

World Journal of *Clinical Cases*

World J Clin Cases 2023 December 6; 11(34): 8094-8241



Contents

Thrice Monthly Volume 11 Number 34 December 6, 2023

EDITORIAL

- 8094** Advances and future directions in keloid research: Pathogenesis, diagnosis and personalized treatment strategies
Zhao SY, Wu D, Cheng C, Xie JH

OPINION REVIEW

- 8099** Mental health implications of suicide rates in South Africa
Edeh NC, Eseadi C
- 8106** Artificial intelligence in sleep medicine: Present and future
Verma RK, Dhillon G, Grewal H, Prasad V, Munjal RS, Sharma P, Buddhavarapu V, Devadoss R, Kashyap R, Surani S

REVIEW

- 8111** Research progress on the relationship between Paneth cells-susceptibility genes, intestinal microecology and inflammatory bowel disease
Zhou QM, Zheng L

ORIGINAL ARTICLE

Case Control Study

- 8126** Case-control analysis of venous thromboembolism risk in non-alcoholic steatohepatitis diagnosed by transient elastography
Suresh MG, Gogtay M, Singh Y, Yadukumar L, Mishra AK, Abraham GM

Retrospective Study

- 8139** Efficacy and safety of tenofovir alafenamide in patients with chronic hepatitis B exhibiting suboptimal response to entecavir
Yuan GC, Chen AZ, Wang WX, Yi XL, Tu L, Peng F, Qiu ZH

Prospective Study

- 8147** Arthroscopic findings after manipulation under anesthesia in idiopathic capsulitis of the shoulder: A prospective study
MLV SK, Mittal R, Chauhan N

CASE REPORT

- 8153** Intra-arterial lipo-prostaglandin E1 infusion for arterial spasm in liver transplantation: A case report
Kim M, Lee HW, Yoon CJ, Lee B, Jo Y, Cho JY, Yoon YS, Lee JS, Han HS
- 8158** Pulmonary fungal infection in a neonate with methylmalonic acidemia: A case report
Gao CF, Wang D, Zeng LK, Tao XW

- 8164** Adult localized Langerhans cell histiocytosis: A case report
Yang PP, Hu SY, Chai XY, Shi XM, Liu LX, Li LE
- 8170** Venous adventitial cystic disease is a very rare disease that can cause deep vein thrombosis: A case report
Bae M, Huh U, Lee CW, Kim JW
- 8176** Rare case of lupus enteritis presenting as colorectum involvement: A case report and review of literature
Gan H, Wang F, Gan Y, Wen L
- 8184** Repeated atrial arrhythmia induced by cochineal red poisoning: A case report
Yang H, Wang YJ, Xu BP, Peng HW, Xu Q, Yu HB
- 8192** Anti-glial fibrillary acidic protein antibody and anti-aquaporin-4 antibody double-positive neuromyelitis optica spectrum disorder: A case report
Jin TY, Lin BT, Dai LJ, Lu X, Gao H, Hu J
- 8200** Thoracic duct cannulation during left internal jugular vein cannulation: A case report
Hwang GH, Eom W
- 8205** Long-term survival of the Sister Mary Joseph nodule originating from breast cancer: A case report
Kanayama K, Tanioka M, Hattori Y, Iida T, Okazaki M
- 8212** Hemophagocytic lymphohistiocytosis with jaundice as first manifestation: A case report
Wang DD, Wu S, Kong BB, Song LL
- 8219** Comprehensive treatment of deep frostbite of multiple fingers after trauma: A case report
Wang XH, Li M, Cheng Y, Wang GJ, Lin GL, Liu WN
- 8228** Bilateral snapping triceps syndrome: A case report
Cho CH, Lim KH, Kim DH
- 8235** Management of post-liver transplantation biliary stricture inaccessible by endoscopic retrograde cholangiopancreatography: A case report
Lee Y, Park CH, Cho E, Kim KH

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Dong-Ling Dai, MBBS, PhD, Chief Doctor, Professor, Department of Endoscopy Center and Gastroenterology, Shenzhen Children's Hospital, Shenzhen 518036, Guangdong Province, China. daidong3529@sina.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (WJCC, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJCC as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Si Zhao; Production Department Director: Xu Guo; Editorial Office Director: Jin-Lei Wang.

NAME OF JOURNAL

World Journal of Clinical Cases

ISSN

ISSN 2307-8960 (online)

LAUNCH DATE

April 16, 2013

FREQUENCY

Thrice Monthly

EDITORS-IN-CHIEF

Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2307-8960/editorialboard.htm>

PUBLICATION DATE

December 6, 2023

COPYRIGHT

© 2023 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 ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

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>



Research progress on the relationship between Paneth cells-susceptibility genes, intestinal microecology and inflammatory bowel disease

Qi-Ming Zhou, Lie Zheng

Specialty type: Infectious diseases

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D, D
Grade E (Poor): 0

P-Reviewer: Maslennikov R, Russia; Nikolić M, Croatia

Received: July 27, 2023

Peer-review started: July 27, 2023

First decision: September 5, 2023

Revised: September 26, 2023

Accepted: November 27, 2023

Article in press: November 27, 2023

Published online: December 6, 2023



Qi-Ming Zhou, Department of Nephrology, Lanxi Hospital of Traditional Chinese Medicine, Lanxi 321100, Zhejiang Province, China

Lie Zheng, Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, Xi'an 710003, Shaanxi Province, China

Corresponding author: Lie Zheng, PhD, Researcher, Department of Gastroenterology, Shaanxi Hospital of Traditional Chinese Medicine, No. 2 Xihuamen, Lianhu District, Xi'an 710003, Shaanxi Province, China. liezhenglielie@126.com

Abstract

Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

Key Words: Susceptibility gene; Paneth cells; Intestinal microecology; Inflammatory bowel disease

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

Citation: Zhou QM, Zheng L. Research progress on the relationship between Paneth cells-susceptibility genes, intestinal microecology and inflammatory bowel disease. *World J Clin Cases* 2023; 11(34): 8111-8125

URL: <https://www.wjgnet.com/2307-8960/full/v11/i34/8111.htm>

DOI: <https://dx.doi.org/10.12998/wjcc.v11.i34.8111>

INTRODUCTION

Inflammatory bowel disease (IBD) is a disorder of the immune system and intestinal microecosystem caused by environmental factors in genetically susceptible people. Paneth cells (PCs) play a central role in IBD pathogenesis, especially in Crohn's disease (CD) development, and their morphology, number and function are regulated by susceptibility genes. In the intestine, PCs participate in the formation of the stem cell microenvironment by secreting antibacterial particles and play a role in helping maintain the intestinal microecology and intestinal mucosal homeostasis. Moreover, PC proliferation and maturation depend on symbiotic flora in the intestine. This paper describes the interactions among susceptibility genes, PCs and intestinal microecology and their effects on IBD occurrence and development.

IBD is a group of chronic, nonspecific inflammatory diseases that include CD and ulcerative colitis (UC). PCs, derived from intestinal pluripotent stem cells, are gradually growing columnar epithelial cells located at the junction of villi and crypts[1]. During differentiation and maturation, PCs migrate to the base of crypts and spread throughout the small intestine. PCs are pyramidal, and the cytoplasm at the "top" of the pyramid is full of coarse and large eosinophilic secretory granules. The main components are α -defensin, lysozyme, phospholipase A2 and other antibacterial substances that can be released into the intestinal cavity and play an important role in the natural defense of the small intestinal mucosa[2]. Due to the high secretion capacity of PCs and their close relationship with intestinal microecology, PC abnormalities and flora disorders often occur in the intestinal inflammatory response[3]. In recent years, PCs have been found throughout the gastrointestinal tract, including the stomach and colon. However, the distribution of PCs throughout the gastrointestinal tract occurs mainly as a response to mucosal inflammation, and PC presence in abnormal areas is called metaplasia. Colorectal PCs are widely found in UC and inflammatory enteritis[4].

In the past 20 years, the results of whole-genome scanning have revealed that IBD susceptibility genes are distributed on chromosomes 1, 3, 4, 5, 6, 7, 10, 12, 14, 16, 19 and X, among which 9 susceptibility genes associated with IBD were named IBD1-9: IBD1 on chromosome 16q, IBD2 on 12p13.2-q24.1, IBD3 on 6p, IBD4 on 14q11-q12, IBD5 on 5q31, IBD6 on 19p13, IBD7 on 1p36, IBD8 on 16p and IBD9 on 3p26[5]. Studies have shown that more than 200 gene loci are associated with IBD susceptibility, including more than 150 that increase the risk of CD[6]. Studies have shown that IBD susceptibility genes can affect the important physiological processes of PC, leading to abnormal PCs and promoting the occurrence and development of intestinal mucosal inflammation[7].

Changes in the intestinal microecology are involved in IBD pathogenesis, which mainly manifests as a flora imbalance, including flora diversity, species and abundance changes. Studies have shown that the abundance of Firmicutes and Bacteroidetes, which dominate the intestinal flora of IBD patients, decreases, while the proportion of Proteobacteria and actinomycetes increases[8]. Therefore, based on the above knowledge, this paper reviews the relationship among PCs, susceptibility genes, intestinal microecology and IBD.

THE ORIGIN AND METAPLASIA OF PCS

In 1745, German anatomist Johann Nathanael Lieberkuhn first described intestinal glands, or crypts, present in the intestines. In 1872, Gustav Schwalbe observed PCs in the crypt of the small intestine. In 1888, the Austrian physician Joseph Paneth described PCs graphically as a group of specialized cylindrical cells in the crypts of the small intestine epithelium, whose cytoplasm is filled with granular matter. The cells have been named PCs in honor of Dr. Paneth. PCs are rare cells in the small intestine that provide the host with protection against microbial invasion. Their function is the secretion of antibacterial proteins.

When bacteria or bacterial antigens invade the body, PCs secrete antibacterial molecules such as defensins between the villi of the bowel to help maintain the gastrointestinal barrier[9]. PCs are characteristic cells of the small intestinal gland, located at the bottom of the gland, the cells are pyramidal, and the top cytoplasm is full of coarse and large eosinophilic secretory particles. Under the electron microscope, the cytoplasm contains a large number of rough endoplasmic reticulum and developed Golgi complexes, and the secretory particles contain defensin and lysozyme, which can kill intestinal microorganisms. Most of the substances secreted by PCs are antibacterial proteins, which are expelled from the

recess of the small intestine and dispersed into the mucosal layer to assist the mucosal immune barrier in its function. Later, PCs were found in the gastrointestinal tract, including the stomach, small intestine and colon[10]. However, PCs in the gastrointestinal tract are mainly found in response to mucous membrane inflammation, which is called metaplasia in abnormal colorectal regions. Paneth cell metaplasia is widespread in inflammatory enteritis.

PHYSIOLOGICAL FUNCTION OF PCS

Providing a niche for small intestinal stem cells in intestinal crypts

In adult mammalian tissues, the small intestine epithelium has a remarkable capacity for self-renewal. The renewal of the small intestinal epithelium depends on stem cells in the small intestinal crypt. Progenitor cells differentiated from small intestinal stem cells migrate from the bottom of the crypt to the small intestinal villi and continue to differentiate into goblet cells, plexus cells, neuroendocrine cells, intestinal epithelial cells and other cells[11]. After differentiation, these cells migrate from the crypt to the apex of the villi, where they gradually die and are replaced by new cells that migrate from the lower end. Intestinal epithelial cells have a life cycle of only four to five days, and this rapid self-renewal is thought to be essential for intestinal integrity. PCs are also derived from small intestine stem cells, but unlike other cells, PCs do not migrate upward after they are produced[12]. They always reside in the crypt, and the lifespan of this group of cells is more than 1 mo.

Intestinal stem cells are located at the base of the crypt, and recent research suggests that there may be two types of stem cells present. One type is crypt base columnar cells (CBC cells), which are spaced apart from PCs at the base of the crypt[13]. The target gene of Wnt, *Lgr5*, is the most representative marker of CBC cells and is expressed on the surface of CBC cells. The other type is static +4 cells, which are located above PCs, and the main markers include *Bmi-1*, *Hopx*, *mTert* and *Lrig1*. Little is known about +4 cells, but studies have shown that there is a close relationship between CBC cells and PCs[14].

The close spatial relationship between PCs and CBC cells has prompted speculation that PCs provide an important niche for stem cells[15]. However, one laboratory refuted this hypothesis. They created a transgenic mouse model in which PCs specifically expressed diphtheria toxin, causing most PCs to be knocked out, but this did not affect the proliferation of CBC cells in the crypt[16]. Later, with the identification of the *Lgr5* marker and the establishment of a crypt system *in vitro*, the hypothesis that PCs provide a niche for stem cells was re-established. *In vitro*, isolated *Lgr5^{hi}* CBC cells hardly grew into crypt bodies[17]. However, when PCs and stem cells were cultured together, the stem cells could differentiate and develop into crypt bodies. Further studies in *in vivo* mouse models, including the Gordon model mentioned earlier, showed that knocking out PCs resulted in the loss of *Lgr5* stem cells[18]. In terms of gene expression, PCs produce not only germicidal substances but also epidermal growth factor, *Wnt3* and Notch ligand *Dll4* in large quantities, providing necessary conditions for PCs to become a niche[19]. In conclusion, PCs provide the necessary niche signal for *Lgr5^{hi}* CBC stem cells (Figure 1).

Regulation of the intestinal flora

PCs contain a large number of endoplasmic reticulum and Golgi complexes, which have a major role in protein secretion. The main secretions of PCs are protein polypeptides with bactericidal ability, such as the cryptdin-related sequence peptide, lysozyme, IIA secretory phospholipase A2 (secretory group IIA phospholipase A2), regenerated insulin-derived proteins REG3 β and REG3 γ , angiogenin 4, and ANG4[20].

Antimicrobial peptides are important effectors in the innate immune response against pathogenic microbial infection. α -Defensins are one of the earliest recognized antimicrobial peptide families. They are the main components of secretory granules in phagocytes[21]. In addition to phagocytes, epithelial cells in various mucous membranes also secrete α -defensin. Mouse PCs secrete several subtypes of defensins, which can be divided into 6 subtypes from 1 to 6 by purification analysis *in vitro*. Immunohistochemical analysis showed that α -defensin was specifically expressed in PCs and was secreted into the intestinal cavity in a polar manner[22]. These α -defensins, which are secreted extracellularly, are thought to have important host defense functions.

Defensins are a class of small (15-20 residues) cationic proteins rich in cysteine. They are amphoteric molecules that can bind to bacterial cell membranes and form transmembrane ion channels, destroying the integrity of the membranes and causing cell contents to leak, thus killing bacteria[23]. At the same time, defensins can inactivate a variety of bacterial toxins by combining with them in order to denature them. However, how intestinal symbiotic bacteria coexist with the abundant bactericidal defensins in the gut has always been a perplexing problem. Recent studies have shown that intestinal symbiotic bacteria usually express dephosphatase (LpxF) to remove negative charges on the surface of bacteria to resist killing by cationic antibacterial peptides such as defensins[24].

Studies have shown that α -defensin secreted by PCs plays an important role in the response to pathogen infection. Gram-positive bacteria, gram-negative bacteria, lipopolysaccharide, muramic acid, muramyl dipeptides, and lipid A all stimulate defensin secretion by PCs in the small intestine[25]. Live fungi and protozoa do not stimulate PC degranulation. When PCs in the mouse small intestine encounter pathogens or pathogen antigens, they secrete granules rich in antimicrobial peptides within a few minutes to kill pathogenic microorganisms[26]. This secretion activity is dose-dependent for the pathogens or pathogen antigens. α -Defensins account for 70% of the total antimicrobial peptide killing activity[27].

It has been found that α -defensin derived from PCs plays an important role in establishing and maintaining the balance of intestinal microecology[28]. Mouse α -defensin is synthesized as a nonactivated precursor peptide and must be cleaved by matrix metalloproteinase 7 (MMP7) to be activated[29]. Two animal models, DEFA5 transgenic mice and MMP7-deficient mice, have been studied. DEFA5 transgenic mice express α -defensin 5 (also known as HD-5), which is an α -

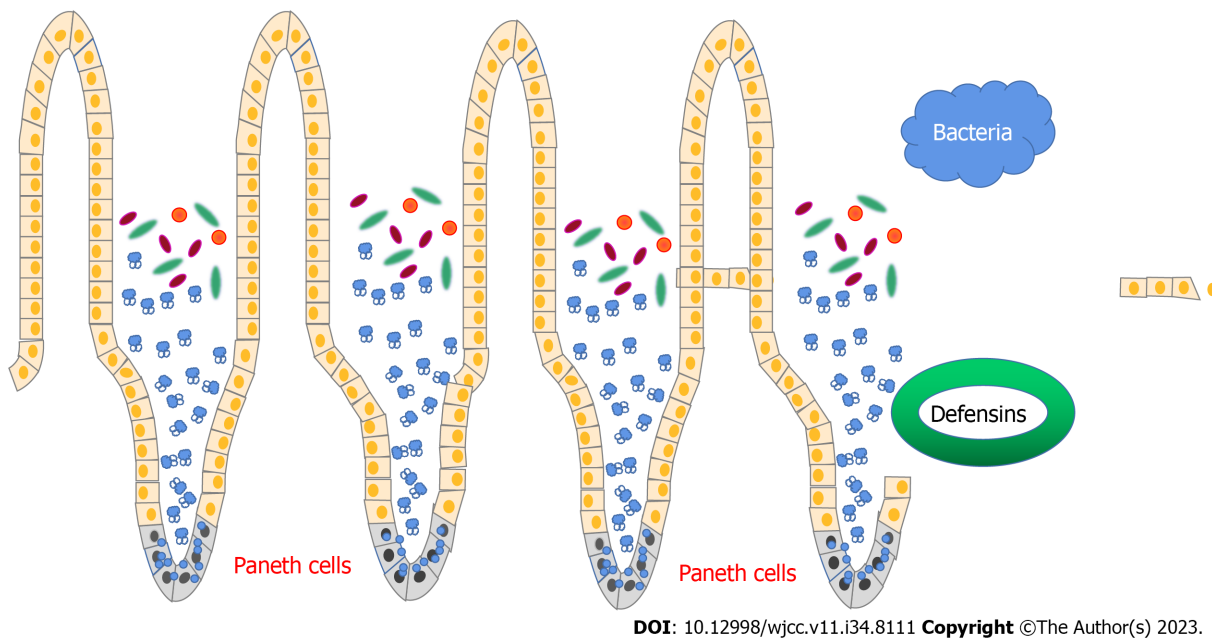


Figure 1 Physiological function of Paneth cells.

defensin overexpression model[30]. MMP7-deficient mice do not produce active α -defensin and are a model of α -defensin deficiency in the small intestine. In both mouse models, the mRNA expression levels of PC effector factors, such as lysozyme, Defa1 and Defcr4 encoding α -defcr4, and the total number of intestinal bacteria did not change significantly, but the composition of intestinal bacteria did[31]. The proportion of Firmicutes in DEFA5 transgenic mice was significantly reduced, while the proportion of Bacteroides was significantly increased, but the opposite result was obtained in MMP7-deficient mice[32]. This suggests that changes in intestinal bacterial composition are dependent on α -defensin but α -defensin does not affect the total number of intestinal bacteria[33]. Moreover, segmented filamentous bacteria, important members of Firmicutes, were barely detected in DEFA5 transgenic mice, and the proportion and number of Th17 cells in the lamina propria were also affected. These results indicate that α -defensins derived from PCs affect the intestinal symbiotic bacterial composition and intestinal homeostasis[34].

PCs not only secrete antimicrobial peptides stored in vesicles under microbial stimulation but also regulate the production of some antimicrobial peptides upon sensing microorganisms[35]. It has been found that the presence of enterobacteria can greatly enhance REG3 γ expression in PCs, the upregulation of REG3 γ expression depends on the MyD88 signaling pathway of the downstream adaptor molecule of the Toll-like receptor (TLR), and the REG3 γ expression is necessary to prevent microbial invasion into the host tissue. Using a model with MyD88 overexpression in PCs, researchers found that PCs directly sense microorganisms through the TLR-MyD88 pathway and activate the expression of MYD88-dependent antimicrobial peptides, such as Reg3 γ [36]. These results demonstrated that MyD88 signaling pathway activation in PCs is sufficient to prevent microbial invasion of the host and does not require MyD88 signaling from other sources, such as bone marrow cells[37]. This study further employed a mouse model with a defensin promoter regulating the expression of diphtheria toxin (CR2-tox176) to deplete PCs and showed that mice with PC depletion did not effectively control intestinal symbiotic and pathogenic bacterial invasion into the spleen and mucosa-associated lymph nodes. Thus, the antibacterial substances derived from PCs are very important for controlling the invasion and diffusion of microorganisms *in vivo*[38].

SUSCEPTIBILITY GENES

The major susceptibility gene on chromosome 16

Nucleotide-binding oligomeric domain protein 2 (NOD2)/CARD15, the first discovered C and D susceptibility gene, is located around the centromeres of chromosome 16 (16q12) and is mainly expressed in macrophages and PCs specific to the small intestinal gland. It encodes 2 CARD domains and 6 LRR (1 eukaryotic repeat) proteins. CARD15 protein activates NF- κ B by recognizing the muramyl dipeptide (MDP) of foreign bacteria and plays a role in the immune response to bacterial LPS[39]. In addition, CARD15 can induce the expression of human β -defensin-2 (HBD-2) in epithelial cells when encountering invading microorganisms, which constitutes the first line of rapid defense of epithelial cells against foreign microorganisms[40]. Therefore, mutation of the CARD15 gene and subsequent alteration of the structure of the encoded protein is a risk factor for CD[41]. Most studies suggest that NOD2/CARD15 is closely related to genetic susceptibility to CD but not to UC. However, the presence of *TL4* or *CD14* gene mutations in conjunction with NOD2/CARD15 mutations increases UC susceptibility. The genes in IBD1 near D16s408 are also associated with the incidence of UC. For example, single allelic mutations increase the incidence of UC, while double allelic mutations can

lead to severe CD[42]. Therefore, although not as significantly as with C and D, the *NOD2* gene is also associated with UC.

The major susceptibility gene on chromosome 12

The human leucine-rich repetitive kinase 2 (LRRK2) gene consists of 51 exons located on chromosome 12q12 and encodes the LRRK2 protein, a multidomain protein composed of 2527 amino acids. LRRK2 is a multidomain protein kinase with a wide range of functions, including vesicle transport and entosis, protein synthesis, immune response regulation, and inflammation[43]. The LRRK2 protein consists of an ARM repeat, ankyrin repeat (ANK), leucine-rich repeat region (LRR), Ras protein complex (ROC), Ras protein C-terminal repeat (COR), kinase domain (MAPKKK) and tryptophan aspartic acid repeat region (WD40)[44]. Three scaffold domains, ANK, LRR and WD40, are involved in interactions with other proteins that can maintain the conformation and stability of those proteins. The ROC domain and MAPKKK domain are related to the GTPase activity and kinase activity of LRRK2, respectively, while the functions of the ARM repeat sequence and COR domain are not clear. Y1699C and R1628P mutations in the ROC domain have been found to be associated with Parkinson disease (PD) and leprosy, respectively[45]. Pathological and physiological studies of LRRK2 have indicated that the LRRK2 domain is significantly related to its various cellular functions, suggesting that LRRK2 is a pivotal protein with a wide range of functions. Gain-of-function mutations in the LRRK2 kinase domain lead to increased LRRK2 kinase activity and play an important role in disease pathogenesis[46].

TL1A gene

Most members of the tumor necrosis factor (TNF)/tumor necrosis factor receptor superfamily proteins (TNFR SFP) are expressed in immune cells and play a key role in the immune response[47]. Tumor necrosis factor ligand 1A (TL1A), a member of the TNFSF family, is the encoding product of the *TNFSF 15* gene, and its expression is increased in the intestinal inflammatory region of patients with IBD[48]. TL1A protein has been found to be expressed in mononuclear macrophages and CD4+/CD8+ lymphocytes in the intestinal lamina propria in patients with CD, and the expression level and the number of positive cells were positively correlated with the severity of intestinal lesions[49]. Furthermore, the number of DR3-positive T lymphocytes increased in the intestinal lamina propria of CD patients. The uniform upregulation of TL1A and DR3 expression indicates that downstream cytokines after TL1A and DR3 binding play an important role in CD[50]. In addition, TL1A helps balance promotion and inhibition of the inflammatory response in the intestinal mucosa in CD. At the initial stage of inflammation, when T cells are recruited to the inflammatory site of intestinal mucosa, TL1A interacts with DR3 to enhance inflammatory cytokine secretion, and these cytokines cause the recruitment and activation of macrophages and neutrophils, stimulating further inflammation[51].

ATG16L1 gene

The *Atg16L1* gene, which is involved in autophagy, is related to CD development and plays an important role in PCs, suggesting the importance of autophagy to the normal physiological function of PCs. CD patients with *Atg16L1* mutations have an altered gut microbiota and abnormal PC granules[52]. A similar phenomenon was observed in mice with low expression of *Atg16L1* protein. Notably, Zhang *et al*[53] found that autophagy of PCs was specifically activated in some CD patients, and this state was not related to mucosal inflammation and *Atg16L1* mutation. This result suggested that in addition to *Atg16L1*, more autophagy-related genes might be involved in the pathological mechanism of CD[54]. Moreover, we do not currently know which genes are involved. Additionally, autophagy and endoplasmic reticulum stress have compensatory effects in PCs. When *Atg16L1* and *Xbp1* were knocked out simultaneously in the intestinal epithelium, mice developed more severe idiopathic enteritis than when either gene was knocked out alone[55].

PHYSIOLOGICAL FUNCTION OF INTESTINAL MICROECOLOGY

Changes in intestinal microecology are involved in IBD pathogenesis and development. Intestinal microecology includes intestinal microbes, intestinal epithelial cells and immune cells, among which intestinal microbes play the most important role in intestinal microecology[56]. Intestinal microorganisms are distributed on the surface of the intestinal cavity and are mainly composed of bacteria, viruses, fungi and parasites, among which the number of bacteria is approximately 10^{14} , approximately 10 times the number of human cells[57]. The total weight of intestinal bacteria is approximately 0.2 kg, accounting for 60% of the dry weight of stool. There are more than 50 bacterial groups and approximately 1100 species, most of which are Bacteroides and Firmicutes (90%), while a small portion are Actinobacteria and Proteus[58]. Many factors have been found to influence the composition of gut microbes. At birth, the environment can directly affect the intestinal microflora, including the birth canal, early diet, antibiotic use, pet contact, sex, and the mother's health, all of which are related to the intestinal microflora composition of infants in the early period[59]. The intestinal microbial diversity of infants under 1 year of age increases rapidly and tends to stabilize at 3 years of age, the intestinal microbial composition becomes more stable at 5 years of age, and Bacteroides dominates. Adult exposure to various environmental factors (such as smoking, air pollution, hygiene habits, stress, diet, drugs, *etc.*) can change the intestinal microbial composition[60].

Evidence suggests that the intestinal barrier plays an important role in intestinal microbial maintenance. The intestinal barrier is composed of intestinal symbiotic bacteria, the intestinal mucous layer, the intestinal epithelium and various lymphocytes in the lamina propria[61]. The intestinal mucus layer covers the intestinal epithelium, and its components are secreted by intestinal epithelial cells; this layer act as a physical barrier between the flora and the intestinal epithelium and provides nutrients and a living environment for the intestinal flora[62]. The mucus layer is rich in mucus secreted by

goblet cells, a variety of antibacterial substances secreted by PCs and ordinary epithelial cells, and IgA secreted by B cells, which are difficult obstacles for intestinal bacteria to cross, effectively preventing contact with and invasion of intestinal epithelium by intestinal bacteria and preventing inflammation[63]. Intestinal epithelial cells include goblet cells, PCs, M cells, neuroendocrine cells and absorptive intestinal epithelial cells, and intestinal epithelial cells are mainly connected by tight junctions, which can prevent the invasion of bacteria and their derivatives[64]. Moreover, there are a variety of gut-associated lymphoid tissues in the intestinal epithelium and lamina propria, such as Peyer's patches in the small intestine and lymphatic follicles and colonic patches in the large intestine[65]. Many immune cells, such as dendritic cells, T lymphocytes and B lymphocytes, exist in these enteric-associated lymphoid tissues. These lymphocytes cooperate with each other to promote immune tolerance and participate in host defense. Among them, M cells and dendritic cells directly sense intestinal contents and transmit information about the intestinal flora to other immune cells, inducing an immune response or tolerance[66].

INTERACTION OF PCS WITH INTESTINAL MICROECOLOGY

PCs regulate intestinal microecology and intestinal epithelial regeneration and differentiation

Normally, PC secretions are slowly released, and degranulation can be caused by feeding, microbial stimulation, and M receptor agonists[67]. There are many bacteria or foreign bacteria in the lumen. PCs can directly detect bacteria and express large quantities of particulate matter containing antibacterial factors through TLRs, which induces degranulation to increase the concentration of antibacterial factors in the intestinal cavity, inhibit the invasion of exogenous microorganisms, and control the microbial population in the small intestine[68]. This is an important reason why the microbial colonization density in the small intestine is lower than that in the large intestine. Therefore, PCs play important roles in controlling the passage of symbiotic bacteria and pathogenic bacteria through the intestinal barrier and in maintaining host and microbiological stability on the mucosal surface[69].

PCs and crypt basal columnar stem cells together constitute the stem cell microenvironment. The epithelial growth factors Wnt3 and Notch act on intestinal stem cells, which can promote self-renewal of intestinal stem cells and immune differentiation of different intestinal cell lines[70]. Therefore, PCs can regulate intestinal microecology and maintain intestinal mucosal homeostasis through mucosal defense and regulation of intestinal epithelial differentiation[71].

The distribution and maturation of PCs depend on intestinal microecology

Studies have shown that the distribution of intestinal bacteria in ordinary wild mice, laboratory mice and specific pathogen-free mice decreased successively, and the distribution of PCs in the same part of the small intestine of mice among these three populations also decreased successively, suggesting that the reduction in the number of bacteria in a certain part of the small intestine could lead to a decrease in the number of PCs in that part of the small intestine[72]. After consumption of amoxicillin for 3 d, the number of PCs in each segment of the small intestine decreased significantly, which may be because amoxicillin, as a broad-spectrum antibacterial, can kill a large number of gram-positive and gram-negative bacilli in the intestine, resulting in a decrease in the total number of bacteria in each segment of the small intestine and then the number of PCs in each segment of the small intestine[73]. However, after 1 d of amoxicillin consumption, the number of PCs in the jejunum and ileum increased significantly, which may be related to the sudden disturbance of intestinal microecology leading to a temporary increase in the number of PCs in a certain period of time, which improves the body's defense function[74].

In normal mice at 4 to 6 wk of age, there is a certain degree of particle abnormality in PCs, but with increasing age, the number of normal PCs gradually increases, while the number of abnormal PCs gradually decreases[75]. However, there is no obvious PC proliferation and maturation with age in germ-free mice. Compared with that in conditions without specific pathogens, the average number of PCs per crypt is lower under completely sterile conditions, and the proportion of the normal form of PCs was almost zero in young and old mice[76]. This finding suggests that the number, morphology, and maturation of normal PCs are dependent on the intestinal flora[77].

Changes in intestinal microecology have an obvious effect on the number of PCs in the small intestine of mice[78]. After *Escherichia coli* (*E. coli*) infection, the number of PCs in each segment of the small intestine of mice is significantly reduced, which may be related to intestinal damage caused by *E. coli* infection[79]. Studies have shown that the intestinal villi of mice infected with *E. coli* have varying degrees of damage, and the longer the infection extends, the more serious the intestinal villus damage, especially duodenum damage, which is the most serious, with thinning of some parts of the intestinal wall and intestinal inflammatory cell infiltration[80]. In addition, the decrease in the number of PCs after *E. coli* infection may be related to the large number of released particles participating in the intestinal inflammatory response [81]. A significant decrease in the number of PCs will lead to a decrease in the barrier defense function of the intestinal tract, resulting in further damage to the small intestine of mice by opportunistic pathogens or infecting *E. coli*[82]. Therefore, with the extension of infection time, the number of PCs is significantly reduced. Thus, the number of PCs is closely related to the intestinal microecological balance.

PANETH CELL ABNORMALITIES AND MICROECOLOGICAL DISORDERS IN IBD

PC abnormalities in IBD patients and mouse models

PCs are an important component of the intestinal epithelial barrier, so it is not surprising that functional abnormalities of

PCs play a role in CD development[83]. The first pathological analysis of small intestine samples from CD patients revealed the presence of intracellular vesicle abnormalities in PCs in these patients[84]. A better understanding of the role of PCs in CD development resulted from the discovery of CD susceptibility genes. A study showed that a CD susceptibility gene was highly expressed in PCs, which supported PCs as the origin of the disease[85]. Recently, it has been found that many CD susceptibility genes are involved in the important physiological activities of PCs, and research on the pathways regulated by these genes has revealed the significance of these pathways in regulating the physiological activities of PCs[86].

The abnormalities of PCs in IBD are mainly reflected in the abnormal quantity, morphology and function of PCs and their secretory granules[87]. Upon morphological examination of PCs from CD patients, abnormal PCs were found in 20%-50% of patients. Changes in susceptibility genes or risk-associated polymorphic sites can also cause PC abnormalities, and the more susceptibility genes CD patients carry, the higher the proportion of abnormal PCs[88]. For example, mutations in the CD susceptibility genes *Atg16 L1* and *Xbp1* resulted in abnormal particle morphology and a reduced number of PC particles in genetically deficient mice and in CD patients. Abnormal particle morphology and antimicrobial protein packaging in PCs were also observed in engineered CD-associated autophagy protein-deficient mice[89].

Microecological dysregulation in IBD patients and mouse models

Many studies have shown that microecological disorders exist in the intestinal tract of both IBD patients and mouse models[90]. Obvious PC defects can be seen in children with CD, and abnormal PCs can cause an increased abundance of inflammatory bacteria (*Corynebacterium*, *Erysipelotrichaceae*, etc.) and reduced abundance of barrier bacteria (*Faecalibacterium*, *Blautia*, etc.). *Prevotella* was found to be significantly enriched in IBD patients with susceptibility genes, which may lead to a loss of intestinal barrier function and in turn to increased epithelial cell penetration and chronic inflammation [91].

PC ABNORMALITIES MEDIATED BY SUSCEPTIBILITY GENES AND MICROECOLOGICAL DISORDERS PROMOTE THE DEVELOPMENT OF INTESTINAL INFLAMMATION

Effects of the *NOD2* gene on PCs and intestinal inflammation

Nod2 is the most significant CD susceptibility gene. In macrophages, *NOD2* recognizes bacterial-derived muramyl dipeptides and activates the immune response[92]. Three major *Nod2* mutants (*R702W*, *G908R* and *L1007insC*) have been found to be associated with the development of CD, resulting in the inability of *NOD2* to effectively activate the downstream immune response[93]. In *NOD2*-deficient mice, α -defensin expression in PCs is decreased, terminal ileal symbiosis was increased, and pathogenic bacteria were enriched. In particular, granulomatous inflammation characterized by increased expression of Th1-related genes and inflammatory cytokines was observed in the ileum of *NOD2*-deficient mice inoculated with *Helicobacter hepatis*[94]. However, the overexpression of α -defensin in mouse PCs *via* transgenic technology resulted in decreased Th1 inflammation. Therefore, *NOD2* can effectively inhibit the development of Th1-induced ileal granulomatous inflammation in mice. It is currently believed that lysozyme sorting in PCs is carried out through a *NOD2-LRRK2-RIP2-Rab2A* pathway dependent on intestinal symbiotic bacterial stimulation[95]. The absence of any one of *NOD2*, *LRRK2*, *RIP2*, *Rab2A* or symbiotic bacteria will cause lysozyme in PCs to be degraded by lysosomes, resulting in the breakdown of the balance between the organism and symbiotic bacteria, thus promoting the occurrence of CD[96].

However, the specific role of *Nod2* mutations in the development of inflammatory enteritis is still under investigation. Because all three *Nod2* mutations reduce the ability of *Nod2* to activate the immune response, *Nod2*^{-/-} mice are widely used to study the role of *NOD2* in inflammatory enteritis[97]. *Nod2* is mainly expressed in PCs and bone marrow-derived lymphocytes in the small intestine. The downregulation of α -defensin expression in *Nod2*^{-/-} mouse PCs was reported to result in a decreased immune response to listeria[98]. It has been found that α -defensin expression in PCs is significantly reduced in patients with ileum CD compared with that in healthy individuals or patients with other types of IBD[99]. The decrease in α -defensin levels in PCs is not affected by intestinal inflammation, suggesting that the decrease in α -defensin levels is not caused by inflammation but is probably an inherent phenomenon that occurs early[100]. There was also a decrease in α -defensin levels in CD patients with 1007fs (*SNP13*) *NOD2* mutations. However, some studies have not been able to identify defects in α -defensin production in *Nod2*^{-/-} mice, which may be related to the genetic background of the mice[101]. Additional studies have shown that *Nod2* functions by regulating the intestinal flora, as *Nod2*^{-/-} mice have an altered intestinal flora, and *Nod2*^{-/-} mice have granulomatous lesions in the ileum after infection with *Helicobacter pylori*, consistent with the pathological state of CD[102]. This granulomatous damage is relieved when PCs of *Nod2*^{-/-} mice are transferred to α -defensin HD5 gene knockout mice.

Effects of *LRRK2* gene deficiency on PCs and intestinal inflammation

TLRs in PCs can activate and promote the formation and secretion of antibacterial particles such as lysozyme after directly sensing intestinal bacteria and their metabolites. *NOD2* secreted by PCs senses the presence of symbiotic bacteria by detecting the cell wall acyl dipeptides of symbiotic bacteria, and symbiotic microbiota-derived signals trigger *NOD2* binding to receptor interaction protein 2 (*RIP2*)[103]. *LRRK2* and *Rab2a* are recruited into dense core vesicles (DCVs) containing lysozyme to regulate the sorting of lysozyme in DCVs[104]. In this process, on the one hand, *LRRK2* can affect the composition of intestinal microorganisms by regulating lysozyme sorting. On the other hand, symbiotic flora constituents can not only guide lysozyme sorting in PCs but also promote symbiosis between the symbiotic flora and host

through the NOD2-LRRK2-Rab2a axis[105].

Cellular life activities depend on the precise transfer and directional transport and secretion of intracellular substance transport systems. If the regulation of the vesicle transport system is abnormal, the normal life activities of cells will be affected[106]. Abnormal PC vesicle transport, characterized by a reduced number of DCVs containing lysozyme, occurs in CD patients[107]. A similar phenomenon was also observed in LRRK2^{-/-} mice. Although the expression level of lysozyme mRNA in the PCs of LRRK2^{-/-} mice was normal, lysozyme deficiency was also found in the intestinal cavity because lysozyme was degraded by intracellular lysosomes[108]. However, other antibacterial substances, such as defensin and islet RegIIIγ, in PCs were not affected by LRRK2 knockout, suggesting that LRRK2 can specifically regulate lysozyme transport and secretion in PCs[109].

CD patients often exhibit significant dysregulation of innate immunity in the intestine. In CD pathogenesis, cytokines such as interferon-γ (IFN-γ), IFN-β, TNF-α and IL-6 can induce and upregulate LRRK2 expression[109]. Additional studies have shown that LRRK2 is involved in inflammatory cytokine production and macrophage chemotaxis in the innate immune response. LRRK2 mutation may regulate the innate immune response in CD14⁺ monocytes[110]. Therefore, abnormal LRRK2 expression may aggravate the innate immune disorder and further damage the tissue.

The NOD(1/2)/RIP2 signaling pathway is an important signaling pathway for the innate immune response to bacterial infection and endoplasmic reticulum stress[111]. LRRK2 enhances the activity of RIP2 by promoting the phosphorylation of RIP2 at Ser176, thus enhancing NOD(1/2)/RIP2 signaling and promoting the production of inflammatory cytokines [112]. Because LRRK2 overexpression activates NF-κB and promotes inflammatory cytokine secretion in lamina propria dendritic cells in mice, an LRRK2 overexpression group exhibited more severe colitis symptoms in DSS-induced colitis mice than a control group (wild-type mice)[113]. LRRK2 inhibitors can reduce LP-induced TNF receptor-related factor 6 (TRAF6) interaction with LRRK2 and inhibit MAPK and NF-κB suppressor protein α (Ik Bα) phosphorylation by inhibiting LLP-induced kinase activity of the LRRK2 protein[114]. Thus, the production of the inflammatory cytokine TNF-α in the dendritic cells of CD patients is reduced, which exerts an anti-inflammatory activity and ameliorates the symptoms of DSS-induced colitis[115]. In addition, a similar phenomenon has been found in macrophages, where LRRK2 defects significantly inhibit the secretion of inflammatory cytokines by macrophages when NOD2 is activated by muramyl dipeptide and NOD1 is activated by γ-D-glutamine-racemo-disaminophenic acid (I-e-DAP) or endoplasmic reticulum stress. In conclusion, LRRK2 can positively regulate the secretion of inflammatory cytokines[116].

However, other studies have shown that LRRK2 has the opposite regulatory effect. Activated T nuclear factor (NFAT) is an important mediator in the immune response, while LRRK2 is a major component of the NRON complex, an inhibitor of NFAT[117]. Normally, LRRK2 can trap NFAT by forming NRON complexes in the cytoplasm, thus sequestering NFAT in the cytoplasm[118]. However, in LRRK2^{-/-} mice, LRRK2 deficiency leads to the failure of NFAT sequestration in the cytoplasm, thus causing NFAT translocation to the nucleus and inducing the transcription of inflammatory cytokines, increasing the level of inflammatory cytokines, increasing susceptibility to DSS-induced colitis and aggravating colitis symptoms[119]. This finding suggests that LRRK2 may also negatively regulate the secretion of inflammatory mediators and cytokines by sequestering NFAT in the cytoplasm.

When LRRK2 is defective or mutated, NFAT regulation is altered, which activates the expression of inflammatory genes in macrophages, exacerbating intestinal inflammation in colitis mouse models and leading to the development of CD[120]. It has also been found that the lysozyme mRNA expression level in the PCs of LRRK2^{-/-} mice was normal, but lysozyme is readily degraded by intracellular lysosomes, while other antibacterial substances in PCs are not affected by LRRK2 deletion, suggesting that LRRK2 regulates lysozyme transport and secretion in PCs[121].

Effects of XBP1 gene deficiency on PCs and intestinal inflammation

Another remarkable genetic factor of the CD unfolded protein response (UPR) is the transcription factor X-box binding protein-1 (XBP-1), which is a key transcription factor in the endoplasmic reticulum stress response and is involved in UPR regulation, endoplasmic reticulum amplification, and the development of hypersecretory cells (such as PCs)[122]. XBP-1 can regulate the number of PCs by preventing apoptosis and mediating cell renewal. Furthermore, mucosal defense function and susceptibility to IBD are affected[123]. The specific clearance of XBP1 from IECs induces endoplasmic reticulum stress, PC loss, reduced lysozyme and defensin expression, increased IEC death and idiopathic enteritis. Similarly, PC-specific clearance of XBP1 can produce similar symptoms of spontaneous ileitis, suggesting that the PC-specific UPR plays an important role in maintaining ileal mucosal homeostasis in mice[124]. Xbp1 knockout in the mouse epithelium resulted in spontaneous enteritis in mice[125]. Pathological analysis showed that the deletion of Xbp1 resulted in endoplasmic reticulum stress and a lack of lysozyme and α-defensin expression in PCs[125]. Therefore, XBP1 may play a partially compensatory role in inhibiting proinflammatory signals, maintaining mucosal homeostasis and assisting PC function in mice, thus supporting the function of PCs[126].

Effects of TL1A overexpression on PCs and intestinal inflammation

TL1A/DR3 (TL1A functional receptor) signal transduction can not only promote the proliferation of T-effector cell subsets but also promote the production of cytokines and accelerate the progression of inflammatory diseases[127]. Different levels of TL1A expression in mice have different effects on PCs and intestinal inflammation. With increasing age, the number of PCs in wild-type mice gradually increased, lysozyme particles gradually matured, and there was no spontaneous ileitis[128]. Although the number of PCs in TL1A^{-/-} mice was reduced, normal lysozyme particle morphology was maintained, so spontaneous ileitis did not occur in older TL1A^{-/-} mice[129]. However, in the TL1A-overexpressing mouse model, the number of PCs increased significantly, and the granules did not mature with age, accompanied by spontaneous ileitis and long-distance intestinal stenosis[130]. However, an anti-TL1A antibody could block TL1A function, reverse colonic fibrosis, and reduce existing colonic inflammation. Therefore, overexpression of TL1A can aggravate proximal intestinal inflammation and fibrous stenosis and promote disease progression[131].

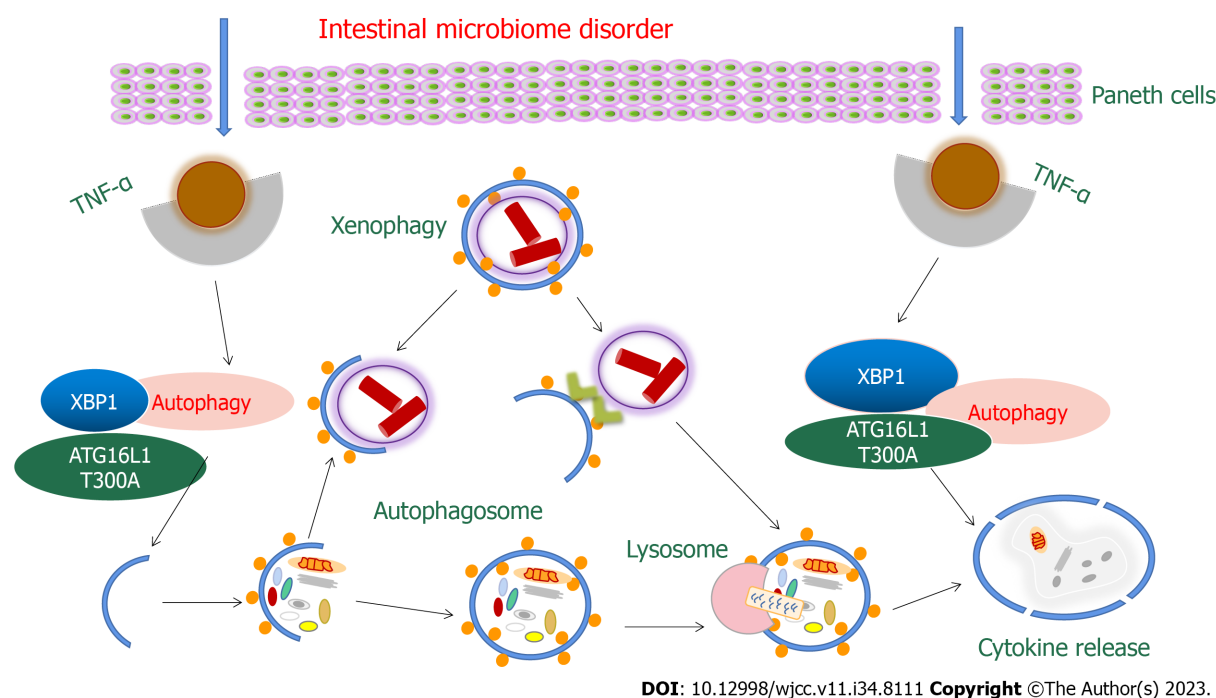


Figure 2 Paneth cells and intestinal inflammation. TNF: Tumor necrosis factor.

Effects of the *ATG16L1* gene on PCs and intestinal inflammation

ATG16L1 is an autophagy-related protein that protects against PC necrosis by participating in autophagosome formation, maintaining autophagy and mitochondrial homeostasis, and preventing PC necrotic apoptosis mediated by $\text{TNF-}\alpha$ [132]. In addition, *ATG16L1* can also play an important role in the pathogenesis of CD by affecting the extracellular secretion of PC particles in patients or activating the transcription factor XBP1 in the endoplasmic reticulum stress response[133]. In IEC-specific *ATG16L1* knockout mice, loss of autophagy resulted in increased IEC sensitivity to TNF-induced cell death. Moreover, since defensins and antimicrobial peptides are mainly secreted by PCs, changes in the abundance distribution of protein components in PCs caused by *ATG16L1* defects may also trigger CD[134].

ATG16L1 T300A is the most important risk-associated polymorphic site of *ATG16L1*. Abnormal particle morphology and antibacterial protein packaging in PCs can be seen in mice injected with *ATG16L1* T300A or in CD patients carrying *ATG16L1* T300A[133]. Lysozyme in PCs is packaged and secreted in secretory autophagy during bacterial infection, and secretory autophagy was inhibited in mice carrying *ATG16L1* T300A in PCs[133]. In addition, *ATG16L1* T300A can also reduce selective autophagy, shorten the remission interval, increase cytokine release and reduce intracellular bacterial clearance, leading to abnormal PCs, early immune infiltration and intestinal ecological disorders[134] (Figure 2).

CONCLUSION

IBD pathogenesis is influenced by genetics, the environment, the intestinal flora and immunity, among which abnormal PCs play a central role. Both susceptibility genes and their risk-associated polymorphic loci can cause the development of abnormal PCs, and the more susceptibility genes a patient carries, the higher the proportion of abnormal PCs. The interaction between abnormal PCs and intestinal microecology is reflected in two aspects. On the one hand, the stability of the intestinal microecology needs to be maintained by the physiological function of PCs, and abnormal PCs can also cause an imbalance in intestinal microecology. On the other hand, the proliferation and maturation of PCs depend on intestinal microecology, and environmental conditions can also aggravate the influence of susceptibility genes on PCs by changing the intestinal microecology. Intestinal microecology and susceptibility genes interact with each other. On the one hand, intestinal microecology can enhance the effect of susceptibility gene expression products and promote the occurrence of IBD. If there is no intestinal flora, abnormal susceptibility genes cannot cause idiopathic enteritis. On the other hand, when IBD-related genes are abnormal, the abundance of specific bacteria in the gut is altered, which can disrupt the intestinal barrier and promote chronic inflammation. In conclusion, susceptibility genes may cause PC abnormalities and intestinal microecological disorders, and the interaction among the three can lead to potential diseases or aggravate existing diseases when they reach a specific functional threshold. In the future, more clinical and disease mechanism studies are needed to identify other genes associated with PC abnormalities and explore the cellular and molecular mechanisms of PC abnormalities caused by susceptibility genes. In addition, exploring ways to restore intestinal homeostasis by regulating the intestinal microecosystem, improving diseases by utilizing the mutual benefit between the host and intestinal flora, and identifying peripheral markers related to CD development and PC activity changes can also provide new methods for the diagnosis, treatment and prognosis of CD.

FOOTNOTES

Author contributions: Zhou QM and Zheng L contributed equally to this work, and both contributed to literature search, drafting of the manuscript, and providing approval of the final version to be published; Zhou QM and Zheng L contributed to the conception and design of the study and performed to the writing of the manuscript.

Conflict-of-interest statement: The authors declare that there are no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (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: <https://creativecommons.org/licenses/by-nc/4.0/>

Country/Territory of origin: China

ORCID number: Qi-Ming Zhou 0009-0007-7149-983x; Lie Zheng 0009-0007-2432-1414.

S-Editor: Yan JP

L-Editor: A

P-Editor: Yan JP

REFERENCES

- 1 Yang E, Shen J. The roles and functions of Paneth cells in Crohn's disease: A critical review. *Cell Prolif* 2021; **54**: e12958 [PMID: 33174662 DOI: 10.1111/cpr.12958]
- 2 Wahida A, Müller M, Hiergeist A, Popper B, Steiger K, Branca C, Tschurtschenthaler M, Engleitner T, Donakonda S, De Coninck J, Öllinger R, Pfautsch MK, Müller N, Silva M, Usluer S, Thiele Orberg E, Böttcher JP, Pfarr N, Anton M, Slotta-Huspenina JB, Nerlich AG, Madl T, Basic M, Bleich A, Berx G, Ruland J, Knolle PA, Rad R, Adolph TE, Vandenabeele P, Kanegane H, Gessner A, Jost PJ, Yabal M. XIAP restrains TNF-driven intestinal inflammation and dysbiosis by promoting innate immune responses of Paneth and dendritic cells. *Sci Immunol* 2021; **6**: eabf7235 [PMID: 34739338 DOI: 10.1126/sciimmunol.abf7235]
- 3 Mei X, Gu M, Li M. Plasticity of Paneth cells and their ability to regulate intestinal stem cells. *Stem Cell Res Ther* 2020; **11**: 349 [PMID: 32787930 DOI: 10.1186/s13287-020-01857-7]
- 4 Hassan M, Juanola O, Keller I, Nanni P, Wolski W, Martínez-López S, Caparrós E, Francés R, Moghadamrad S. Paneth Cells Regulate Lymphangiogenesis under Control of Microbial Signals during Experimental Portal Hypertension. *Biomedicines* 2022; **10** [PMID: 35884808 DOI: 10.3390/biomedicines10071503]
- 5 Guo F, Cai D, Li Y, Gu H, Qu H, Zong Q, Bao W, Chen A, Liu HY. How Early-Life Gut Microbiota Alteration Sets Trajectories for Health and Inflammatory Bowel Disease? *Front Nutr* 2021; **8**: 690073 [PMID: 34422881 DOI: 10.3389/fnut.2021.690073]
- 6 Zhao H, Zhang W, Cheng D, You L, Huang Y, Lu Y. Investigating dysbiosis and microbial treatment strategies in inflammatory bowel disease based on two modified Koch's postulates. *Front Med (Lausanne)* 2022; **9**: 1023896 [PMID: 36438062 DOI: 10.3389/fmed.2022.1023896]
- 7 De Bruyn M, Ceuleers H, Hanning N, Berg M, De Man JG, Hulpiau P, Hermans C, Stenman UH, Koistinen H, Lambeir AM, De Winter BY, De Meester I. Proteolytic Cleavage of Bioactive Peptides and Protease-Activated Receptors in Acute and Post-Colitis. *Int J Mol Sci* 2021; **22** [PMID: 34639054 DOI: 10.3390/ijms221910711]
- 8 Ganna A, Satterstrom FK, Zekavat SM, Das I, Kurki MI, Churchhouse C, Alfoldi J, Martin AR, Havulinna AS, Byrnes A, Thompson WK, Nielsen PR, Karczewski KJ, Saarentaus E, Rivas MA, Gupta N, Pietiläinen O, Emdin CA, Lescai F, Bybjerg-Grauholm J, Flannick J, GoT2D/T2D-GENES Consortium, Mercader JM, Udler M; SIGMA Consortium Helmsley IBD Exome Sequencing Project; FinMetSeq Consortium; iPSYCH-Broad Consortium, Laakso M, Salomaa V, Hultman C, Ripatti S, Hämäläinen E, Moilanen JS, Kärkkö J, Kuusimäki O, Nordentoft M, Hougaard DM, Mors O, Werge T, Mortensen PB, MacArthur D, Daly MJ, Sullivan PF, Locke AE, Palotie A, Børge AD, Kathiresan S, Neale BM. Quantifying the Impact of Rare and Ultra-rare Coding Variation across the Phenotypic Spectrum. *Am J Hum Genet* 2018; **102**: 1204-1211 [PMID: 29861106 DOI: 10.1016/j.ajhg.2018.05.002]
- 9 Fu Q, Song T, Ma X, Cui J. Research progress on the relationship between intestinal microecology and intestinal bowel disease. *Animal Model Exp Med* 2022; **5**: 297-310 [PMID: 35962562 DOI: 10.1002/ame2.12262]
- 10 Sun T, Xue M, Yang J, Pei Z, Zhang N, Qin K, Liang H. Metabolic regulation mechanism of fucoidan via intestinal microecology in diseases. *J Sci Food Agric* 2021; **101**: 4456-4463 [PMID: 33682122 DOI: 10.1002/jsfa.11202]
- 11 Zhu G, Hu J, Xi R. The cellular niche for intestinal stem cells: a team effort. *Cell Regen* 2021; **10**: 1 [PMID: 33385259 DOI: 10.1186/s13619-020-00061-5]
- 12 Won JH, Choi JS, Jun JI. CCN1 interacts with integrins to regulate intestinal stem cell proliferation and differentiation. *Nat Commun* 2022; **13**: 3117 [PMID: 35660741 DOI: 10.1038/s41467-022-30851-1]
- 13 Wallaey C, Garcia-Gonzalez N, Libert C. Paneth cells as the cornerstones of intestinal and organismal health: a primer. *EMBO Mol Med* 2023; **15**: e16427 [PMID: 36573340 DOI: 10.15252/emmm.202216427]
- 14 Verdile N, Mirmahmoudi R, Brevini TAL, Gandolfi F. Evolution of pig intestinal stem cells from birth to weaning. *Animal* 2019; **13**: 2830-2839 [PMID: 31199215 DOI: 10.1017/S1751731119001319]
- 15 Vishy CE, Swietlicki EA, Gazit V, Amara S, Heslop G, Lu J, Levin MS, Rubin DC. Epimorphin regulates the intestinal stem cell niche via effects on the stromal microenvironment. *Am J Physiol Gastrointest Liver Physiol* 2018; **315**: G185-G194 [PMID: 29631377 DOI: 10.1152/ajpgi.00224.2017]
- 16 Naser AN, Lu Q, Chen YH. Three-Dimensional Culture of Murine Colonic Crypts to Study Intestinal Stem Cell Function Ex Vivo. *J Vis Exp* 2022 [PMID: 36314830 DOI: 10.3791/64534]

- 17 **Lanik WE**, Xu L, Luke CJ, Hu EZ, Agrawal P, Liu VS, Kumar R, Bolock AM, Ma C, Good M. Breast Milk Enhances Growth of Enteroids: An Ex Vivo Model of Cell Proliferation. *J Vis Exp* 2018 [PMID: 29553558 DOI: 10.3791/56921]
- 18 **Glal D**, Sudhakar JN, Lu HH, Liu MC, Chiang HY, Liu YC, Cheng CF, Shui JW. ATF3 Sustains IL-22-Induced STAT3 Phosphorylation to Maintain Mucosal Immunity Through Inhibiting Phosphatases. *Front Immunol* 2018; **9**: 2522 [PMID: 30455690 DOI: 10.3389/fimmu.2018.02522]
- 19 **Wehkamp J**, Stange EF. An Update Review on the Paneth Cell as Key to Ileal Crohn's Disease. *Front Immunol* 2020; **11**: 646 [PMID: 32351509 DOI: 10.3389/fimmu.2020.00646]
- 20 **Ma Q**, Li Y, Li P, Wang M, Wang J, Tang Z, Wang T, Luo L, Wang C, Zhao B. Research progress in the relationship between type 2 diabetes mellitus and intestinal flora. *Biomed Pharmacother* 2019; **117**: 109138 [PMID: 31247468 DOI: 10.1016/j.biopha.2019.109138]
- 21 **Yang W**, Yu T, Huang X, Bilotta AJ, Xu L, Lu Y, Sun J, Pan F, Zhou J, Zhang W, Yao S, Maynard CL, Singh N, Dann SM, Liu Z, Cong Y. Intestinal microbiota-derived short-chain fatty acids regulation of immune cell IL-22 production and gut immunity. *Nat Commun* 2020; **11**: 4457 [PMID: 32901017 DOI: 10.1038/s41467-020-18262-6]
- 22 **Liu Z**, Dai X, Zhang H, Shi R, Hui Y, Jin X, Zhang W, Wang L, Wang Q, Wang D, Wang J, Tan X, Ren B, Liu X, Zhao T, Pan J, Yuan T, Chu C, Lan L, Yin F, Cadenas E, Shi L, Zhao S. Gut microbiota mediates intermittent-fasting alleviation of diabetes-induced cognitive impairment. *Nat Commun* 2020; **11**: 855 [PMID: 32071312 DOI: 10.1038/s41467-020-14676-4]
- 23 **Song X**, Sun X, Oh SF, Wu M, Zhang Y, Zheng W, Geva-Zatorsky N, Jupp R, Mathis D, Benoist C, Kasper DL. Microbial bile acid metabolites modulate gut RORγ(+) regulatory T cell homeostasis. *Nature* 2020; **577**: 410-415 [PMID: 31875848 DOI: 10.1038/s41586-019-1865-0]
- 24 **Li G**, Lin J, Zhang C, Gao H, Lu H, Gao X, Zhu R, Li Z, Li M, Liu Z. Microbiota metabolite butyrate constrains neutrophil functions and ameliorates mucosal inflammation in inflammatory bowel disease. *Gut Microbes* 2021; **13**: 1968257 [PMID: 34494943 DOI: 10.1080/19490976.2021.1968257]
- 25 **Li H**, Xiang Y, Zhu Z, Wang W, Jiang Z, Zhao M, Cheng S, Pan F, Liu D, Ho RCM, Ho CSH. Rifaximin-mediated gut microbiota regulation modulates the function of microglia and protects against CUMS-induced depression-like behaviors in adolescent rat. *J Neuroinflammation* 2021; **18**: 254 [PMID: 34736493 DOI: 10.1186/s12974-021-02303-y]
- 26 **Lin S**, Mukherjee S, Li J, Hou W, Pan C, Liu J. Mucosal immunity-mediated modulation of the gut microbiome by oral delivery of probiotics into Peyer's patches. *Sci Adv* 2021; **7** [PMID: 33980483 DOI: 10.1126/sciadv.abf0677]
- 27 **Zhu Y**, Wang X, Zhu L, Tu Y, Chen W, Gong L, Pan T, Lin H, Lin J, Sun H, Ge Y, Wei L, Guo Y, Lu C, Chen Y, Xu L. Lactobacillus rhamnosus GG combined with inosine ameliorates alcohol-induced liver injury through regulation of intestinal barrier and Treg/Th1 cells. *Toxicol Appl Pharmacol* 2022; **439**: 115923 [PMID: 35176292 DOI: 10.1016/j.taap.2022.115923]
- 28 **Li R**, Zhou R, Wang H, Li W, Pan M, Yao X, Zhan W, Yang S, Xu L, Ding Y, Zhao L. Gut microbiota-stimulated cathepsin K secretion mediates TLR4-dependent M2 macrophage polarization and promotes tumor metastasis in colorectal cancer. *Cell Death Differ* 2019; **26**: 2447-2463 [PMID: 30850734 DOI: 10.1038/s41418-019-0312-y]
- 29 **Shil A**, Chichger H. Artificial Sweeteners Negatively Regulate Pathogenic Characteristics of Two Model Gut Bacteria, *E. coli* and *E. faecalis*. *Int J Mol Sci* 2021; **22** [PMID: 34063332 DOI: 10.3390/ijms22105228]
- 30 **Hu J**, Wang C, Huang X, Yi S, Pan S, Zhang Y, Yuan G, Cao Q, Ye X, Li H. Gut microbiota-mediated secondary bile acids regulate dendritic cells to attenuate autoimmune uveitis through TGR5 signaling. *Cell Rep* 2021; **36**: 109726 [PMID: 34551302 DOI: 10.1016/j.celrep.2021.109726]
- 31 **Xu Y**, Zhu J, Feng B, Lin F, Zhou J, Liu J, Shi X, Lu X, Pan Q, Yu J, Zhang Y, Li L, Cao H. Immunosuppressive effect of mesenchymal stem cells on lung and gut CD8(+) T cells in lipopolysaccharide-induced acute lung injury in mice. *Cell Prolif* 2021; **54**: e13028 [PMID: 33738881 DOI: 10.1111/cpr.13028]
- 32 **Luck H**, Khan S, Kim JH, Copeland JK, Revelo XS, Tsai S, Chakraborty M, Cheng K, Tao Chan Y, Nøhr MK, Clemente-Casares X, Perry MC, Ghazarian M, Lei H, Lin YH, Coburn B, Okrainec A, Jackson T, Poutanen S, Gaisano H, Allard JP, Guttman DS, Conner ME, Winer S, Winer DA. Gut-associated IgA(+) immune cells regulate obesity-related insulin resistance. *Nat Commun* 2019; **10**: 3650 [PMID: 31409776 DOI: 10.1038/s41467-019-11370-y]
- 33 **Tyler CJ**, Guzman M, Lundborg LR, Yeasmin S, Zgajnar N, Jedlicka P, Bamias G, Rivera-Nieves J. Antibody secreting cells are critically dependent on integrin α4β7/MAdCAM-1 for intestinal recruitment and control of the microbiota during chronic colitis. *Mucosal Immunol* 2022; **15**: 109-119 [PMID: 34433904 DOI: 10.1038/s41385-021-00445-z]
- 34 **Lyu S**, Pan F, Ge H, Yang Q, Duan X, Feng M, Liu X, Zhang T, Liu J. Fermented egg-milk beverage alleviates dextran sulfate sodium-induced colitis in mice through the modulation of intestinal flora and short-chain fatty acids. *Food Funct* 2022; **13**: 702-715 [PMID: 34935826 DOI: 10.1039/d1fo03040j]
- 35 **Pan LJ**, Ma SY, Wen J, Zhang XQ, Xing HJ, Jia CS. Direct contact moxibustion promotes apoptosis of gastric cancer cells in rats by regulating intestinal flora. *J Tradit Chin Med* 2021; **41**: 943-952 [PMID: 34939391 DOI: 10.19852/j.cnki.jtcm.2021.06.011]
- 36 **Mao Q**, Pan H, Zhang Y, Zhu Q, Hong Y, Huang Z, Li Y, Feng X, Fang Y, Chen W, Chen P, Shen B, Ouyang H, Liang Y. GelNB molecular coating as a biophysical barrier to isolate intestinal irritating metabolites and regulate intestinal microbial homeostasis in the treatment of inflammatory bowel disease. *Bioact Mater* 2023; **19**: 251-267 [PMID: 35510173 DOI: 10.1016/j.bioactmat.2022.04.001]
- 37 **Yu J**, He X, Wei A, Liu T, Zhang Q, Pan Y, Hao Z, Yang L, Yuan Y, Zhang Z, Zhang C, Hao C, Liu Z, Li W. HPS1 Regulates the Maturation of Large Dense Core Vesicles and Lysozyme Secretion in Paneth Cells. *Front Immunol* 2020; **11**: 560110 [PMID: 33224134 DOI: 10.3389/fimmu.2020.560110]
- 38 **Li Y**, Li H, Tong H, Maegleev M, Gu Z. Outer membrane vesicles derived from heatstroke-associated intestinal microbiota promote multiple organ injury in mice. *Microb Pathog* 2022; **170**: 105653 [PMID: 35753600 DOI: 10.1016/j.micpath.2022.105653]
- 39 **Schmitt H**, Neurath MF, Atreya R. Role of the IL23/IL17 Pathway in Crohn's Disease. *Front Immunol* 2021; **12**: 622934 [PMID: 33859636 DOI: 10.3389/fimmu.2021.622934]
- 40 **Ruan J**, Schlüter D, Naumann M, Waisman A, Wang X. Ubiquitin-modifying enzymes as regulators of colitis. *Trends Mol Med* 2022; **28**: 304-318 [PMID: 35177326 DOI: 10.1016/j.molmed.2022.01.006]
- 41 **Wu Y**, Murray GK, Byrne EM, Sidorenko J, Visscher PM, Wray NR. GWAS of peptic ulcer disease implicates *Helicobacter pylori* infection, other gastrointestinal disorders and depression. *Nat Commun* 2021; **12**: 1146 [PMID: 33608531 DOI: 10.1038/s41467-021-21280-7]
- 42 **Kumar A**, Priyamvada S, Ge Y, Jayawardena D, Singhal M, Anbazhagan AN, Chatterjee I, Dayal A, Patel M, Zadeh K, Saksena S, Alrefai WA, Gill RK, Zadeh M, Zhao N, Mohamadze M, Dudeja PK. A Novel Role of SLC26A3 in the Maintenance of Intestinal Epithelial Barrier Integrity. *Gastroenterology* 2021; **160**: 1240-1255.e3 [PMID: 33189700 DOI: 10.1053/j.gastro.2020.11.008]

- 43 **Kim S**, Lee JY, Shin SG, Kim JK, Silwal P, Kim YJ, Shin NR, Kim PS, Won M, Lee SH, Kim SY, Sasai M, Yamamoto M, Kim JM, Bae JW, Jo EK. ESRRA (estrogen related receptor alpha) is a critical regulator of intestinal homeostasis through activation of autophagic flux *via* gut microbiota. *Autophagy* 2021; **17**: 2856-2875 [PMID: 33172329 DOI: 10.1080/15548627.2020.1847460]
- 44 **Sazonovs A**, Stevens CR, Venkataraman GR, Yuan K, Avila B, Abreu MT, Ahmad T, Allez M, Ananthakrishnan AN, Atzmon G, Baras A, Barrett JC, Barzilai N, Beaugier L, Beecham A, Bernstein CN, Bitton A, Bokemeyer B, Chan A, Chung D, Cleynen I, Cosnes J, Cutler DJ, Daly A, Damas OM, Datta LW, Dawany N, Devoto M, Dodge S, Ellinghaus E, Fachal L, Farkkila M, Faubion W, Ferreira M, Franchimont D, Gabriel SB, Ge T, Georges M, Gettler K, Giri M, Glaser B, Goerg S, Goyette P, Graham D, Hämäläinen E, Haritunians T, Heap GA, Hiltunen M, Hoepfner M, Horowitz JE, Irving P, Iyer V, Jalas C, Kelsen J, Khalili H, Kirschner BS, Kontula K, Koskela JT, Kugathasan S, Kupcinskas J, Lamb CA, Laudes M, Lévesque C, Levine AP, Lewis JD, Loefflerinckx C, Loescher BS, Louis E, Mansfield J, May S, McCauley JL, Mengesha E, Mni M, Moayyedi P, Moran CJ, Newberry RD, O'Charoen S, Okou DT, Oldenburg B, Ostrer H, Palotie A, Paquette J, Pekow J, Peter I, Pierik MJ, Ponsioen CY, Pontikos N, Prescott N, Pulver AE, Rahmouni S, Rice DL, Saavalainen P, Sands B, Sartor RB, Schiff ER, Schreiber S, Schumm LP, Segal AW, Seksik P, Shawky R, Sheikh SZ, Silverberg MS, Simmons A, Skeiceviciene J, Sokol H, Solomonson M, Somineni H, Sun D, Targan S, Turner D, Uhlig HH, van der Meulen AE, Vermeire S, Verstockt S, Voskuil MD, Winter HS, Young J; Belgium IBD Consortium; Cedars-Sinai IBD; International IBD Genetics Consortium; NIDDK IBD Genetics Consortium; NIHR IBD BioResource; Regeneron Genetics Center; SHARE Consortium; SPARC IBD Network; UK IBD Genetics Consortium, Duerr RH, Franke A, Brant SR, Cho J, Weersma RK, Parkes M, Xavier RJ, Rivas MA, Rioux JD, McGovern DPB, Huang H, Anderson CA, Daly MJ. Large-scale sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility. *Nat Genet* 2022; **54**: 1275-1283 [PMID: 36038634 DOI: 10.1038/s41588-022-01156-2]
- 45 **Nasser J**, Bergman DT, Fulco CP, Guckelberger P, Doughty BR, Patwardhan TA, Jones TR, Nguyen TH, Ulirsch JC, Lekschas F, Mualim K, Natri HM, Weeks EM, Munson G, Kane M, Kang HY, Cui A, Ray JP, Eisenhaure TM, Collins RL, Dey K, Pfister H, Price AL, Epstein CB, Kundaje A, Xavier RJ, Daly MJ, Huang H, Finucane HK, Hacohen N, Lander ES, Engreitz JM. Genome-wide enhancer maps link risk variants to disease genes. *Nature* 2021; **593**: 238-243 [PMID: 33828297 DOI: 10.1038/s41586-021-03446-x]
- 46 **Lin R**, Wu W, Chen H, Gao H, Wu X, Li G, He Q, Lu H, Sun M, Liu Z. GPR65 promotes intestinal mucosal Th1 and Th17 cell differentiation and gut inflammation through downregulating NIAK2. *Clin Transl Med* 2022; **12**: e771 [PMID: 35343079 DOI: 10.1002/ctm2.771]
- 47 **Zheng HB**, de la Morena MT, Suskind DL. The Growing Need to Understand Very Early Onset Inflammatory Bowel Disease. *Front Immunol* 2021; **12**: 675186 [PMID: 34122435 DOI: 10.3389/fimmu.2021.675186]
- 48 **Gettler K**, Levantovsky R, Moscati A, Giri M, Wu Y, Hsu NY, Chuang LS, Sazonovs A, Venkateswaran S, Korie U, Chasteau C; UK IBD Genetics Consortium, National Institute of Diabetes, Digestive and Kidney Diseases Inflammatory Bowel Disease Genetics Consortium, Duerr RH, Silverberg MS, Snapper SB, Daly MJ, McGovern DP, Brant SR, Rioux JD, Kugathasan S, Anderson CA, Itan Y, Cho JH. Common and Rare Variant Prediction and Penetrance of IBD in a Large, Multi-ethnic, Health System-based Biobank Cohort. *Gastroenterology* 2021; **160**: 1546-1557 [PMID: 33359885 DOI: 10.1053/j.gastro.2020.12.034]
- 49 **Tuganbaev T**, Mor U, Bashiardes S, Liwinski T, Nobs SP, Leshem A, Dori-Bachash M, Thaïss CA, Pinker EY, Ratiner K, Adlung L, Federici S, Kleimayer C, Moresi C, Yamada T, Cohen Y, Zhang X, Massalha H, Massasa E, Kuperman Y, Koni PA, Harmelin A, Gao N, Itzkovitz S, Honda K, Shapiro H, Elinav E. Diet Diurnally Regulates Small Intestinal Microbiome-Epithelial-Immune Homeostasis and Enteritis. *Cell* 2020; **182**: 1441-1459.e21 [PMID: 32888430 DOI: 10.1016/j.cell.2020.08.027]
- 50 **Sharma D**, Malik A, Guy CS, Karki R, Vogel P, Kanneganti TD. Pylrin Inflammasome Regulates Tight Junction Integrity to Restrict Colitis and Tumorigenesis. *Gastroenterology* 2018; **154**: 948-964.e8 [PMID: 29203393 DOI: 10.1053/j.gastro.2017.11.276]
- 51 **Djouina M**, Waxin C, Leprêtre F, Tardivel M, Tillement O, Vasseur F, Figeac M, Bongiovanni A, Sebda S, Desreumaux P, Launay D, Dubuquoy L, Body-Malapel M, Vignal C. Gene/environment interaction in the susceptibility of Crohn's disease patients to aluminum. *Sci Total Environ* 2022; **850**: 158017 [PMID: 35973536 DOI: 10.1016/j.scitotenv.2022.158017]
- 52 **Garcia-Carbonell R**, Yao SJ, Das S, Guma M. Dysregulation of Intestinal Epithelial Cell RIPK Pathways Promotes Chronic Inflammation in the IBD Gut. *Front Immunol* 2019; **10**: 1094 [PMID: 31164887 DOI: 10.3389/fimmu.2019.01094]
- 53 **Zhang H**, Cui Z, Cheng D, Du Y, Guo X, Gao R, Chen J, Sun W, He R, Ma X, Peng Q, Martin BN, Yan W, Rong Y, Wang C. RNF186 regulates EFN1 (ephrin B1)-EPHB2-induced autophagy in the colonic epithelial cells for the maintenance of intestinal homeostasis. *Autophagy* 2021; **17**: 3030-3047 [PMID: 33280498 DOI: 10.1080/15548627.2020.1851496]
- 54 **Saul D**, Leite Barros L, Wixom AQ, Gellhaus B, Gibbons HR, Faubion WA, Kosinsky RL. Cell Type-Specific Induction of Inflammation-Associated Genes in Crohn's Disease and Colorectal Cancer. *Int J Mol Sci* 2022; **23** [PMID: 35328501 DOI: 10.3390/ijms23063082]
- 55 **Rusu I**, Mennillo E, Bain JL, Li Z, Sun X, Ly KM, Rosli YY, Naser M, Wang Z, Advincula R, Achacoso P, Shao L, Razani B, Klein OD, Marson A, Turnbaugh JA, Turnbaugh PJ, Malynn BA, Ma A, Kattah MG. Microbial signals, MyD88, and lymphotoxin drive TNF-independent intestinal epithelial tissue damage. *J Clin Invest* 2022; **132** [PMID: 35077396 DOI: 10.1172/JCI154993]
- 56 **Lin S**, Wang Z, Lam KL, Zeng S, Tan BK, Hu J. Role of intestinal microecology in the regulation of energy metabolism by dietary polyphenols and their metabolites. *Food Nutr Res* 2019; **63** [PMID: 30814920 DOI: 10.29219/fnr.v63.1518]
- 57 **Cui S**, Jiang J, Li B, Ross RP, Stanton C, Zhao J, Zhang H, Yang B, Chen W. Effects of the short-term administration of *Pediococcus pentosaceus* on physiological characteristics, inflammation, and intestinal microecology in mice. *Food Funct* 2021; **12**: 1695-1707 [PMID: 33502422 DOI: 10.1039/d0fo02948c]
- 58 **Mu J**, Lin Q, Liang Y. An update on the effects of food-derived active peptides on the intestinal microecology. *Crit Rev Food Sci Nutr* 2022; **1-15** [PMID: 35791779 DOI: 10.1080/10408398.2022.2094889]
- 59 **Guo K**, Yan Y, Zeng C, Shen L, He Y, Tan Z. Study on Baohe Pills Regulating Intestinal Microecology and Treating Diarrhea of High-Fat and High-Protein Diet Mice. *Biomed Res Int* 2022; **2022**: 6891179 [PMID: 35620223 DOI: 10.1155/2022/6891179]
- 60 **Wang J**, Liang J, He M, Xie Q, Wu Q, Shen G, Zhu B, Yu J, Yu L, Tan X, Wei L, Ren J, Lv Y, Deng L, Yin Q, Zhou H, Wu W, Zhang M, Yang W, Qiao M, Shu R, Xia Z, Li Z, Huang Z, Hu W, Wang L, Liu Z, Pi G, Ren H, Ji Y, Qi X, Chen P, Shao L, Chen F, Xu X, Chen W, Wang Q, Guo Z; Tumor and Microecology Committee of China Anti-Cancer Association. Chinese expert consensus on intestinal microecology and management of digestive tract complications related to tumor treatment (version 2022). *J Cancer Res Ther* 2022; **18**: 1835-1844 [PMID: 36647940 DOI: 10.4103/jcrt.jcrt_1444_22]
- 61 **Zheng L**, Ji YY, Wen XL, Duan SL. Fecal microbiota transplantation in the metabolic diseases: Current status and perspectives. *World J Gastroenterol* 2022; **28**: 2546-2560 [PMID: 35949351 DOI: 10.3748/wjg.v28.i23.2546]
- 62 **Zheng L**, Wen XL, Duan SL. Role of metabolites derived from gut microbiota in inflammatory bowel disease. *World J Clin Cases* 2022; **10**: 2660-2677 [PMID: 35434116 DOI: 10.12998/wjcc.v10.i9.2660]

- 63 **Zheng L**, Duan SL, Dai YC, Wu SC. Role of adherent invasive *Escherichia coli* in pathogenesis of inflammatory bowel disease. *World J Clin Cases* 2022; **10**: 11671-11689 [PMID: [36405271](#) DOI: [10.12998/wjcc.v10.i32.11671](#)]
- 64 **Zheng L**, Duan SL, Wen XL, Dai YC. Molecular regulation after mucosal injury and regeneration in ulcerative colitis. *Front Mol Biosci* 2022; **9**: 996057 [PMID: [36310594](#) DOI: [10.3389/fmolb.2022.996057](#)]
- 65 **Zhang P**, Jia J, Jiang P, Zheng W, Li X, Song S, Ai C. Polysaccharides from edible brown seaweed *Undaria pinnatifida* are effective against high-fat diet-induced obesity in mice through the modulation of intestinal microecology. *Food Funct* 2022; **13**: 2581-2593 [PMID: [35166281](#) DOI: [10.1039/d1fo04012j](#)]
- 66 **Pan ST**, Wang RC, Su YZ, Hsieh YC, Chuang SS. Lymphomatous effusion of monomorphic epitheliotropic intestinal T-cell lymphoma is characterized by azurophilic granules and is a dismal sign: Report of two new cases with literature review. *Diagn Cytopathol* 2021; **49**: E247-E252 [PMID: [33387400](#) DOI: [10.1002/dc.24690](#)]
- 67 **Hang JF**, Yuan CT, Chang KC, Wang RC, Chen BJ, Hsieh PP, Huang WT, Chuang WY, Chen TW, Yeh YC, Lin SY, Hsiao CH, Chou SC, Tseng CE, Pan ST, Chang SL, Chuang SS. Targeted Next-generation Sequencing Reveals a Wide Morphologic and Immunophenotypic Spectrum of Monomorphic Epitheliotropic Intestinal T-Cell Lymphoma. *Am J Surg Pathol* 2022; **46**: 1207-1218 [PMID: [35551151](#) DOI: [10.1097/PAS.0000000000001914](#)]
- 68 **Pan S**, Hong F, Li L, Guo Y, Qiao X, Zhang J, Xu P, Zhai Y. Melatonin Attenuates Dextran Sodium Sulfate Induced Colitis in Obese Mice. *Pharmaceuticals (Basel)* 2021; **14** [PMID: [34451919](#) DOI: [10.3390/ph14080822](#)]
- 69 **Gu M**, Pan S, Deng W, Li Q, Qi Z, Chen C, Bai N. Effects of glutamine on the IKK/I κ B/NF- κ B system in the enterocytes of turbot *Scophthalmus maximus* L. stimulated with soya-saponins. *Fish Shellfish Immunol* 2021; **119**: 373-378 [PMID: [34688862](#) DOI: [10.1016/j.fsi.2021.10.027](#)]
- 70 **Zhang S**, Hu H, He W, Muhammad Z, Wang L, Liu F, Pan S. Regulatory Roles of Pectin Oligosaccharides on Immunoglobulin Production in Healthy Mice Mediated by Gut Microbiota. *Mol Nutr Food Res* 2019; **63**: e1801363 [PMID: [31116489](#) DOI: [10.1002/mnfr.201801363](#)]
- 71 **Gu M**, Pan S, Li Q, Qi Z, Deng W, Bai N. Protective effects of glutamine against soy saponins-induced enteritis, tight junction disruption, oxidative damage and autophagy in the intestine of *Scophthalmus maximus* L. *Fish Shellfish Immunol* 2021; **114**: 49-57 [PMID: [33887442](#) DOI: [10.1016/j.fsi.2021.04.013](#)]
- 72 **Tan Y**, Chen Q, Pan S, An W, Xu H, Xing Y, Zhang J. LMOD1, an oncogene associated with Lauren classification, regulates the metastasis of gastric cancer cells through the FAK-AKT/mTOR pathway. *BMC Cancer* 2022; **22**: 474 [PMID: [35488236](#) DOI: [10.1186/s12885-022-09541-0](#)]
- 73 **Tao M**, Li R, Zhang Z, Wu T, Xu T, Zogona D, Huang Y, Pan S, Xu X. Vitexin and Isovitexin Act through Inhibition of Insulin Receptor to Promote Longevity and Fitness in *Caenorhabditis elegans*. *Mol Nutr Food Res* 2022; **66**: e2100845 [PMID: [35413150](#) DOI: [10.1002/mnfr.202100845](#)]
- 74 **Hong F**, Pan S, Xu P, Xue T, Wang J, Guo Y, Jia L, Qiao X, Li L, Zhai Y. Melatonin Orchestrates Lipid Homeostasis through the Hepatointestinal Circadian Clock and Microbiota during Constant Light Exposure. *Cells* 2020; **9** [PMID: [32093272](#) DOI: [10.3390/cells9020489](#)]
- 75 **Pan ST**, Ko YH, Tan SY, Chuang SS. Primary cutaneous peripheral T-cell lymphoma with a late relapse solely in the ileum mimicking monomorphic epitheliotropic intestinal T-cell lymphoma. *Pathol Res Pract* 2018; **214**: 2106-2109 [PMID: [30477646](#) DOI: [10.1016/j.prp.2018.10.002](#)]
- 76 **Peng H**, Bai H, Pan Y, Li J, Pei Z, Liao Y, Wu C, Li C, Tao L, Zhong S, Ma C, Chen Z, Li X, Gong Y, Wang L, Li F. Immunological pathogenesis of Bovine *E. coli* infection in a model of *C. elegans*. *BMC Microbiol* 2022; **22**: 311 [PMID: [36539715](#) DOI: [10.1186/s12866-022-02733-5](#)]
- 77 **Asadi Karam MR**, Habibi M, Bouzari S. Urinary tract infection: Pathogenicity, antibiotic resistance and development of effective vaccines against Uropathogenic *Escherichia coli*. *Mol Immunol* 2019; **108**: 56-67 [PMID: [30784763](#) DOI: [10.1016/j.molimm.2019.02.007](#)]
- 78 **Oberic AM**, Fiebig-Comyn AA, Tsai CN, Elhenawy W, Coombes BK. Antibiotics Potentiate Adherent-Invasive *E. coli* Infection and Expansion. *Inflamm Bowel Dis* 2019; **25**: 711-721 [PMID: [30496418](#) DOI: [10.1093/ibd/izy361](#)]
- 79 **Manges AR**, Geum HM, Guo A, Edens TJ, Fibke CD, Pitout JDD. Global Extraintestinal Pathogenic *Escherichia coli* (ExPEC) Lineages. *Clin Microbiol Rev* 2019; **32** [PMID: [31189557](#) DOI: [10.1128/CMR.00135-18](#)]
- 80 **Lee JB**, Kim SK, Yoon JW. Pathophysiology of enteropathogenic *Escherichia coli* during a host infection. *J Vet Sci* 2022; **23**: e28 [PMID: [35187883](#) DOI: [10.4142/jvs.21160](#)]
- 81 **Liu H**, Xu M, He Q, Wei P, Ke M, Liu S. Untargeted serum metabolomics reveals specific metabolite abnormalities in patients with Crohn's disease. *Front Med (Lausanne)* 2022; **9**: 814839 [PMID: [36160171](#) DOI: [10.3389/fmed.2022.814839](#)]
- 82 **Kattah MG**, Milush JM, Burt T, McCabe RP Jr, Whang MI, Ma A, Mahadevan U. Anti-TNF and thiopurine therapy in pregnant IBD patients does not significantly alter a panel of B-cell and T-cell subsets in 1-year-old infants. *Clin Transl Gastroenterol* 2018; **9**: 143 [PMID: [29618720](#) DOI: [10.1038/s41424-018-0018-3](#)]
- 83 **Neubauer K**, Woźniak-Stolarska B, Krzystek-Korpacka M. Peripheral Lymphocytes of Patients with Inflammatory Bowel Disease Have Altered Concentrations of Key Apoptosis Players: Preliminary Results. *Biomed Res Int* 2018; **2018**: 4961753 [PMID: [30515402](#) DOI: [10.1155/2018/4961753](#)]
- 84 **Almazni I**, Stapley RJ, Khan AO, Morgan NV. A comprehensive bioinformatic analysis of 126 patients with an inherited platelet disorder to identify both sequence and copy number genetic variants. *Hum Mutat* 2020; **41**: 1848-1865 [PMID: [32935436](#) DOI: [10.1002/humu.24114](#)]
- 85 **Wu J**, Lv X, Zhu S, Li T, Cheng H, Chen J. Critical Roles of Balanced Innate Lymphoid Cell Subsets in Intestinal Homeostasis, Chronic Inflammation, and Cancer. *J Immunol Res* 2019; **2019**: 1325181 [PMID: [31781671](#) DOI: [10.1155/2019/1325181](#)]
- 86 **Lu X**, Wang H, Zhang J, Jin K, Ma L, Wang Y, Yang S, Wang X, Shen Q, Zhou T, Xu H, Zhang W. Comparison of Gut Viral Communities in Atopic Dermatitis and Healthy Children. *Front Med (Lausanne)* 2022; **9**: 835467 [PMID: [35265642](#) DOI: [10.3389/fmed.2022.835467](#)]
- 87 **Belibasakis GN**, Bostanci N, Marsh PD, Zaura E. Applications of the oral microbiome in personalized dentistry. *Arch Oral Biol* 2019; **104**: 7-12 [PMID: [31153099](#) DOI: [10.1016/j.archoralbio.2019.05.023](#)]
- 88 **Sun Y**, Liu X, Sun L, Men M, Wang B, Deng L, Zhao L, Han Y, Jong C, Bi R, Zhao M, Li X, Liu W, Shi S, Gai Z, Xu X. Microecological insight to fungal structure and key fungal communities regulating nitrogen transformation based on spatial heterogeneity during cow manure composting by multi-angle and multi-aspect analyses. *Waste Manag* 2022; **142**: 132-142 [PMID: [35219063](#) DOI: [10.1016/j.wasman.2022.02.013](#)]
- 89 **Kang J**, Sun M, Chang Y, Chen H, Zhang J, Liang X, Xiao T. Butyrate ameliorates colorectal cancer through regulating intestinal microecological disorders. *Anticancer Drugs* 2023; **34**: 227-237 [PMID: [36305358](#) DOI: [10.1097/CAD.0000000000001413](#)]

- 90 **Tian Z**, Zhang Y, Zheng Z, Zhang M, Zhang T, Jin J, Zhang X, Yao G, Kong D, Zhang C, Wang Z, Zhang Q. Gut microbiome dysbiosis contributes to abdominal aortic aneurysm by promoting neutrophil extracellular trap formation. *Cell Host Microbe* 2022; **30**: 1450-1463.e8 [PMID: 36228585 DOI: 10.1016/j.chom.2022.09.004]
- 91 **Huang X**, Li M, Huang Y, Yang H, Geng Y, Ouyang P, Chen D, Yin L, Yang S, Jiang J, Luo W, He Z. Microbiome analysis reveals microecological advantages of emerging ditchless rice-crayfish co-culture mode. *Front Microbiol* 2022; **13**: 892026 [PMID: 35935240 DOI: 10.3389/fmicb.2022.892026]
- 92 **Liu J**, Xiao L, Nie H, Pan Y, Liu Y, Zhang Z, Lin X, Zhang Y, Cai J, Yang M, Zhang L, Xu A, Zhu C. Microecological preparation combined with an modified low-carbon diet improves glucolipid metabolism and cardiovascular complication in obese patients. *Diabetol Metab Syndr* 2021; **13**: 77 [PMID: 34256811 DOI: 10.1186/s13098-021-00697-6]
- 93 **Zhang H**, Jin S, Ji A, Zhang C, Shi S. Correlation between Vaginal Microecological Status and Prognosis of CIN Patients with High-Risk HPV Infection. *Biomed Res Int* 2022; **2022**: 3620232 [PMID: 35463993 DOI: 10.1155/2022/3620232]
- 94 **Du H**, Ding S, Gao L, Zeng J, Lu J. Microecological investigation and comparison of two clinical methods to evaluate axillary osmidrosis. *Mol Med Rep* 2020; **22**: 4207-4212 [PMID: 33000232 DOI: 10.3892/mmr.2020.11528]
- 95 **Yang L**, Fan W, Xu Y. Chameleon-like microbes promote microecological differentiation of Daqu. *Food Microbiol* 2023; **109**: 104144 [PMID: 36309458 DOI: 10.1016/j.fm.2022.104144]
- 96 **Xiang Y**, Zhang S, Cui Z, Yang Y. Exploring the effect of microecological agents on postoperative immune function in patients undergoing liver cancer surgery: a systematic review and meta-analysis. *Ann Palliat Med* 2021; **10**: 11615-11627 [PMID: 34872286 DOI: 10.21037/apm-21-2669]
- 97 **Ma Y**, Chen X, Khan MZ, Xiao J, Cao Z. A Combination of Novel Microecological Agents and Molasses Role in Digestibility and Fermentation of Rice Straw by Facilitating the Ruminant Microbial Colonization. *Front Microbiol* 2022; **13**: 948049 [PMID: 35910602 DOI: 10.3389/fmicb.2022.948049]
- 98 **Tan J**, Zhou H, Deng J, Sun J, Zhou X, Tang Y, Qin W. Effectiveness of Microecological Preparations for Improving Renal Function and Metabolic Profiles in Patients With Chronic Kidney Disease. *Front Nutr* 2022; **9**: 850014 [PMID: 36172526 DOI: 10.3389/fnut.2022.850014]
- 99 **Gurses SA**, Banskar S, Stewart C, Trimoski B, Dziarski R, Gupta D. Nod2 protects mice from inflammation and obesity-dependent liver cancer. *Sci Rep* 2020; **10**: 20519 [PMID: 33239685 DOI: 10.1038/s41598-020-77463-7]
- 100 **Takada R**, Watanabe T, Hara A, Sekai I, Kurimoto M, Otsuka Y, Masuta Y, Yoshikawa T, Kamata K, Minaga K, Kudo M. NOD2 deficiency protects mice from the development of adoptive transfer colitis through the induction of regulatory T cells expressing forkhead box P3. *Biochem Biophys Res Commun* 2021; **568**: 55-61 [PMID: 34186435 DOI: 10.1016/j.bbrc.2021.06.068]
- 101 **Butera A**, Di Paola M, Pavarini L, Strati F, Pindo M, Sanchez M, Cavalieri D, Boirivant M, De Filippo C. Nod2 Deficiency in mice is Associated with Microbiota Variation Favouring the Expansion of mucosal CD4+ LAP+ Regulatory Cells. *Sci Rep* 2018; **8**: 14241 [PMID: 30250234 DOI: 10.1038/s41598-018-32583-z]
- 102 **Wong SY**, Coffre M, Ramanan D, Hines MJ, Gomez LE, Peters LA, Schadt EE, Koralov SB, Cadwell K. B Cell Defects Observed in Nod2 Knockout Mice Are a Consequence of a Dock2 Mutation Frequently Found in Inbred Strains. *J Immunol* 2018; **201**: 1442-1451 [PMID: 30012848 DOI: 10.4049/jimmunol.1800014]
- 103 **Goethel A**, Turpin W, Rouquier S, Zanello G, Robertson SJ, Streutker CJ, Philpott DJ, Croitoru K. Nod2 influences microbial resilience and susceptibility to colitis following antibiotic exposure. *Mucosal Immunol* 2019; **12**: 720-732 [PMID: 30651577 DOI: 10.1038/s41385-018-0128-y]
- 104 **Lee C**, Choi C, Kang HS, Shin SW, Kim SY, Park HC, Hong SN. NOD2 Supports Crypt Survival and Epithelial Regeneration after Radiation-Induced Injury. *Int J Mol Sci* 2019; **20** [PMID: 31480799 DOI: 10.3390/ijms20174297]
- 105 **Umiker B**, Lee HH, Cope J, Ajami NJ, Laine JP, Fregeau C, Ferguson H, Alves SE, Sciammetta N, Kleinschek M, Salmon M. The NLRP3 inflammasome mediates DSS-induced intestinal inflammation in Nod2 knockout mice. *Innate Immun* 2019; **25**: 132-143 [PMID: 30774010 DOI: 10.1177/1753425919826367]
- 106 **Arbez N**, He X, Huang Y, Ren M, Liang Y, Nucifora FC, Wang X, Pei Z, Tessarolo L, Smith WW, Ross CA. G2019S-LRRK2 mutation enhances MPTP-linked Parkinsonism in mice. *Hum Mol Genet* 2020; **29**: 580-590 [PMID: 31813996 DOI: 10.1093/hmg/ddz271]
- 107 **Cheng X**, Wu X, Zhang Y, Li W, Feng L, You H, Yang S, Yang D, Chen X, Pan X. LRRK2 Deficiency Aggravates Sleep Deprivation-Induced Cognitive Loss by Perturbing Synaptic Pruning in Mice. *Brain Sci* 2022; **12** [PMID: 36138936 DOI: 10.3390/brainsci12091200]
- 108 **Albanese F**, Domenicale C, Volta M, Morari M. Modeling Parkinson's disease in LRRK2 mice: focus on synaptic dysfunction and the autophagy-lysosomal pathway. *Biochem Soc Trans* 2022; **50**: 621-632 [PMID: 35225340 DOI: 10.1042/BST20211288]
- 109 **Yan J**, Yu W, Wang G, Lu C, Liu C, Jiang L, Jiang Z, Liang Z, Liu D. LRRK2 deficiency mitigates colitis progression by favoring resolution of inflammation and restoring homeostasis of gut microbiota. *Genomics* 2022; **114**: 110527 [PMID: 36455749 DOI: 10.1016/j.ygeno.2022.110527]
- 110 **Kozina E**, Byrne M, Smeyne RJ. Mutant LRRK2 in lymphocytes regulates neurodegeneration via IL-6 in an inflammatory model of Parkinson's disease. *NPJ Parkinsons Dis* 2022; **8**: 24 [PMID: 35292674 DOI: 10.1038/s41531-022-00289-9]
- 111 **Ning B**, Guo G, Gu C, Xu J, Bibic A, He X, Liu H, Chen L, Wei Z, Duan W, Liu P, Lu H, van Zijl PCM, Ross CA, Smith W, Hua J. Mutant G2019S-LRRK2 Induces Abnormalities in Arteriolar Cerebral Blood Volume in Mouse Brains: An MRI Study. *Neurodegener Dis* 2020; **20**: 65-72 [PMID: 33152738 DOI: 10.1159/000510387]
- 112 **Shani V**, Safory H, Szargel R, Wang N, Cohen T, Elghani FA, Hamza H, Savyon M, Radziszewsky I, Shaulov L, Rott R, Lim KL, Ross CA, Bandopadhyay R, Zhang H, Engelender S. Physiological and pathological roles of LRRK2 in the nuclear envelope integrity. *Hum Mol Genet* 2019; **28**: 3982-3996 [PMID: 31626293 DOI: 10.1093/hmg/ddz245]
- 113 **Lara Ordóñez AJ**, Fernández B, Fdez E, Romo-Lozano M, Madero-Pérez J, Llobestael E, Baekelandt V, Aiastrui A, López de Munaín A, Melrose HL, Civiero L, Hilfiker S. RAB8, RAB10 and RILPL1 contribute to both LRRK2 kinase-mediated centrosomal cohesion and ciliogenesis deficits. *Hum Mol Genet* 2019; **28**: 3552-3568 [PMID: 31428781 DOI: 10.1093/hmg/ddz201]
- 114 **Chen X**, Xie C, Tian W, Sun L, Zheng W, Hawes S, Chang L, Kung J, Ding J, Chen S, Le W, Cai H. Parkinson's disease-related Leucine-rich repeat kinase 2 modulates nuclear morphology and genomic stability in striatal projection neurons during aging. *Mol Neurodegener* 2020; **15**: 12 [PMID: 32075681 DOI: 10.1186/s13024-020-00360-0]
- 115 **Wallings RL**, Tansey MG. LRRK2 regulation of immune-pathways and inflammatory disease. *Biochem Soc Trans* 2019; **47**: 1581-1595 [PMID: 31769472 DOI: 10.1042/BST20180463]
- 116 **Tian Y**, Lv J, Su Z, Wu T, Li X, Hu X, Zhang J, Wu L. LRRK2 plays essential roles in maintaining lung homeostasis and preventing the development of pulmonary fibrosis. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 34446559 DOI: 10.1073/pnas.2106685118]

- 117 **Marchand A**, Drouyer M, Sarchione A, Chartier-Harlin MC, Taymans JM. LRRK2 Phosphorylation, More Than an Epiphenomenon. *Front Neurosci* 2020; **14**: 527 [PMID: [32612495](#) DOI: [10.3389/fnins.2020.00527](#)]
- 118 **Liu Z**, Xu E, Zhao HT, Cole T, West AB. LRRK2 and Rab10 coordinate macropinocytosis to mediate immunological responses in phagocytes. *EMBO J* 2020; **39**: e104862 [PMID: [32853409](#) DOI: [10.15252/embj.2020104862](#)]
- 119 **Zhao Y**, Zhang W, Huo M, Wang P, Liu X, Wang Y, Li Y, Zhou Z, Xu N, Zhu H. XBP1 regulates the protumoral function of tumor-associated macrophages in human colorectal cancer. *Signal Transduct Target Ther* 2021; **6**: 357 [PMID: [34667145](#) DOI: [10.1038/s41392-021-00761-7](#)]
- 120 **Wang Q**, Bu Q, Liu M, Zhang R, Gu J, Li L, Zhou J, Liang Y, Su W, Liu Z, Wang M, Lian Z, Lu L, Zhou H. XBP1-mediated activation of the STING signalling pathway in macrophages contributes to liver fibrosis progression. *JHEP Rep* 2022; **4**: 100555 [PMID: [36185574](#) DOI: [10.1016/j.jhepr.2022.100555](#)]
- 121 **Song M**, Sandoval TA, Chae CS, Chopra S, Tan C, Rutkowski MR, Raundhal M, Chaurio RA, Payne KK, Konrad C, Bettigole SE, Shin HR, Crowley MJP, Cerliani JP, Kossenkov AV, Motorykin I, Zhang S, Manfredi G, Zamarin D, Holcomb K, Rodriguez PC, Rabinovich GA, Conejo-Garcia JR, Glimcher LH, Cubillos-Ruiz JR. IRE1 α -XBP1 controls T cell function in ovarian cancer by regulating mitochondrial activity. *Nature* 2018; **562**: 423-428 [PMID: [30305738](#) DOI: [10.1038/s41586-018-0597-x](#)]
- 122 **Zhao N**, Cao J, Xu L, Tang Q, Dobrolecki LE, Lv X, Talukdar M, Lu Y, Wang X, Hu DZ, Shi Q, Xiang Y, Wang Y, Liu X, Bu W, Jiang Y, Li M, Gong Y, Sun Z, Ying H, Yuan B, Lin X, Feng XH, Hartig SM, Li F, Shen H, Chen Y, Han L, Zeng Q, Patterson JB, Kaiparettu BA, Putluri N, Sicheri F, Rosen JM, Lewis MT, Chen X. Pharmacological targeting of MYC-regulated IRE1/XBP1 pathway suppresses MYC-driven breast cancer. *J Clin Invest* 2018; **128**: 1283-1299 [PMID: [29480818](#) DOI: [10.1172/JCI95873](#)]
- 123 **Zhang Z**, Qian Q, Li M, Shao F, Ding WX, Lira VA, Chen SX, Sebag SC, Hotamisligil GS, Cao H, Yang L. The unfolded protein response regulates hepatic autophagy by sXBP1-mediated activation of TFEB. *Autophagy* 2021; **17**: 1841-1855 [PMID: [32597296](#) DOI: [10.1080/15548627.2020.1788889](#)]
- 124 **Valatas V**, Kolios G, Bamias G. TL1A (TNFSF15) and DR3 (TNFRSF25): A Co-stimulatory System of Cytokines With Diverse Functions in Gut Mucosal Immunity. *Front Immunol* 2019; **10**: 583 [PMID: [30972074](#) DOI: [10.3389/fimmu.2019.00583](#)]
- 125 **Zhang J**, Zhang D, Pan Y, Liu X, Xu J, Qiao X, Cui W, Dong L. The TL1A-DR3 Axis in Asthma: Membrane-Bound and Secreted TL1A Co-Determined the Development of Airway Remodeling. *Allergy Asthma Immunol Res* 2022; **14**: 233-253 [PMID: [35255540](#) DOI: [10.4168/aa.2022.14.2.233](#)]
- 126 **Jacob N**, Kumagai K, Abraham JP, Shimodaira Y, Ye Y, Luu J, Blackwood AY, Castanon SL, Stamps DT, Thomas LS, Gonsky R, Shih DQ, Michelsen KS, Targan SR. Direct signaling of TL1A-DR3 on fibroblasts induces intestinal fibrosis in vivo. *Sci Rep* 2020; **10**: 18189 [PMID: [33097818](#) DOI: [10.1038/s41598-020-75168-5](#)]
- 127 **Steele H**, Sachen K, McKnight AJ, Soloff R, Herro R. Targeting TL1A/DR3 Signaling Offers a Therapeutic Advantage to Neutralizing IL13/IL4R α in Muco-Secretory Fibrotic Disorders. *Front Immunol* 2021; **12**: 692127 [PMID: [34305924](#) DOI: [10.3389/fimmu.2021.692127](#)]
- 128 **Clarke AW**, Poulton L, Shim D, Mabon D, Butt D, Pollard M, Pande V, Husten J, Lyons J, Tian C, Doyle AG. An anti-TL1A antibody for the treatment of asthma and inflammatory bowel disease. *MAbs* 2018; **10**: 664-677 [PMID: [29436901](#) DOI: [10.1080/19420862.2018.1440164](#)]
- 129 **Machida K**, Aw M, Salter BMA, Ju X, Mukherjee M, Gauvreau GM, O'Byrne PM, Nair P, Sehmi R. The Role of the TL1A/DR3 Axis in the Activation of Group 2 Innate Lymphoid Cells in Subjects with Eosinophilic Asthma. *Am J Respir Crit Care Med* 2020; **202**: 1105-1114 [PMID: [32584596](#) DOI: [10.1164/rccm.201909-1722OC](#)]
- 130 **Aden K**, Tran F, Ito G, Sheibani-Tezerji R, Lipinski S, Kuiper JW, Tschurtschenthaler M, Saveljeva S, Bhattacharyya J, Häslér R, Bartsch K, Luzius A, Jentzsch M, Falk-Paulsen M, Stengel ST, Welz L, Schwarzer R, Rabe B, Barchet W, Krautwald S, Hartmann G, Pasparakis M, Blumberg RS, Schreiber S, Kaser A, Rosenstiel P. ATG16L1 orchestrates interleukin-22 signaling in the intestinal epithelium via cGAS-STING. *J Exp Med* 2018; **215**: 2868-2886 [PMID: [30254094](#) DOI: [10.1084/jem.20171029](#)]
- 131 **Chesney KL**, Men H, Hankins MA, Bryda EC. The Atg16 L1 gene: characterization of wild type, knock-in, and knock-out phenotypes in rats. *Physiol Genomics* 2021; **53**: 269-281 [PMID: [33818130](#) DOI: [10.1152/physiolgenomics.00114.2020](#)]
- 132 **Zhang Z**, Guo M, Li Y, Shen M, Kong D, Shao J, Ding H, Tan S, Chen A, Zhang F, Zheng S. RNA-binding protein ZFP36/TTP protects against ferroptosis by regulating autophagy signaling pathway in hepatic stellate cells. *Autophagy* 2020; **16**: 1482-1505 [PMID: [31679460](#) DOI: [10.1080/15548627.2019.1687985](#)]
- 133 **Xu Y**, Zhou P, Cheng S, Lu Q, Nowak K, Hopp AK, Li L, Shi X, Zhou Z, Gao W, Li D, He H, Liu X, Ding J, Hottiger MO, Shao F. A Bacterial Effector Reveals the V-ATPase-ATG16L1 Axis that Initiates Xenophagy. *Cell* 2019; **178**: 552-566.e20 [PMID: [31327526](#) DOI: [10.1016/j.cell.2019.06.007](#)]
- 134 **Oestreich AK**, Chadchan SB, Popli P, Medvedeva A, Rowen MN, Stephens CS, Xu R, Lydon JP, Demayo FJ, Jungheim ES, Moley KH, Kommagani R. The Autophagy Gene Atg16L1 is Necessary for Endometrial Decidualization. *Endocrinology* 2020; **161** [PMID: [31875883](#) DOI: [10.1210/endocr/bqz039](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: bpgoffice@wjgnet.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

