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Research Progress on the Correlation Between Gut Microbiota and Acute Pancreatitis

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Abstract: ***The role of intestinal dysbiosis in the occurrence and development of acute pancreatitis (AP) is becoming increasingly clear. Biomarkers such as intestinal microbiota diversity, changes in the abundance of key bacteria, intestinal barrier function markers and their metabolites provide a new perspective for early prediction of the severity of SAP and the assessment of prognosis due to their non-invasive and dynamic monitoring characteristics. This article systematically reviews the relationship between the above indicators and the severity and prognosis of AP, discusses the mechanism, and reviews the clinical application status, challenges and future transformation directions of treatment strategies based on gut microbiota regulation, aiming to provide new ideas for the precise management of AP.***

Keywords: Acute Pancreatitis, Gut Microbiota, Biomarkers, Microbiota Metabolites, Gut-pancreatic Axis**.**

1. Introduction

Acute pancreatitis (AP) is a clinical syndrome characterized by the abnormal activation of pancreatic enzymes, leading to autodigestion of the pancreas and the initiation of systemic inflammatory responses [1]. Severe acute pancreatitis (SAP) is frequently complicated by multiple organ failure (MOF), resulting in a high mortality rate. Emerging evidence indicates that the gut microbiota plays a pivotal role in the pathogenesis and progression of AP through the "gut–pancreas axis". During the course of AP, intestinal ischemia, hypoxia, and an inflammatory cytokine storm among other factors compromise the integrity of the intestinal mucosal barrier, promoting bacterial translocation and microbial dysbiosis. Subsequently, endotoxins such as lipopolysaccharides (LPS) enter the systemic circulation, activating signaling pathways including TLR4/NF-κB and NLRP3 inflammasome, thereby contributing to a "gut-derived second hit" that exacerbates pancreatic necrosis and systemic inflammatory response syndrome (SIRS) [2-5]. Consequently, the gut microbiota and its associated biomarkers not only contribute to disease progression but also represent promising candidates for novel predictive tools and therapeutic interventions. This article reviews recent advances in microbiota-related biomarkers and regulatory strategies, with a focus on their potential clinical applications.

2. Imbalance in the Structure and Function of the Intestinal Flora

The gut is the most enriched ecosystem of microorganisms in the human body. Mendelian randomized studies confirmed a causal association between gut microbiota composition and the severity of AP (IVW method $P=1.2\times10^{-5}$) [6]. During the course of AP, dysbiosis of the intestinal microbiota contributes to disease exacerbation through multiple pathophysiological mechanisms. These findings indicate that the gut microbiota is not merely a passive bystander but an active contributor to disease progression. Consequently, both the structural and functional integrity of the intestinal microbiota serve as critical indicators for assessing the severity of AP.

2.1 Reduced Flora Diversity: Prominent Predictive Value

The diversity of gut microbiota serves as a fundamental indicator of ecological stability, encompassing both α-diversity and β-diversity. α-Diversity reflects species richness within an individual sample, exemplified by metrics such as the Shannon index, while β-diversity denotes the differences among multiple samples, illustrated by measures like the Bray-Curtis distance. In cases of AP, particularly SAP, intestinal flora diversity is significantly diminished compared to healthier populations and patients with mild acute pancreatitis (MAP). Notably, the extent of α-diversity reduction exhibits a significant negative correlation with pancreatic necrosis extent, organ failure incidence, and mortality rates [7]. This decline in α-diversity can persist for up to three months or even extend to one year following an episode of AP, underscoring its potential utility as a stable predictor. Research conducted by Zou et al. demonstrated that baseline microbiota characteristics outperformed traditional APACHE II scores in predicting SAP severity; their study reported an area under the curve (AUC) value of 0.754 for SAP prediction [8]. Additionally, another investigation revealed that α-diversity was negatively correlated with patients' length of hospital stay, while Bray-Curtis distance showed significant correlations with both severity and duration of hospitalization in AP patients. Furthermore, substantial differences were observed in β-diversity between individuals who succumbed to AP and those who survived [9], indicating that β-diversity may serve as a crucial indicator for assessing disease severity and prognosis.

The diversity of gut microbiota is influenced by various factors including genetics, age, immune status, dietary patterns, antibiotic usage, and living environment. Research indicates that deficiencies in beneficial nutrients within the diet can lead to reduced alpha diversity among AP patients; this effect is notably pronounced in diabetic individuals suffering from AP [10]. It is worth noting that the use of broad-spectrum antibiotics is an important factor leading to a significant decrease in the diversity of the microbiota of AP patients. Gou et al. developed a random forest prediction model based on the intestinal flora characteristics of AP patients, identifying three predictive models of microbial

composition that play a dominant role in the progression of AP (AUC=0.94). These models outperformed the traditional APACHE II score (AUC=0.86) in predicting the incidence of SAP, demonstrating high specificity and sensitivity [11]. Consequently, investigating changes in the intestinal flora profile among patients with AP holds substantial significance for forecasting disease severity. The integration of gut microbiota analysis with machine learning and artificial intelligence may emerge as a pivotal research avenue for enhancing diagnosis and treatment strategies for AP in future studies.

2.2 Imbalance in Specific Microbiota Abundance: Distinct Pathogenic and Protective Effects

Patients suffering from AP typically exhibit an imbalance characterized by "enrichment of opportunistic pathogenic bacteria coupled with a reduction in beneficial bacteria." This dysbiosis exacerbates the condition through mechanisms such as immune dysregulation and metabolic disturbances. Six candidate bacteria, namely Escherichia-Shigella, Proteobacteria, Enterococcus, Bacteroidetes, Bifidobacterium, and Prevotella, have been identified to be closely associated with disease progression in AP [4].

2.2.1 Enrichment of Opportunistic Pathogenic Bacteria:

Yu et al. demonstrated that Bacteroides is the predominant bacterial genus in the intestines of patients with MAP, while Escherichia and Shigella are most frequently observed in individuals suffering from Moderately Severe Acute Pancreatitis (MSAP). Enterococcus is notably representative in the intestinal microbiota of patients with SAP [12]. The abundance of Enterococcus was significantly elevated in SAP cases, and its levels exhibited a positive correlation with pancreatic necrosis and organ failure, demonstrating high predictive value (AUC 0.85) [5]. The pathogenic mechanisms involved include: 1) Damage to the intestinal mucosal barrier: This process activates signaling pathways such as Toll-like receptor 4 (TLR4)/MyD88/p38 mitogen-activated protein kinase (MAPK), inducing an endoplasmic reticulum stress response [13], which compromises intestinal epithelial cells, increases intestinal permeability, and facilitates bacterial translocation; 2) Immune dysregulation: The translocation of gut microbiota triggers an immune response wherein pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) are recognized by immune cells. This recognition activates NF-κB and NLRP3 inflammasomes, promoting the release of pro-inflammatory cytokines such as IL-1β and IL-18 [14]; 3) Impaired metabolic function: There is inhibition of beneficial metabolite production, including short-chain fatty acids (SCFAs). Current research indicates that reconstructing the gut microbiome, stabilizing the intestinal mucosal epithelial barrier, and inhibiting inflammatory mediators can aid in restoring intestinal homeostasis, promoting the recovery of pancreatic function and preventing and protecting other organ functions pancreatic function [15].

2.2.2 Reduction of beneficial bacteria:

The abundance of Lactobacillus, Bifidobacterium and butyate-producing bacteria (such as Roseburia and Prevotella) is significantly reduced in patients with AP and is negatively correlated with the severity of the disease [7]. Wang et al. found that the abundance of beneficial bacteria in SAP patients decreased significantly. The reduction of beneficial bacteria led to a decrease in the abundance of the glycolytic pathway in SAP, affecting energy supply and aggravating the patient's condition [16]. They correlated the gut microbiota with clinical features and confirmed that the severity of AP, serum ALB, CRP and Ca+ levels were related to the species composition of the microbiota. The research also found that supplementing zinc can help restore the abundance of beneficial bacteria in the flora and improve intestinal barrier function. Supplementation of Lactobacillus can increase the density of lysozyme and Pantenschi cells, regulate the mRNA expression of antimicrobial peptide genes (Lyz-1 and Defa5) and NOD-like receptor pathway genes (Nod2), and thereby reduce pancreatic and intestinal damage [17]. Liu et al. found that in the AP induction model, Lactobacillus was the bacterial genus with the highest initial content, while the relative abundance of Lactobacillus in the SAP group almost disappeared after 72 hours, which to some extent could reflect the severity of AP patients [18].Its possible protective mechanisms include: 1) Maintaining the integrity of the intestinal mucosal barrier by promoting the expression of Occludin (ZO-1); 2) Its metabolites (such as lactic acid and butyric acid) can inhibit the TLR4/NF-κB/NLRP3 pathway, regulate macrophage polarization, and exert anti-inflammatory and immunomodulatory effects; 3) Competitively inhibit pathogenic bacteria and alleviate the severity of the disease. Supplementing probiotics (such as bifidobacterium and Lactobacillus) or fecal microbiota transplantation (FMT) to increase the abundance of intestinal probiotics has shown potential in improving the intestinal mucosal barrier, reducing inflammatory responses and lowering the rate of organ failure in both animal models and some clinical studies. However, more high-quality clinical studies are still needed to prove its effect in reducing the mortality rate of SAP [19].

2.2.3 Imbalance in the ratio of microbiota structure:

The ratio of Bacteroidetes to Firmicutes (B/F ratio) is an important indicator of intestinal homeostasis, and the balance between the two is crucial for digestive and metabolic functions. In healthy individuals, the B/F ratio is 0.5 to 1.0. The B/F ratio was significantly decreased (<0.3) in patients with AP and was a sensitive indicator of intestinal homeostasis disruption. A persistently low B/F ratio (<0.3) is significantly associated with an increased risk of pancreatic necrosis range, organ failure, and infectious pancreatic necrosis (IPN) [20]. Restoring this ratio (>0.8) may significantly alleviate pancreatic inflammation and improve prognosis [21]. Future research needs to further clarify the dynamic variation law of the B/F ratio and its regulatory mechanism. For instance, by integrating metagenomic analysis of the key roles of specific bacterial species (such as Bacteroides fragilis in the genus Bacteroides) in inflammatory pathways, or developing microecological preparations that target and regulate the B/F ratio.

2.2.4 Dysbiosis of fungal communities:

Intestinal microbiota dysbiosis in AP patients includes not

only bacterial dysbiosis, but also fungal dysbiosis. Studies have found that the diversity of intestinal fungal communities in patients with AP is significantly reduced, such as the abundance of Ascomycota and basidiomycota, which is decreased, while the abundance of Candida is significantly increased. Moreover, the Shannon index of fungi is positively correlated with CTSI score and serum WBC and IL-6 levels, and negatively correlated with PCT [22]. It is suggested that dysbiosis of the fungal flora may serve as a prognostic marker for AP. Dietary factors can significantly affect the composition of the fungal flora. After high-fat diet intervention, the α diversity of intestinal fungi ($p<0.05$) increased significantly, and the composition of fungi (β diversity, $p<0.05$) changed significantly [23]. At present, there is no consistent evidence to support the preventive use of antifungal drugs in patients with AP. Therefore, the clinical value of fungal community imbalance as a prognostic marker for AP still requires further in-depth research.

3. Markers of Intestinal Barrier Dysfunction

Systemic inflammation induced by AP can directly damage the tight junction of intestinal mucosal epithelial cells, increase the permeability of intestinal mucosa, lead to bacterial/toxin translocation, activate TLR4/NF-κB pathway, and aggravate pancreatic necrosis and systemic inflammatory response. Thus, intestinal mucosal barrier damage is a central link in the progression of AP to SAP.

3.1 Diamine Oxidase (DAO)

DAO is a cytosolic enzyme in the lamina propria of the intestinal mucosa, which is involved in the catabolism of histamine and polyamines. When the intestinal mucosal barrier is damaged, a large amount of it is released into the blood, and the higher the level, the more serious the intestinal mucosal barrier is damaged. Cheng et al. found that DAO levels began to increase 6 hours after AP, DAO levels were directly related to the severity of AP within 24 hours of hospitalization, DAO could predict gastrointestinal injury (AUC=0.879), and serum DAO levels in SAP patients were significantly higher than those in MAP patients [24]. Clinical observation confirmed that the increase of serum DAO level in AP patients was positively correlated with the severity (such as Ranson score, APACHE II score, BISAP score). Elevated DAO often indicates disruption of the intestinal mucosal barrier, and bacteria and endotoxin in the gut penetrate the intestinal mucosa into the portal vein system and lymphatic system. These PAMPs further activate the systemic immune system, exacerbate local and systemic pancreatic inflammatory responses, and form a cycle of "pancreatitis-intestinal injury-infection/sepsis-aggravation of pancreatitis", which significantly increases the incidence and mortality of MOF. DAO combined with angiopoietin-2 (Ang-2) can improve the predictive efficacy of MOF (AUC=0.89) [25]. Therefore, dynamic monitoring of serum DAO level is of great value in judging the prognosis of AP.

3.2 Tight Junction Protein (ZO-1, Occludin)

Tight junction proteins are key structural proteins that maintain the integrity of the intestinal mechanical barrier. In pancreatic acinar cells, the tight-junction barrier formed by these proteins is essential to prevent the abnormal release of digestive enzymes into the tissue space. Experimental AP model showed that the distribution of ZO-1 and Occludin in pancreatic acinar cells was disordered, the expression was down-regulated or the phosphorylation was abnormal before the inflammation occurred [26]. The level of tight junction proteins in serum or tissues of AP patients is decreased, and it is negatively correlated with the severity of AP [27]. Quercetin or sodium butyrate can restore the expression of tight junction proteins by inhibiting the TLR4/MyD88/p38 MAPK signaling pathway, thereby improving the prognosis of AP [28]. Tight junction proteins are not only an indicator of the severity of AP, but also a potential therapeutic target. In the future, whether ZO-1/Occludin degradation products or related signaling molecules in serum or tissues can be used as new biomarkers to evaluate the severity and prognosis of AP can be further explored. The possibility of intervening the AP process by protecting or repairing the tight junction (TJ) barrier (such as using antioxidants, specific anti-inflammatory molecules, ERS regulators, and autophagy regulators, etc.) can also be studied.

3.3 D-Lactic Acid (DLA)

DLA is mainly metabolized by intestinal bacteria, and its serum concentration is closely related to the integrity of intestinal barrier function. The serum D-lactate level in healthy people was very low (<0.2mmol/L). In the process of the occurrence and development of AP, the intestinal permeability increases and D-lactate enters the blood through the damaged mucosal barrier, which may aggravate the systemic inflammatory response by activating a variety of signaling pathways and lead to multiple organ dysfunction. The study by Su et al. showed that serum D-lactate levels peaked after 12 hours after AP [29]. In another AP animal model experiment, the blood DLA level of SAP rats was significantly increased at 0 h, 48 h and 72 h ($P<0.001$), rhubarb treatment at 0h could significantly reduce DLA level and effectively improve intestinal injury and mucosal barrier function [30]. DLA may be used as a serum marker to guide early intervention. Zeng et al. found that Escherichia and Shigella were positively correlated with DLA, and Escherichia coli may aggravate ileal histological damage and intestinal barrier dysfunction through TLR4-ERS axis [31]. The decrease of D-lactate after FMT is synchronized with the recovery of barrier function, which further demonstrates the value of DLA in reflecting intestinal injury. DLA may be used as a potential biomarker for early identification of SAP and assessment of disease severity.

3.4 Lipopolysaccharide (LPS)

Outer membrane components of LPS Gram-negative bacteria, reflecting flora translocation and metabolic endotoxemia. LPS enters the blood through intestinal mucosal epithelium translocation, binds to Toll-like receptor 4 (TLR4) and myeloid differentiation factor 2 (MDα2), and activates TLR4/NF-κB and other inflammatory pathways to aggravate systemic inflammation and multi-organ damage (such as lung injury) [32]. LPS can also interact with metabolites of intestinal flora to drive inflammatory cascades, and increased serum LPS levels are positively correlated with the severity of AP (especially SAP) [17]. LPS/TLR4 signaling pathway is

the core bridge connecting intestinal barrier destruction, endotoxemia and excessive inflammatory response in acute pancreatitis. TLR4 gene deletion mice aggravate the dysbacteriosis and the severity of AP due to abnormal LPS signaling pathway. Butyrate supplementation can reduce the level of LPS and reduce intestinal injury. Therefore, interventions targeting LPS/TLR4 signaling pathway, such as removing LPS, blocking TLR4 or its downstream signaling molecules, and protecting the intestinal barrier, are important therapeutic targets for AP.

4. Disorder and Regulation of Microbiota Metabolic Products

Microbiota metabolites are active molecules produced by intestinal microorganisms through the fermentation of substrates such as dietary fiber, and their metabolic activities are highly interrelated, and they are key mediators of "gut-pancreatic axis" communication, and their disorders are deeply involved in AP progression.

4.1 Short-chain Fatty Acids (SCFAs)

SCFAs (such as butyric acid, propionic acid, and acetic acid) have strong anti-inflammatory and intestinal barrier maintenance effects and are important energy sources for intestinal epithelial cells. The level of SCFAs is negatively correlated with the severity of AP and the risk of MOF [9]. Compared with MAP, SAP has fewer beneficial bacteria that can produce SCFAs and a weaker glycolytic capacity, which are characteristic changes in the intestinal microbiome of SAP patients. Supplementing SCFAs (such as sodium butyrate) or probiotics/prebiotics that promote their production (such as oligosaccharides and llose) can alleviate pancreatic inflammation, repair the intestinal barrier, and lower infection and mortality rates through mechanisms such as inhibiting the TLR4/NF-κB pathway, up-regulating tight junction protein expression, and reducing neutrophil infiltration [33]. After treatment, the differential metabolic pathways with increased microbiota abundance in AP patients (such as the Clostridium butyricum acid-producing fermentation pathway) [16] promote the production of SCFAs, thereby alleviating the symptoms of pancreatitis. Clinical trials have shown that supplementing dietary fiber can shorten the recovery time of intestinal function (4.0 days vs. 2.0 days), and significantly reduce the levels of DAO, DLA, and LPS in AP patients ($P < 0.05$) [34]. Increasing the production of SCFAs or supplementing SCFAs are important targets for promoting the recovery of intestinal function in patients with AP.

4.2 Tryptophan Metabolites:

Tryptophan metabolites are mainly regulated in homeostasis through the kynurenine pathway and the 5-hydroxytryptamine pathway, and their metabolic balance is crucial for maintaining immune and neurological functions. The depletion of tryptophan is positively correlated with the severity of AP. The ratio between 3-hydroxykyrenurine and tryptophan is positively correlated with the severity of AP, and the change occurs earlier than that of CRP. Activation of the kynurenine pathway is associated with pancreatic necrosis and MOF. A reduction in beneficial indole derivatives (such as indole-3-propionic acid) often indicates an increased risk of infection or death in patients with AP [35]. Studies suggest that tryptophan metabolites (such as certain indole derivatives) can activate the SIRT3-PRDX5 pathway by inhibiting histone deacetylase (HDAC), thereby increasing histone acetylation of specific genes like Rftn1. This can inhibit the activation of M1 macrophages, regulate lipid metabolism, reduce inflammation and apoptosis, and improve prognosis [36]. Inhibiting kynurenine 3-monooxygenase (KMO) can reduce the accumulation of toxic metabolites, significantly improve pancreatic injury, and prevent the occurrence of MOF.

4.3 Trimethylamine Oxide (TMAO)

TMAO significantly increases when AP occurs and is closely related to inflammatory responses, oxidative stress and pancreatic cell apoptosis. Research has found that in hyperlipidemic AP, TMAO produced by intestinal microbiota metabolism aggravates pancreatic inflammation, oxidative stress and apoptosis by activating pathways such as TLR4/p65, and its level is positively correlated with the severity of AP, the extent of pancreatic necrosis and the risk of organ failure [37, 38]. TMAO is also associated with cardiovascular complications of AP, possibly related to its stimulation of the expression of tumor necrosis factor -α, interleukin (IL) -6 and IL-1β. The current view holds that TMAO is a biomarker of significant clinical importance in the early diagnosis, severe stratification and prognosis assessment of AP.

4.4 Bile Acids (BAs)

During AP, dysbiosis of the microbiota leads to a reduction in the production of secondary bile acids and an accumulation of primary bile acids, activating inflammatory signaling pathways in the pancreas and liver. These pathways participate in the pathophysiological regulation of AP through the "gut-liver axis" and the "gut-pancreatic axis", thereby exacerbating pancreatic injury [39]. A reduction in secondary bile acids or an imbalance in the proportion of primary bile acids is associated with a poor prognosis of AP. Guo et al. found through metabolomics that the concentration of BAs significantly decreased in the acute phase of AP and greatly increased in the recovery phase. The expression level of sulfocholic acid (TCA) was significantly elevated in MSAP. Taurodeoxycholic acid (TCDCA) and TCA were significantly correlated with SAP and positively correlated with serum calcium [40]. TCDCA and TCA can aggravate pancreatic injury by activating trypsinogen and inducing mitochondrial dysfunction, etc. Some BAs counteract these effects by inhibiting apoptosis, and thus have the potential to alleviate disease progression. Supplementation of exogenous bile acids or regulation of the microbiota to restore bile acid metabolic homeostasis has shown protective effects in animal models [41]. Bile acids, as mediators of the interaction between the intestinal flora and the pancreas, their metabolic profile changes can not only reflect the severity of AP, but also may become biomarkers for predicting pancreatic necrosis, organ failure and clinical prognosis. Their clinical translational value still needs to be explored.

5. Therapeutic Strategies Based on the Regulation of Intestinal Flora

5.1 Microecological Preparations

The use of microecological preparations in patients with AP not only regulates the intestinal flora, such as increasing probiotics like Lactobacillus and Bifidobacterium, but also regulates lipid metabolism-related transcription factors through lipid assimilation and adsorption, influencing lipid transport and absorption, improving lipid metabolic homeostasis, and achieving lipid-lowering effects [42]. Liu The latter is of great significance for hyperlipidemic AP. Liu et al. ‘s research confirmed that supplementing probiotics can lower triglyceride levels and thereby improve lung damage caused by AP [43]. In addition to supplementing probiotics, the supplementation of prebiotics and synbiotics is also widely used in the treatment of AP patients. Prebiotics such as fructooligosaccharides and lactulose can promote the proliferation of beneficial bacteria and the production of SCFAs, improve intestinal mucosal barrier function and regulate intestinal immune homeostasis, and alleviate pancreatic injury [44]. Many strains of the gut microbiota show heterogeneity, demonstrating genomic diversity. For instance, different strains of Escherichia coli have distinct functions, ranging from those promoting food digestion and probiotic effects to those mediating intestinal invasion. Therefore, the future direction of supplementing microecological preparations during AP treatment is individualized and precise microbiota regulation. For instance, the integration of multi-omics technologies (metagenomics, metabolomics) and artificial intelligence can be utilized to analyze the microbiota metabolic characteristics of AP patients, thereby achieving individualized and differentiated treatment. Supplement specific functional strains (such as Bifidobacterium lactis V9 and Lactobacillus P8 with lipid-lowering effects); Develop novel microecological preparations targeting metabolic pathways (such as the SCFAs-TLR4 axis), etc.

5.2 Early Enteral Nutrition (EEN)

Current research suggests that EEN can effectively maintain the integrity of the intestinal mucosal barrier and immune function in patients with AP, maintain the balance of intestinal flora, stimulate intestinal peristalsis, increase visceral blood volume, and reduce bacterial transmigration, thereby promoting the recovery of AP patients and reducing the incidence and mortality of SAP [45]. The best time to start EEN is still controversial at present. Scholars from the Nutrition society suggest initiating EEN within 24 hours after admission to AP patients to ensure they receive recombinant enteral nutrition and energy supply, thereby reducing disease progression and promoting recovery. However, considering that the severe inflammatory response in the early stage leads to intestinal ischemia and hypoxia, premature enteral nutrition may instead aggravate intestinal damage and microbiota translocation, etc., some scholars suggest initiating it within 48 to 72 hours after admission to AP patients. The condition of AP patients can vary from mild to severe, and the disease progresses and changes rapidly. For different AP patients, a reasonable EEN treatment plan should be selected on an individualized basis to promote the repair of the intestinal mucosal barrier and exert its immune function, ultimately achieving the effect of improving the condition of AP patients and promoting their recovery. In addition, the formula of EEN is currently a research hotspot: for instance, adding probiotics (such as bifidobacteria), prebiotics (such as oligosaccharides), and immune nutrients (glutamine, arginine, omega-3 fatty acids) can promote the repair of the intestinal mucosal barrier and alleviate systemic or local inflammatory responses in patients with AP [46, 47]. The research also found that obese AP patients benefit more significantly from EEN. For instance, the addition of the prebiotic inulin can effectively improve pancreatic necrosis and systemic inflammatory responses, and increase the abundance of SCFAs and probiotics [48]. The mechanism may be related to the fact that microecological preparations can participate in regulating the “gut-pancreatic axis”.

5.3 Fecal Microbiota Transplantation (FMT)

In recent years, fecal microbiota transplantation technology, as an innovative therapy for regulating intestinal microecology, has gradually attracted attention for its potential in the treatment of AP, but its clinical application is still in the exploration stage. FMT reshapes the intestinal microecology of patients by transplanting the microbiota of healthy donors. Some studies (including case reports and small-scale clinical studies) have reported that FMT or washing microbiota transplantation (WMT) can increase beneficial bacteria in the intestines of AP patients, reduce inflammatory indicators, lower the incidence of MOF in AP patients, and improve the prognosis of SAP patients [49, 50]. However, the research results of some randomized controlled trials did not observe the benefit of FMT in the treatment of AP, and even suggested potential risks, such as the discovery of elevated D-lactic acid in patients, etc [51]. Zhu et al. ‘s research found that FMT on AP experimental mice aggravated pancreatic injury and led to deterioration of the AP condition in mice [52]. Therefore, the efficacy, safety, optimal timing, donor selection and transplantation approach of FMT in the treatment of AP all require large-scale, high-quality multi-center RCTS and in-depth mechanism studies to be clarified.

5.4 Regulation of Traditional Chinese Medicine

At present, Western medicine mainly treats AP with fluid resuscitation, nutritional support and inhibition of pancreatic enzyme activity, but there is a lack of specific targeted drugs. In recent years, traditional Chinese medicine has demonstrated unique advantages in the treatment of AP by regulating the balance of intestinal flora. Its multi-target and multi-pathway mechanism of action provides new ideas for the clinical management of AP. Research indicates that both traditional Chinese medicine compound prescriptions (such as Dachengqi Decoction, Qingyi Decoction, Qingjie Huagang Decoction, and Dachahu Decoction) and single drugs (Rhubarb, Salvia miltiorrhiza, Gardenia, and Mirabilis) have good auxiliary effects on the treatment of AP. The possible mechanisms include: regulating the microbiota structure (reducing pathogenic bacteria such as Escherichia coli - Shigella and increasing beneficial bacteria such as Lactobacillus), repairing the intestinal mucosal barrier (reducing DAO, D-lactic acid and upregulating tight junction proteins), inhibiting inflammatory pathways (such as NLRP3 and MAPK), improving microcirculation, etc. [53, 54]. Dachengqi Decoction shortens the first defecation time of AP patients and significantly reduces the levels of CRP, PCT and IL-6 in AP patients [55]. Network pharmacology studies have

revealed its complex mechanism of action, such as the regulation of multiple signaling pathways and apoptosis by Qingyi Decoction, effectively alleviating the inflammatory storm and pancreatic edema in patients with AP and reducing the severity of AP [54]. The integrated model of traditional Chinese and Western medicine (such as the combination of traditional Chinese medicine with hemofiltration and the supplementation of probiotics, etc.) has broad prospects. However, at present, traditional Chinese medicine (TCM) treatment for AP also faces many challenges. The mechanism of TCM compound preparations in treating diseases is often rather complex, and high-quality clinical evidence (especially large-sample RCTs) is relatively insufficient at present. In the future, it is necessary to combine multi-omics technology to deeply analyze the interaction mechanism of "TCM - microbiota - host", and promote the standardized application of TCM in the treatment of AP.

6. Summary and Outlook

Biological markers related to the gut microbiota, with their significant advantages of being non-invasive and dynamically monitorable, have the potential to become new indicators for the early risk stratification, severity assessment and prognosis prediction of AP. Therapeutic strategies based on microbiota regulation, such as microecological preparations, optimized EEN, FMT/WMT, and traditional Chinese medicine treatment, have shown certain clinical transformation potential in the treatment of AP, especially in maintaining the integrity of the intestinal mucosal barrier and reducing the inflammatory response of AP patients. However, its clinical application still faces challenges: 1) Insufficient standardization of microbiota detection (such as sample collection, DNA extraction, sequencing platforms and bioinformatics analysis, etc.); 2) Dynamic monitoring is costly (frequent detection of microbiota and metabolomics increases medical burden); 3) Individual differences interfere with prediction (such as genetic factors, dietary factors, whether AP patients use antibiotics, etc.); 4) Transformation bottleneck: Most mechanism research and intervention effect evidence are derived from animal models. There is an urgent need to design rigorous large-scale population studies (especially multi-center RCTS) to verify their clinical efficacy, safety and cost-effectiveness. The efficacy and mechanism of FMT, new microecological preparations and traditional Chinese medicine compound prescriptions need to be explored more deeply. 5) Innovative therapeutic targets: Targeted intervention research on fungal communities, specific strain-metabolite axes, and bile acid-microbiota interactions is still in its infancy.

The study of gut microbiota has opened up a new perspective for understanding the pathophysiological mechanism of AP, and its related biological markers and treatment strategies represent an important development direction for the precise management of AP. Overcoming existing challenges, deepening mechanism research and accelerating clinical transformation are expected to significantly improve the prognosis of AP patients.

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