IBD than in healthy controls[84]. *Listeria* forms resistant biofilms on several surfaces including synthetic as well as gut epithelium. The biofilm formation is regulated by QS autoinducer 2 genes *luxS* and *pfs*. Chen *et al*[85] studied the presence of *L. monocytogenes* in gut biopsies of IBD patients and controls in New Zealand and reported no direct role of *L. monocytogenes* in causing IBD. Another study by Huijsdens *et al*[86] also reported a similar result. However, Ooi *et al*[87] found *L. monocytogenes* responsible for causing mucosal inflammation in healthy individuals. Another recent study by Miranda-Bautista *et al*[88] confirmed the presence of *L. monocytogenes* in patients of CD and concluded that IBD patients are at a serious risk of *L. monocytogenes* infection.

Numerous studies also demonstrate a relation between *Salmonella enterica* infection and IBD. It has been reported that IBD and *Salmonella* infection with coinciding medical and histological symptoms in an elderly woman. This case study reports that colitis may be associated with *Salmonella* infection[89]. There are various other studies which elucidate the high risk of *S. enterica* infection in IBD[90-92].

Even though these studies have shown a relationship between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable.

Prominence in India

The majority of IBD has been reported in northern Europe and North America, whereas it has been considered rare among Asians and Africans. But, in the past two decades cases of such western diseases have been witnessed in India, including UC and CD, and the number of affected individuals is rising alarmingly[93]. Detailed studies regarding epidemiology and pathogenesis of IBD are lacking in developing countries like India due to neglected health care services, lack of reliable data collection and patient based studies[93,94].

Several studies have reported the possible involvement of specific pathogens in IBD. Verma *et al*[95] described that different sets of bacteria are responsible for pathogenesis of UC and CD. An increase in Gram-positive *Eubacterium* and *Peptostreptococcus* was reported in CD patients but not in UC patients, whereas *Campylobacter spp*. significantly increased in both CD and UC patients. A study by Patra *et al*[96] reported the presence of various serogroups of adherent *Escherichia coli* in rectal biopsies of individuals and associated it with epithelial damage and CD. Banerjee *et al*[97] reported occurrence of parasitic and viral infections (such as *Ankylostoma duodenale, Strongyloides stercoralis, Entamoeba histolytica, etc*) in UC patients by analysis of stool samples and rectal biopsies. Iyer *et al*[98] investigated the relationship between intestinal infections (with *Clostridium difficile* and other parasites) and UC. They reported that the presence of such infections in UC patients deteriorated the condition and is associated with disease severity. Tripathi *et al*[99] detected the presence of *Salmonella enterica* in the stool of 80% of UC patients and concluded an active infection of *Salmonella sp*. in IBD.

Another recent study examined the gut microbiota profile of vegetarian and non-

vegetarian healthy individuals and IBD individuals and colon carcinoma and reported that IBD and colon cancer patients had higher proportions of *Bacteroidetes* than *Firmicutes*[100]. Several studies discuss the food-borne infection of *Listeria monocytogenes* in India. In another study[101] established the expression of virulence gene regulator *prfA* in *L. monocytogenes* infecting mammalian host, which helps in formation of resistant biofilms and virulence. Expression of *prfA* was also studied in co-cultured biofilms with *B. subtilis*, which made *L. monocytogenes* less virulent in such biofilms.

Several studies have also been conducted regarding the anti-biofilm nature and probiotic properties of lactic acid bacteria against pathogenic bacteria. Kaur *et al*[102] reported the action of *Lactobacillus spp*. against diarrhea causing *Vibrio cholerae*, which causes high mortality in developing countries like India. Another study examined the antimicrobial action of *Lactobacillus spp*. from curd and milk against several human infecting pathogens such as *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Salmonella enterica serovar Typhi, Bacillus cereus, Listeria monocytogenes* and *Shigella flexneri[103]*. Furthermore, in some studies it has been demonstrated the antimicrobial action of thirteen *Lactobacillus* isolates from the gastrointestinal track of broiler chicken against *Escherichia coli* and pathogenic fungi such as *Aspergillus niger, Aspergillus flavus, Penicillium expansum, Penicillium roqueforti and Candida albicans, etc*[104-106]. The lactic acid bacteria showed effective inhibition against these pathogens.

CONCLUSION

The understanding of gut microbiota in terms of composition and its complex interaction in both normal and diseased conditions has been assisted by the use of molecular, metagenomics and meta transcriptomics techniques. Even though several studies (as mentioned above) have shown relationships between pathogens and IBD, a specific pathogenic microbe being responsible for CD or UC is still debatable. Also, detailed research has been done for gut microbiota and IBD, but the molecular basis of their virulence and biofilm formation still remains to be discovered. This has hampered the generation of effective therapeutic agents for IBD that would benefit a high percentage of the world population affected by the disease. Therefore, we need to understand the pathogenesis of IBD and develop strong treatment strategies against it.

REFERENCES

1 **Steed H**, Macfarlane GT, Macfarlane S. Prebiotics, synbiotics and inflammatory bowel disease. *Mol Nutr Food Res* 2008; **52**: 898-905 [PMID: 18383235 DOI: 10.1002/mnfr.200700139]
2 **Macfarlane GT**, Blackett KL, Nakayama T, Steed H, Macfarlane S. The gut microbiota in inflammatory bowel disease. *Curr Pharm Des* 2009; **15**: 1528-1536 [PMID: 19442170]
3 **Reiff C**, Kelly D. Inflammatory bowel disease, gut bacteria and probiotic therapy. *Int J Med Microbiol* 2010; **300**: 25-33 [PMID: 19800289 DOI: 10.1016/j.ijmm.2009.08.004]
4 **Swidsinski A**, Loening-Baucke V, Herber A. Mucosal flora in Crohn's disease and ulcerative colitis - an overview. *J Physiol Pharmacol* 2009; **60** Suppl 6: 61-71 [PMID: 20224153]
5 **Swidsinski A**, Weber J, Loening-Baucke V, Hale LP, Lochs H. Spatial organization and composition of the mucosal flora in patients with inflammatory bowel disease. *J Clin Microbiol* 2005; **43**: 3380-3389 [PMID: 16000463 DOI: 10.1128/JCM.43.7.3380-3389.2005]
6 **Baumgart M**, Dogan B, Rishniw M, Weitzman G, Bosworth B, Yantiss R, Orsi RH, Wiedmann M, McDonough P, Kim SG, Berg D, Schukken Y, Scherl E, Simpson KW. Culture independent analysis of ileal mucosa reveals a selective increase in invasive Escherichia coli of novel phylogeny relative to depletion of Clostridiales in Crohn's disease involving the ileum. *ISME J* 2007; **1**: 403-418 [PMID: 18043660 DOI: 10.1038/ismej.2007.52]
7 **Loftus EV**. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology* 2004; **126**: 1504-1517 [PMID: 15168363]
8 **Drescher K**, Nadell CD, Stone HA, Wingreen NS, Bassler BL. Solutions to the public goods dilemma in bacterial biofilms. *Curr Biol* 2014; **24**: 50-55 [PMID: 24332540 DOI: 10.1016/j.cub.2013.10.030]
9 **Miller MB**, Bassler BL. Quorum sensing in bacteria. *Annu Rev Microbiol* 2001; **55**: 165-199 [PMID: 11544353 DOI: 10.1146/annurev.micro.55.1.165]
10 **Pirzer U**, Schönhaar A, Fleischer B, Hermann E, Meyer zum Büschenfelde KH. Reactivity of infiltrating T lymphocytes with microbial antigens in Crohn's disease. *Lancet* 1991; **338**: 1238-1239 [PMID: 1682646]
11 **Macpherson A**, Khoo UY, Forgacs I, Philpott-Howard J, Bjarnason I. Mucosal antibodies in inflammatory bowel disease are directed against intestinal bacteria. *Gut* 1996; **38**: 365-375 [PMID: 8675088]
12 **Orholm M**, Munkholm P, Langholz E, Nielsen OH, Sørensen TI, Binder V. Familial occurrence of inflammatory bowel disease. *N Engl J Med* 1991; **324**: 84-88 [PMID: 1984188 DOI: 10.1056/NEJM199101103240203]
13 **Shanahan F**. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and ecotherapeutics. *Gastroenterology* 2001; **120**: 622-635 [PMID: 11179240]

14 **Bach JF**. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002; **347**: 911-920 [PMID: 12239261 DOI: 10.1056/NEJMra020100]
15 **Fiocchi C**. Inflammatory bowel disease: etiology and pathogenesis. *Gastroenterology* 1998; **115**: 182-205 [PMID: 9649475]
16 **Rhodes J**, Thomas GA. Smoking: good or bad for inflammatory bowel disease? *Gastroenterology* 1994; **106**: 807-810 [PMID: 8119552]
17 **Koutroubakis I**, Manousos ON, Meuwissen SG, Pena AS. Environmental risk factors in inflammatory bowel disease. *Hepatogastroenterology* 1996; **43**: 381-393 [PMID: 8714231]
18 **Mawdsley JE**, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut* 2005; **54**: 1481-1491 [PMID: 16162953 DOI: 10.1136/gut.2005.064261]
19 **Cámara RJ**, Ziegler R, Begré S, Schoepfer AM, von Känel R; Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) group. The role of psychological stress in inflammatory bowel disease: quality assessment of methods of 18 prospective studies and suggestions for future research. *Digestion* 2009; **80**: 129-139 [PMID: 19657191 DOI: 10.1159/000226087]
20 **Bitton A**, Sewitch MJ, Peppercorn MA, deB Edwardes MD, Shah S, Ransil B, Locke SE. Psychosocial determinants of relapse in ulcerative colitis: a longitudinal study. *Am J Gastroenterol* 2003; **98**: 2203-2208 [PMID: 14572569 DOI: 10.1111/j.1572-0241.2003.07717.x]
21 **Mardini HE**, Kip KE, Wilson JW. Crohn's disease: a two-year prospective study of the association between psychological distress and disease activity. *Dig Dis Sci* 2004; **49**: 492-497 [PMID: 15139504]
22 **Franke A**, Hampe J, Rosenstiel P, Becker C, Wagner F, Häsler R, Little RD, Huse K, Ruether A, Balschun T, Wittig M, Elsharawy A, Mayr G, Albrecht M, Prescott NJ, Onnie CM, Fournier H, Keith T, Radelof U, Platzer M, Mathew CG, Stoll M, Krawczak M, Nürnberg P, Schreiber S. Systematic association mapping identifies NELL1 as a novel IBD disease gene. *PLoS One* 2007; **2**: e691 [PMID: 17684544 DOI: 10.1371/journal.pone.0000691]
23 **Barrett JC**, Hansoul S, Nicolae DL, Cho JH, Duerr RH, Rioux JD, Brant SR, Silverberg MS, Taylor KD, Barmada MM, Bitton A, Dassopoulos T, Datta LW, Green T, Griffiths AM, Kistner EO, Murtha MT, Regueiro MD, Rotter JI, Schumm LP, Steinhart AH, Targan SR, Xavier RJ; NIDDK IBD Genetics Consortium, Libioulle C, Sandor C, Lathrop M, Belaiche J, Dewit O, Gut I, Heath S, Laukens D, Mni M, Rutgeerts P, Van Gossum A, Zelenika D, Franchimont D, Hugot JP, de Vos M, Vermeire S, Louis E; Belgian-French IBD Consortium; Wellcome Trust Case Control Consortium, Cardon LR, Anderson CA, Drummond H, Nimmo E, Ahmad T, Prescott NJ, Onnie CM, Fisher SA, Marchini J, Ghori J, Bumpstead S, Gwilliam R, Tremelling M, Deloukas P, Mansfield J, Jewell D, Satsangi J, Mathew CG, Parkes M, Georges M, Daly MJ. Genome-wide association defines more than 30 distinct susceptibility loci for Crohn's disease. *Nat Genet* 2008; **40**: 955-962 [PMID: 18587394 DOI: 10.1038/ng.175]
24 **Eckburg PB**, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. *Science* 2005; **308**: 1635-1638 [PMID: 15831718 DOI: 10.1126/science.1110591]
25 **Frank DN**, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A* 2007; **104**: 13780-13785 [PMID: 17699621 DOI: 10.1073/pnas.0706625104]
26 **Ott SJ**, Kühbacher T, Musfeldt M, Rosenstiel P, Hellmig S, Rehman A, Drews O, Weichert W, Timmis KN, Schreiber S. Fungi and inflammatory bowel diseases: Alterations of composition and diversity. *Scand J Gastroenterol* 2008; **43**: 831-841 [PMID: 18584522 DOI: 10.1080/00365520801935434]
27 **Tamboli CP**, Neut C, Desreumaux P, Colombel JF. Dysbiosis as a prerequisite for IBD. *Gut* 2004; **53**: 1057 [PMID: 15194668]
28 **Glasser AL**, Boudeau J, Barnich N, Perruchot MH, Colombel JF, Darfeuille-Michaud A. Adherent invasive Escherichia coli strains from patients with Crohn's disease survive and replicate within macrophages without inducing host cell death. *Infect Immun* 2001; **69**: 5529-5537 [PMID: 11500426]
29 **Rolhion N**, Barnich N, Bringer MA, Glasser AL, Ranc J, Hébuterne X, Hofman P, Darfeuille-Michaud A. Abnormally expressed ER stress response chaperone Gp96 in CD favours adherent-invasive Escherichia coli invasion. *Gut* 2010; **59**: 1355-1362 [PMID: 20587550 DOI: 10.1136/gut.2010.207456]
30 **Bibiloni R**, Mangold M, Madsen KL, Fedorak RN, Tannock GW. The bacteriology of biopsies differs between newly diagnosed, untreated, Crohn's disease and ulcerative colitis patients. *J Med Microbiol* 2006; **55**: 1141-1149 [PMID: 16849736 DOI: 10.1099/jmm.0.46498-0]
31 **Nibali L**, Henderson B, Sadiq ST, Donos N. Genetic dysbiosis: the role of microbial insults in chronic inflammatory diseases. *J Oral Microbiol* 2014; 6 [PMID: 24578801 DOI: 10.3402/jom.v6.22962]
32 **Turner JR**. Intestinal mucosal barrier function in health and disease. *Nat Rev Immunol* 2009; **9**: 799-809 [PMID: 19855405 DOI: 10.1038/nri2653]
33 **Merga Y**, Campbell BJ, Rhodes JM. Mucosal barrier, bacteria and inflammatory bowel disease: possibilities for therapy. *Dig Dis* 2014; **32**: 475-483 [PMID: 24969297 DOI: 10.1159/000358156]
34 **Michielan A**, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. *Mediators Inflamm* 2015; **2015**: 628157 [PMID: 26582965 DOI: 10.1155/2015/628157]
35 **Abraham C**, Medzhitov R. Interactions between the host innate immune system and microbes in inflammatory bowel disease. *Gastroenterology* 2011; **140**: 1729-1737 [PMID: 21530739 DOI: 10.1053/j.gastro.2011.02.012]
36 **Kato LM**, Kawamoto S, Maruya M, Fagarasan S. The role of the adaptive immune system in regulation of gut microbiota. *Immunol Rev* 2014; **260**: 67-75 [PMID: 24942682 DOI: 10.1111/imr.12185]
37 **Parkes M**. Evidence from genetics for a role of autophagy and innate immunity in IBD pathogenesis. *Dig Dis* 2012; **30**: 330-333 [PMID: 22796792 DOI: 10.1159/000338119]
38 **Man SM**, Kaakoush NO, Mitchell HM. The role of bacteria and pattern-recognition receptors in Crohn's disease. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 152-168 [PMID: 21304476 DOI: 10.1038/nrgastro.2011.3]
39 **Vindigni SM**, Zisman TL, Suskind DL, Damman CJ. The intestinal microbiome, barrier function, and immune system in inflammatory bowel disease: a tripartite pathophysiological circuit with implications for new therapeutic directions. *Therap Adv Gastroenterol* 2016; **9**: 606-625 [PMID: 27366227 DOI: 10.1177/1756283X16644242]
40 **Fernandes P**, MacSharry J, Darby T, Fanning A, Shanahan F, Houston A, Brint E. Differential expression of key regulators of Toll-like receptors in ulcerative colitis and Crohn's disease: a role for Tollip and peroxisome proliferator-activated receptor gamma? *Clin Exp Immunol* 2016; **183**: 358-368 [PMID: 26462859 DOI: 10.1111/cei.12732]

41 **Braun V**, Patzer SI. Intercellular communication by related bacterial protein toxins: colicins, contact-dependent inhibitors, and proteins exported by the type VI secretion system. *FEMS Microbiol Lett* 2013; **345**: 13-21 [PMID: 23701660 DOI: 10.1111/1574-6968.12180]

42 **Rebuffat S**. Microcins in action: amazing defence strategies of Enterobacteria. *Biochem Soc Trans* 2012; **40**: 1456-1462 [PMID: 23176498 DOI: 10.1042/BST20120183]

43 **Degnan PH**, Barry NA, Mok KC, Taga ME, Goodman AL. Human gut microbes use multiple transporters to distinguish vitamin B analogs and compete in the gut. *Cell Host Microbe* 2014; **15**: 47-57 [PMID: 24439897 DOI: 10.1016/j.chom.2013.12.007]

44 **Seth EC**, Taga ME. Nutrient cross-feeding in the microbial world. *Front Microbiol* 2014; **5**: 350 [PMID: 25071756 DOI: 10.3389/fmicb.2014.00350]

45 **Raffatellu M**, George MD, Akiyama Y, Hornsby MJ, Nuccio SP, Paixao TA, Butler BP, Chu H, Santos RL, Berger T, Mak TW, Tsolis RM, Bevins CL, Solnick JV, Dandekar S, Bäumler AJ. Lipocalin-2 resistance confers an advantage to Salmonella enterica serotype Typhimurium for growth and survival in the inflamed intestine. *Cell Host Microbe* 2009; **5**: 476-486 [PMID: 19454351 DOI: 10.1016/j.chom.2009.03.011]

46 **Griffin AS**, West SA, Buckling A. Cooperation and competition in pathogenic bacteria. *Nature* 2004; **430**: 1024-1027 [PMID: 15329720 DOI: 10.1038/nature02744]

47 **Nogueira T**, Rankin DJ, Touchon M, Taddei F, Brown SP, Rocha EP. Horizontal gene transfer of the secretome drives the evolution of bacterial cooperation and virulence. *Curr Biol* 2009; **19**: 1683-1691 [PMID: 19800234 DOI: 10.1016/j.cub.2009.08.056]

48 **van Hemert S**, Meijerink M, Molenaar D, Bron PA, de Vos P, Kleerebezem M, Wells JM, Marco ML. Identification of Lactobacillus plantarum genes modulating the cytokine response of human peripheral blood mononuclear cells. *BMC Microbiol* 2010; **10**: 293 [PMID: 21080958 DOI: 10.1186/1471-2180-10-293]

49 **Dickschat JS**. Quorum sensing and bacterial biofilms. *Nat Prod Rep* 2010; **27**: 343-369 [PMID: 20179876 DOI: 10.1039/b804469b]

50 **Lukáš F**, Gorenc G, Kopecný J. Detection of possible AI-2-mediated quorum sensing system in commensal intestinal bacteria. *Folia Microbiol (Praha)* 2008; **53**: 221-224 [PMID: 18661296 DOI: 10.1007/s12223-008-0030-1]

51 **Hammer BK**, Bassler BL. Quorum sensing controls biofilm formation in Vibrio cholerae. *Mol Microbiol* 2003; **50**: 101-104 [PMID: 14507367]

52 **Engebrecht J**, Nealson K, Silverman M. Bacterial bioluminescence: isolation and genetic analysis of functions from Vibrio fischeri. *Cell* 1983; **32**: 773-781 [PMID: 6831560]

53 **Pearson JP**, Passador L, Iglewski BH, Greenberg EP. A second N-acylhomoserine lactone signal produced by Pseudomonas aeruginosa. *Proc Natl Acad Sci U S A* 1995; **92**: 1490-1494 [PMID: 7878006]

54 **Ochsner UA**, Reiser J. Autoinducer-mediated regulation of rhamnolipid biosurfactant synthesis in Pseudomonas aeruginosa. *Proc Natl Acad Sci U S A* 1995; **92**: 6424-6428 [PMID: 7604006]

55 **Novick RP**, Projan SJ, Kornblum J, Ross HF, Ji G, Kreiswirth B, Vandenesch F, Moghazeh S. The agr P2 operon: an autocatalytic sensory transduction system in Staphylococcus aureus. *Mol Gen Genet* 1995; **248**: 446-458 [PMID: 7565609]

56 **Morfeldt E**, Taylor D, von Gabain A, Arvidson S. Activation of alpha-toxin translation in Staphylococcus aureus by the trans-encoded antisense RNA, RNAIII. *EMBO J* 1995; **14**: 4569-4577 [PMID: 7556100]

57 **Goliska E**, Tomusiak A, Gosiewski T, Więcek G, Machul A, Mikołajczyk D, Bulanda M, Heczko PB, Strus M. Virulence factors of Enterococcus strains isolated from patients with inflammatory bowel disease. *World J Gastroenterol* 2013; **19**: 3562-3572 [PMID: 23801857 DOI: 10.3748/wjg.v19.i23.3562]

58 **Andrews CN**, Griffiths TA, Kaufman J, Vergnolle N, Surette MG, Rioux KP. Mesalazine (5-aminosalicylic acid) alters faecal bacterial profiles, but not mucosal proteolytic activity in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2011; **34**: 374-383 [PMID: 21671966 DOI: 10.1111/j.1365-2036.2011.04732.x]

59 **Peng JC**, Shen J, Ran ZH. Novel agents in the future: Therapy beyond anti-TNF agents in inflammatory bowel disease. *J Dig Dis* 2014; **15**: 585-590 [PMID: 25251263 DOI: 10.1111/1751-2980.12193]

60 **Bejaoui M**, Sokol H, Marteau P. Targeting the Microbiome in Inflammatory Bowel Disease: Critical Evaluation of Current Concepts and Moving to New Horizons. *Dig Dis* 2015; **33** Suppl 1: 105-112 [PMID: 26366577 DOI: 10.1159/000437104]

61 **Maccaferri S**, Vitali B, Klinder A, Kolida S, Ndagijimana M, Laghi L, Calanni F, Brigidi P, Gibson GR, Costabile A. Rifaximin modulates the colonic microbiota of patients with Crohn's disease: an in vitro approach using a continuous culture colonic model system. *J Antimicrob Chemother* 2010; **65**: 2556-2565 [PMID: 20852272 DOI: 10.1093/jac/dkq345]

62 **Cammarota G**, Ianiro G, Cianci R, Bibbò S, Gasbarrini A, Currò D. The involvement of gut microbiota in inflammatory bowel disease pathogenesis: potential for therapy. *Pharmacol Ther* 2015; **149**: 191-212 [PMID: 25561343 DOI: 10.1016/j.pharmthera.2014.12.006]

63 **Henker J**, Müller S, Laass MW, Schreiner A, Schulze J. Probiotic Escherichia coli Nissle 1917 (EcN) for successful remission maintenance of ulcerative colitis in children and adolescents: an open-label pilot study. *Z Gastroenterol* 2008; **46**: 874-875 [PMID: 18810672 DOI: 10.1055/s-2008-1027463]

64 **Holzapfel WH**, Haberer P, Geisen R, Björkroth J, Schillinger U. Taxonomy and important features of probiotic microorganisms in food and nutrition. *Am J Clin Nutr* 2001; **73**: 365S-373S [PMID: 11157343 DOI: 10.1093/ajcn/73.2.365s]

65 **Figueroa-González I**, Quijano G, Ramírez G, Cruz-Guerrero A. Probiotics and prebiotics--perspectives and challenges. *J Sci Food Agric* 2011; **91**: 1341-1348 [PMID: 21445871 DOI: 10.1002/jsfa.4367]

66 **Salas-Jara MJ**, Ilabaca A, Vega M, García A. Biofilm Forming Lactobacillus: New Challenges for the Development of Probiotics. *Microorganisms* 2016; 4 [PMID: 27681929 DOI: 10.3390/microorganisms4030035]

67 **Walter J**, Britton RA, Roos S. Host-microbial symbiosis in the vertebrate gastrointestinal tract and the Lactobacillus reuteri paradigm. *Proc Natl Acad Sci U S A* 2011; **108** Suppl 1: 4645-4652 [PMID: 20615995 DOI: 10.1073/pnas.1000099107]

68 **Ben Omar N**, Abriouel H, Keleke S, Sánchez Valenzuela A, Martínez-Cañamero M, Lucas López R, Ortega E, Gálvez A. Bacteriocin-producing Lactobacillus strains isolated from poto poto, a Congolese fermented maize product, and genetic fingerprinting of their plantaricin operons. *Int J Food Microbiol* 2008; **127**: 18-25 [PMID: 18620772 DOI: 10.1016/j.ijfoodmicro.2008.05.037]

69 **Mokoena MP**. Lactic Acid Bacteria and Their Bacteriocins: Classification, Biosynthesis and Applications against Uropathogens: A Mini-Review. *Molecules* 2017; 22 [PMID: 28933759 DOI:

10.3390/molecules22081255]
70 **Borody TJ**, Paramsothy S, Agrawal G. Fecal microbiota transplantation: indications, methods, evidence, and future directions. *Curr Gastroenterol Rep* 2013; **15**: 337 [PMID: 23852569 DOI: 10.1007/s11894-013-0337-1]
71 **Petrof EO**, Khoruts A. From stool transplants to next-generation microbiota therapeutics. *Gastroenterology* 2014; **146**: 1573-1582 [PMID: 24412527 DOI: 10.1053/j.gastro.2014.01.004]
72 **Cohen SA**, Gold BD, Oliva S, Lewis J, Stallworth A, Koch B, Eshee L, Mason D. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr* 2014; **59**: 516-521 [PMID: 24897165 DOI: 10.1097/MPG.0000000000000449]
73 **Tilg H**, Kaser A. Diet and relapsing ulcerative colitis: take off the meat? *Gut* 2004; **53**: 1399-1401 [PMID: 15361484 DOI: 10.1136/gut.2003.035287]
74 **Karner M**, Kocjan A, Stein J, Schreiber S, von Boyen G, Uebel P, Schmidt C, Kupcinskas L, Dina I, Zuelch F, Keilhauer G, Stremmel W. First multicenter study of modified release phosphatidylcholine "LT-02" in ulcerative colitis: a randomized, placebo-controlled trial in mesalazine-refractory courses. *Am J Gastroenterol* 2014; **109**: 1041-1051 [PMID: 24796768 DOI: 10.1038/ajg.2014.104]
75 **Ulluwishewa D**, Anderson RC, McNabb WC, Moughan PJ, Wells JM, Roy NC. Regulation of tight junction permeability by intestinal bacteria and dietary components. *J Nutr* 2011; **141**: 769-776 [PMID: 21430248 DOI: 10.3945/jn.110.135657]
76 **Wang N**, Wang G, Hao J, Ma J, Wang Y, Jiang X, Jiang H. Curcumin ameliorates hydrogen peroxide-induced epithelial barrier disruption by upregulating heme oxygenase-1 expression in human intestinal epithelial cells. *Dig Dis Sci* 2012; **57**: 1792-1801 [PMID: 22392462 DOI: 10.1007/s10620-012-2094-7]
77 **Ma R**, Liu F, Yap SF, Lee H, Leong RW, Riordan SM, Grimm MC, Zhang L. The Growth and Protein Expression of Inflammatory Bowel Disease-Associated Campylobacter concisus Is Affected by the Derivatives of the Food Additive Fumaric Acid. *Front Microbiol* 2018; **9**: 896 [PMID: 29867807 DOI: 10.3389/fmicb.2018.00896]
78 **Arora Z**, Mukewar S, Wu X, Shen B. Risk factors and clinical implication of superimposed Campylobacter jejuni infection in patients with underlying ulcerative colitis. *Gastroenterol Rep (Oxf)* 2016; **4**: 287-292 [PMID: 26159630 DOI: 10.1093/gastro/gov029]
79 **Cahill RJ**, Foltz CJ, Fox JG, Dangler CA, Powrie F, Schauer DB. Inflammatory bowel disease: an immunity-mediated condition triggered by bacterial infection with Helicobacter hepaticus. *Infect Immun* 1997; **65**: 3126-3131 [PMID: 9234764]
80 **Halme L**, Rautelin H, Leidenius M, Kosunen TU. Inverse correlation between Helicobacter pylori infection and inflammatory bowel disease. *J Clin Pathol* 1996; **49**: 65-67 [PMID: 8666689]
81 **Luther J**, Dave M, Higgins PD, Kao JY. Association between Helicobacter pylori infection and inflammatory bowel disease: a meta-analysis and systematic review of the literature. *Inflamm Bowel Dis* 2010; **16**: 1077-1084 [PMID: 19760778 DOI: 10.1002/ibd.21116]
82 **Saebo A**, Vik E, Lange OJ, Matuszkiewicz L. Inflammatory bowel disease associated with Yersinia enterocolitica O:3 infection. *Eur J Intern Med* 2005; **16**: 176-182 [PMID: 15967332 DOI: 10.1016/j.ejim.2004.11.008]
83 **Ruckdeschel K**, Roggenkamp A, Schubert S, Heesemann J. Differential contribution of Yersinia enterocolitica virulence factors to evasion of microbicidal action of neutrophils. *Infect Immun* 1996; **64**: 724-733 [PMID: 8641773]
84 **Chiba M**, Fukushima T, Koganei K, Nakamura N, Masamune O. Listeria monocytogenes in the colon in a case of fulminant ulcerative colitis. *Scand J Gastroenterol* 1998; **33**: 778-782 [PMID: 9712246]
85 **Chen W**, Li D, Paulus B, Wilson I, Chadwick VS. Detection of Listeria monocytogenes by polymerase chain reaction in intestinal mucosal biopsies from patients with inflammatory bowel disease and controls. *J Gastroenterol Hepatol* 2000; **15**: 1145-1150 [PMID: 11106094]
86 **Huijsdens XW**, Linskens RK, Taspinar H, Meuwissen SG, Vandenbroucke-Grauls CM, Savelkoul PH. Listeria monocytogenes and inflammatory bowel disease: detection of Listeria species in intestinal mucosal biopsies by real-time PCR. *Scand J Gastroenterol* 2003; **38**: 332-333 [PMID: 12737451]
87 **Ooi ST**, Lorber B. Gastroenteritis due to Listeria monocytogenes. *Clin Infect Dis* 2005; **40**: 1327-1332 [PMID: 15825036 DOI: 10.1086/429324]
88 **Miranda-Bautista J**, Padilla-Suárez C, Bouza E, Muñoz P, Menchén L, Marín-Jiménez I. Listeria monocytogenes infection in inflammatory bowel disease patients: case series and review of the literature. *Eur J Gastroenterol Hepatol* 2014; **26**: 1247-1252 [PMID: 25171025 DOI: 10.1097/MEG.0000000000000188]
89 **Nimmons D**, Limdi JK. Elderly patients and inflammatory bowel disease. *World J Gastrointest Pharmacol Ther* 2016; **7**: 51-65 [PMID: 26855812 DOI: 10.4292/wjgpt.v7.i1.51]
90 **Ferreira RB**, Gill N, Willing BP, Antunes LC, Russell SL, Croxen MA, Finlay BB. The intestinal microbiota plays a role in Salmonella-induced colitis independent of pathogen colonization. *PLoS One* 2011; **6**: e20338 [PMID: 21633507 DOI: 10.1371/journal.pone.0020338]
91 **Gradel KO**, Nielsen HL, Schønheyder HC, Ejlertsen T, Kristensen B, Nielsen H. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. *Gastroenterology* 2009; **137**: 495-501 [PMID: 19361507 DOI: 10.1053/j.gastro.2009.04.001]
92 **Ternhag A**, Törner A, Svensson A, Ekdahl K, Giesecke J. Short- and long-term effects of bacterial gastrointestinal infections. *Emerg Infect Dis* 2008; **14**: 143-148 [PMID: 18258094 DOI: 10.3201/eid1401.070524]
93 **Kedia S**, Ahuja V. Epidemiology of Inflammatory Bowel Disease in India: The Great Shift East. *Inflamm Intest Dis* 2017; **2**: 102-115 [PMID: 30018961 DOI: 10.1159/000465522]
94 **Ray G**. Inflammatory bowel disease in India - Past, present and future. *World J Gastroenterol* 2016; **22**: 8123-8136 [PMID: 27688654 DOI: 10.3748/wjg.v22.i36.8123]
95 **Verma R**, Verma AK, Ahuja V, Paul J. Real-time analysis of mucosal flora in patients with inflammatory bowel disease in India. *J Clin Microbiol* 2010; **48**: 4279-4282 [PMID: 20861337 DOI: 10.1128/JCM.01360-10]
96 **Patra S**, Samal SC, Kang G, Pulimood A, Mathan M, Ramakrishna BS. Adherent Escherichia coli in colorectal mucosal biopsies: a histological and ultrastructural evaluation. *Indian J Pathol Microbiol* 2012; **55**: 485-489 [PMID: 23455785 DOI: 10.4103/0377-4929.107786]
97 **Banerjee D**, Deb R, Dar L, Mirdha BR, Pati SK, Thareja S, Falodia S, Ahuja V. High frequency of parasitic and viral stool pathogens in patients with active ulcerative colitis: report from a tropical country. *Scand J Gastroenterol* 2009; **44**: 325-331 [PMID: 19040190 DOI: 10.1080/00365520802556809]
98 **Iyer VH**, Augustine J, Pulimood AB, Ajjampur SS, Ramakrishna BS. Correlation between coinfection

with parasites, cytomegalovirus, and Clostridium difficile and disease severity in patients with ulcerative colitis. *Indian J Gastroenterol* 2013; **32**: 115-118 [PMID: 23408260 DOI: 10.1007/s12664-012-0302-1]

99 **Tripathi MK**, Pratap CB, Dixit VK, Singh TB, Shukla SK, Jain AK, Nath G. Ulcerative Colitis and Its Association with Salmonella Species. *Interdiscip Perspect Infect Dis* 2016; **2016**: 5854285 [PMID: 26904116 DOI: 10.1155/2016/5854285]

100 **Bamola VD**, Ghosh A, Kapardar RK, Lal B, Cheema S, Sarma P, Chaudhry R. Gut microbial diversity in health and disease: experience of healthy Indian subjects, and colon carcinoma and inflammatory bowel disease patients. *Microb Ecol Health Dis* 2017; **28**: 1322447 [PMID: 28588430 DOI: 10.1080/16512235.2017.1322447]

101 **Tirumalai PS**, Prakash S. Expression of virulence genes by Listeria monocytogenes J0161 in natural environment. *Braz J Microbiol* 2012; **43**: 834-843 [PMID: 24031897 DOI: 10.1590/S1517-83822012000200050]

102 **Kaur S**, Sharma P, Kalia N, Singh J, Kaur S. Anti-biofilm Properties of the Fecal Probiotic Lactobacilli Against Vibrio spp. *Front Cell Infect Microbiol* 2018; **8**: 120 [PMID: 29740541 DOI: 10.3389/fcimb.2018.00120]

103 **Sharma C**, Singh BP, Thakur N, Gulati S, Gupta S, Mishra SK, Panwar H. Antibacterial effects of Lactobacillus isolates of curd and human milk origin against food-borne and human pathogens. *3 Biotech* 2017; **7**: 31 [PMID: 28401466 DOI: 10.1007/s13205-016-0591-7]

104 **Russo P**, Arena MP, Fiocco D, Capozzi V, Drider D, Spano G. Lactobacillus plantarum with broad antifungal activity: A promising approach to increase safety and shelf-life of cereal-based products. *Int J Food Microbiol* 2017; **247**: 48-54 [PMID: 27240933 DOI: 10.1016/j.ijfoodmicro.2016.04.027]

105 **Fisher SA**, Tremelling M, Anderson CA, Gwilliam R, Bumpstead S, Prescott NJ, Nimmo ER, Massey D, Berzuini C, Johnson C, Barrett JC, Cummings FR, Drummond H, Lees CW, Onnie CM, Hanson CE, Blaszczyk K, Inouye M, Ewels P, Ravindrarajah R, Keniry A, Hunt S, Carter M, Watkins N, Ouwehand W, Lewis CM, Cardon L; Wellcome Trust Case Control Consortium, Lobo A, Forbes A, Sanderson J, Jewell DP, Mansfield JC, Deloukas P, Mathew CG, Parkes M, Satsangi J. Genetic determinants of ulcerative colitis include the ECM1 locus and five loci implicated in Crohn's disease. *Nat Genet* 2008; **40**: 710-712 [PMID: 18438406 DOI: 10.1038/ng.145]

106 **Rioux JD**, Xavier RJ, Taylor KD, Silverberg MS, Goyette P, Huett A, Green T, Kuballa P, Barmada MM, Datta LW, Shugart YY, Griffiths AM, Targan SR, Ippoliti AF, Bernard EJ, Mei L, Nicolae DL, Regueiro M, Schumm LP, Steinhart AH, Rotter JI, Duerr RH, Cho JH, Daly MJ, Brant SR. Genome-wide association study identifies new susceptibility loci for Crohn disease and implicates autophagy in disease pathogenesis. *Nat Genet* 2007; **39**: 596-604 [PMID: 17435756 DOI: 10.1038/ng2032]



Published By Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com



© 2019 Baishideng Publishing Group Inc. All rights reserved.