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Basic Research on ANCA Positivity in Ulcerative Colitis

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Abstract: *Ulcerative colitis (UC) is a chronic non-specific inflammatory bowel disease with incompletely elucidated pathogenesis, presenting with chronic abdominal pain, diarrhea and mucopurulent-bloody stools. Its lesions, confined to the colorectal mucosa and submucosa with continuous-diffuse distribution, may extend proximally to the whole colon and terminal ileum. UC develops from the interplay of environmental, genetic and gut microecological factors, and its incidence is rising globally, with distinct epidemiological differences between Western and Asian populations. Anti-neutrophil cytoplasmic antibodies (ANCA), including perinuclear ANCA (pANCA) and cytoplasmic ANCA (cANCA), are autoantibodies against neutrophil-monocyte cytoplasmic components. ANCA seropositivity occurs in 20%-60% of UC patients, predominantly the pANCA subtype, and is associated with more severe disease, higher relapse risk and frequent complications. Though ANCA serves as a signature marker for ANCA-associated vasculitides, accumulating data have detected serum PR3-ANCA and pANCA in 40%-70% of UC cases. The exact pathogenic roles of ANCA in UC remain controversial. Based on updated evidence, this review systematically summarizes the diagnostic utility, pathological mechanisms, clinical correlates and therapeutic implications of ANCA in UC.*

Keywords: *Ulcerative Colitis; Anti-Neutrophil Cytoplasmic Antibody (ANCA); Proteinase 3-ANCA (PR3-ANCA); Neutrophil Extracellular Traps (NETs)*

1. Diagnostic Value of ANCA for UC

1.1 Differentiation between Ulcerative Colitis (UC) and Crohn's Disease (CD)

As the main subtypes of inflammatory bowel diseases (IBDs), accurate differentiation between UC and Crohn's disease (CD) is crucial for clinical treatment decisions and prognosis evaluation. In recent years, the value of ANCA typing detection in IBD classification diagnosis has become increasingly prominent. Liron Birimberg-Schwartz et al. systematically evaluated the diagnostic utility of pANCA and ASCA in IBD-unclassified (IBDU), Crohn's colitis (CC), and UC in a multicenter retrospective study of 406 pediatric IBD patient[s[2]. The study found that the positive rate of pANCA was significantly higher in UC patients than in CD patients (64% vs. 30%), while the positive rate of ASCA was significantly higher in CC patients than in UC patients (40% vs. 6%). Although the pANCA+/ASCA− combination had a 94% positive predictive value for UC, its limitations in sensitivity (65%) and specificity (66%) suggest that a single serological marker is insufficient to independently differentiate IBD subtypes[2]. Notably, the study by Michael P. Horn's team further revealed the unique value of PR3-ANCA in pediatric UC. By analyzing serological data from 61 pediatric IBD patients, PR3-ANCA showed a diagnostic specificity of up to 93% and a sensitivity of 58% for UC, with a positive predictive value of 90%, and was significantly associated with extensive colonic lesions [3]. The study also constructed a four-antibody diagnostic model including PR3-ANCA, xANCA, pANCA, and ASCA IgG, which achieved an AUC of 90.8% in the training cohort and remained 84.1% in the validation cohort, significantly outperforming traditional marker combinations and providing a new strategy for early precise classification of pediatric IBD[3] .

Domestic studies in the Chinese population also confirmed the value of ANCA typing in differentiating UC from CD. Xu Y et al. found that the positive rate of PR3-ANCA was significantly higher in Chinese UC patients than in CD patients, and this antibody was associated with the extent of colonic lesions in UC patients, with a higher positive rate in total colitis UC patients[4]; a retrospective

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study by Zhang S et al. also showed that combined detection of pANCA and ASCA could improve the accuracy of subtype differentiation in Chinese IBD patients to 78%, significantly higher than single marker detection[5]. In addition, Tang H et al. found that ANCA subtypes were correlated with disease phenotypes in IBD patients, and UC patients positive for PR3-ANCA were more likely to present with mucopurulent bloody stools and severe colitis, providing clinical phenotypic references for differential diagnosis[6].

Both studies indicate that ANCA typing (especially PR3-ANCA) has important value in UC diagnosis, but its clinical application needs to be combined with multi-antibody combinations to improve diagnostic efficiency. In addition, serological markers have limited predictive value for disease behavior; for example, dual ASCA positivity is associated with a complex disease course in CD, while pANCA+/ASCA− may indicate that UC patients require more aggressive biologic therapy [2][3]. Anti-glycan antibodies such as anti-GP2 and ASCA have likewise been linked to a more complicated disease course in IBD[7] ,whereas in a population-based cohort ASCA was only modestly more common among individuals who later developed Crohn's disease, indicating that a single serological marker has limited predictive value[8].Future large-scale prospective studies are needed to verify the dynamic changes of these markers and their correlation with treatment response to further optimize the individualized diagnosis and treatment pathway of IBD.

1.2 Association with Other Diseases

Existing research shows that ANCA positivity is not only related to the type and severity of UC but also may indicate a higher risk of concurrent other autoimmune diseases, reflecting the shared immune disorders among autoimmune diseases [1][2]. For example, ANCA has a clear pathological association with vasculitis: PR3-ANCA is a specific marker of typical ANCA-associated vasculitides such as granulomatosis with polyangiitis (GPA), and PR3-ANCA can also be detected in UC patients [3][9][10][11]. This overlap in target antigens suggests that UC and vasculitis may share similar immune response patterns—abnormal activation of neutrophils producing autoantibodies that attack vascular endothelium and intestinal mucosa[2]. Clinically, UC and ANCA-associated vasculitides often coexist; for example, a study investigated the comorbidity of ANCA-associated vasculitides and IBD[1], and cases have reported that PR3-ANCA-positive UC patients present with leukocytoclastic vasculitis, manifesting as cutaneous purpura and arthritis [14][15]. At a deeper level, UC and vasculitis share common immune mechanisms: both involve immune system "dysregulation"—loss of tolerance to self-tissues. UC patients produce autoantibodies against various myeloid granule proteins (such as PR3), and this extensive immune abnormality may damage both the intestine and blood vessels [10][11]; in addition, genetic and environmental factors play a role, such as genes including *TNFRSF1B* that may affect the susceptibility to both diseases [13], and environmental factors such as intestinal flora disturbance may amplify autoimmune responses [12].

Extraintestinal complications of PR3-ANCA-positive UC are not limited to vasculitis. Multiple clinical case reports have found various rare extraintestinal manifestations, such as Ishikawa T et al. reporting a PR3-ANCA-positive UC patient with aseptic nasal septal abscess and phlebitis, with clinical features highly similar to GPA[16]; Kirito Y et al. reported a PR3-ANCA-positive UC patient with abducens neuropathy, suggesting that ANCA-mediated immune injury can involve the nervous system[17]; Yang CW et al. reported an adolescent PR3-ANCA-positive UC patient presenting with recurrent intestinal pseudo-obstruction, with PR3 expression confirmed by immunohistochemistry in the lesion [18]. Yashiro K et al. also described nodular scleritis accompanied by pyoderma gangrenosum in a patient with active UC, indicating that ocular involvement may occur as an extraintestinal manifestation of UC[19].These cases all indicate the systemic immune injury characteristics of ANCA-positive UC. In addition, ANCA is closely related to primary sclerosing cholangitis (PSC). Hov JR et al. found that ANCA-positive PSC patients were more likely to have concurrent UC, and these patients had faster liver fibrosis progression [20]; Guglielmi V et al. further confirmed that pANCA can be used as a prognostic predictor for PSC patients with UC, with a significantly higher incidence of biliary stricture in positive patients [21].

This association has important reminders for clinical diagnosis and treatment. First, special attention should be paid during diagnosis: the detection rate of low-titer PR3-ANCA in UC patients can reach 18%–57.6%[22], which may interfere with the judgment of vasculitis. Therefore, laboratory examinations should be more detailed; for example, in suspected vasculitis, high-titer PR3-ANCA is more likely to indicate GPA, while low-titer PR3-ANCA should alert to UC; detection methods also matter—chemiluminescence is more sensitive for UC-related PR3-ANCA, with a lower detection rate by enzyme-linked immunosorbent assay [23][24]. In treatment and management, ANCA-positive UC patients with

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symptoms such as cutaneous purpura and renal dysfunction should be screened for vasculitis in a timely manner[14]; such patients may require dual immunosuppressive therapy such as glucocorticoids combined with biologics, and care should be taken to avoid recurrence of vasculitis induced by drugs such as azathioprine[12]. In addition to PR3-ANCA, UC patients have other ANCA subtypes such as anti-cathepsin G antibodies, and exploring the significance of these subtypes may better predict comorbidity risks [11][26]. However, current research on comorbidity mechanisms is mostly cross-sectional, and long-term follow-up cohort studies are needed to clarify the risk and predictive factors (such as changes in antibody titer) of vasculitis in ANCA-positive UC patients[22][25].

2. Correlation between ANCA and UC Disease Activity and Prognosis

2.1 Assessment of Disease Activity

In recent years, the importance of ANCA in assessing UC disease activity has gradually increased. As an autoantibody, ANCA mainly targets proteinase 3 (PR3) and myeloperoxidase (MPO), among which PR3-ANCA plays a particularly prominent role in UC [3][9][10]. Multiple studies have found that PR3-ANCA levels are closely related to UC disease activity and can be used as an important indicator for assessing UC activity[11][26] .For example, PR3-ANCA-positive patients have significantly higher Mayo scores (a common index comprehensively evaluating UC activity based on symptoms, signs, endoscopic findings, and histology) and endoscopic severity scores than negative patients[11]. PR3-ANCA-positive UC patients exhibited significantly higher disease-activity-related Mayo and endoscopic scores than PR3-ANCA-negative counterparts. Moreover, the higher the PR3-ANCA titer, the more severe the mucosal injury, indicating that it can not only assist in the diagnosis of UC but also reflect disease activity [11] [26].

Prospective cohort studies further verified the value of ANCA in assessing UC disease activity. Kovacs G et al. followed up UC patients for a long time and found that dynamic changes in PR3-ANCA titer were closely related to disease recurrence; patients with a ≥2-fold increase in titer had a 3.2-fold higher risk of disease recurrence within 6 months [28]; Xu Y et al. reached a similar conclusion in Chinese UC patients, with PR3-ANCA titer positively correlated with fecal calprotectin levels, which can be used as a non-invasive indicator for assessing intestinal mucosal inflammation [4]. In addition, a pediatric IBD study by Kim JM et al. showed that PR3-ANCA-positive pediatric UC patients had significantly higher disease activity scores than negative patients and were more likely to have moderate to severe colitis, suggesting that this antibody is also an effective indicator of disease activity in the pediatric population [22].

This correlation has practical clinical value, as detecting PR3-ANCA can help doctors judge the condition more accurately and formulate personalized treatment plans [22]. For example, PR3-ANCA-positive patients may require more aggressive treatment to control inflammation, while negative patients may be managed with relatively mild strategies [26]. In short, PR3-ANCA plays an important clinical role in the diagnosis and daily management of UC, providing valuable references for both doctors and patients [11] [27].

2.2 Prediction of Treatment Response

In recent years, more and more studies have shown that ANCA, especially PR3-ANCA, has important value in predicting treatment response in UC patients. Aoyama Y et al. demonstrated that PR3-ANCA positivity was significantly associated with poor response to glucocorticoid therapy in patients with moderate-to-severe UC [26]. In their cohort, PR3-ANCA positivity was more frequent among steroid non-responders, and multivariate analysis identified PR3-ANCA positivity as an independent risk factor for steroid-refractory disease [26]. Imakiire S et al. (2022) further confirmed that PR3-ANCA titers were moderately positively correlated with endoscopic disease severity in UC patients ($r=0.356$, $P<0.001$) [11]. Higher PR3-ANCA levels were observed in patients with more severe disease phenotypes, although the study did not report risk estimates for individual severe complications such as toxic megacolon or intestinal perforation.

Notably, Li D et al. first proposed an association between *TNFRSF1B* gene polymorphism and ANCA-positive UC, finding that *TNFRSF1B* variants were more common in ANCA-positive patients and associated with poor response to TNF inhibitor therapy [13]. The same study further found that combined assessment of PR3-ANCA serostatus and *TNFRSF1B* genetic variants may help improve the prediction of anti-TNF therapeutic response in IBD patients, providing an important basis for

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individualized treatment strategies for UC patients[13]. In addition, In a pediatric IBD cohort, Laass MW et al. (2022) observed that PR3-ANCA positivity was significantly more common among children with UC-associated primary sclerosing cholangitis (PSC) compared with UC patients without PSC (68.2% versus 30.8%, P=0.0014) [10]. This finding indicates that PR3-ANCA is closely linked to PSC in paediatric ulcerative colitis.. Mumtaz S et al. noted in a 2024 review that ANCA-positive UC patients are more prone to systemic vasculitis manifestations, with more complex conditions and greater treatment difficulty, requiring multidisciplinary collaborative management [1]. Abu-Freha N et al. found in the Bedouin Arab population that the ANCA positive rate in UC patients was significantly higher than in other ethnic groups, and was closely related to disease severity and extraintestinal manifestations, suggesting that ethnic genetic background may affect ANCA expression and its predictive value for treatment response [29]. Kim JM et al. pointed out in a pediatric IBD study that PR3-ANCA has high specificity in differentiating UC from CD, with a positive rate of 42% in pediatric UC patients and only 8% in pediatric CD patients (P<0.001); this antibody can be used as an auxiliary diagnostic tool to further guide treatment decisions [22].

ANCA status is also related to the response to biologic therapy in UC patients. An early study by Kevans D et al. found that ANCA-positive UC patients had a significantly lower response rate to TNF inhibitors than negative patients and were more likely to develop secondary loss of response[30]; for UC patients undergoing surgery, Kelly OB et al. found that ANCA-positive patients had a higher incidence of postoperative pouchitis and a poorer response to infliximab [31]. In addition, the predictive value of ANCA for treatment response varies among ethnic groups. A Moroccan population study by Abakarim O et al. showed that ANCA-positive UC patients had a lower response rate to 5-aminosalicylic acid drugs and were more likely to require escalation to immunosuppressive therapy [32], consistent with findings in the Bedouin Arab population [29], suggesting that ethnic factors should be included in the treatment response prediction system.

In summary, ANCA, especially PR3-ANCA, has important value in predicting treatment response in UC patients. Combined detection of ANCA with other biomarkers (such as *TNFRSF1B*) can further improve prediction accuracy and provide an important basis for individualized treatment of UC patients.

3. The Role of ANCA in the Pathogenesis of UC

3.1 Neutrophil Extracellular Traps and Inflammatory Amplification

In the past 5 years, with the deepening of research on the pathogenesis of UC, ANCA has been found to play a key role, especially by inducing neutrophils to release Neutrophil Extracellular Traps (NETs) to amplify intestinal inflammation. Wen C et al. first revealed the interaction mechanism between ANCA and NETs in an experimental colitis model. They found that ANCA can specifically bind to antigens on the surface of neutrophils, activate intracellular signaling pathways, and then induce neutrophils to release NETs [12]. NETs are reticular structures composed of DNA, histones, and antimicrobial peptides. Although they have the function of capturing and killing pathogens under normal conditions, their excessive release in UC patients leads to continuous damage to the intestinal mucosa and aggravated inflammatory response.

Further studies found that targeted inhibition of neonatal Fc receptor (FcRn) can significantly accelerate ANCA clearance, thereby reducing NET formation. Experimental data from Wen C et al. showed that after FcRn inhibition, the colonic histopathological score of experimental animals decreased significantly from an average of 8.5 to 4.2 (P<0.001), with significantly reduced intestinal mucosal inflammation, ulcer formation, and inflammatory cell infiltration [12]. In addition, the expression levels of NET markers (such as extracellular DNA and histones) in intestinal tissue also decreased significantly, further confirming the mechanism of ANCA-mediated inflammation amplification through NETs.

Roitsch S et al. developed a novel flow cytometry detection method based on NETs, which can more sensitively detect the interaction between ANCA and NETs[23]. Deutschmann C et al. identified chitinase-3-like protein 1 (CHI3L1) as a novel neutrophil antigenic target in Crohn's disease[33]. This technique provides an important tool for in-depth study of the mechanism of ANCA-induced NETs and a new method for clinical monitoring of inflammatory activity in UC patients. In addition, Aoyama Y et al. demonstrated that PR3-ANCA positivity was associated with poor response to glucocorticoid therapy in patients with moderate-to-severe UC[26]. Accumulating evidence indicates that NETs are not only involved in the inflammatory amplification process of UC but may also serve as potential biomarkers for assessing disease severity. Imakiire S et al. further pointed out that PR3-ANCA-positive patients are

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more prone to severe intestinal mucosal damage and extraintestinal manifestations such as primary sclerosing cholangitis (PSC), which may be related to chronic inflammation and tissue damage caused by continuous NET release [11], further emphasizing the potential role of NETs in extraintestinal manifestations of UC. Meanwhile, Mumtaz S et al. systematically summarized the common pathological mechanism of ANCA and NETs in UC and ANCA-associated vasculitides [1]. They pointed out that excessive NET release is not limited to the intestinal mucosa but can also lead to systemic vasculitis, suggesting that NETs may be a bridge connecting intestinal inflammation and extraintestinal manifestations. In a case of adolescent UC with systemic small-vessel vasculitis reported by Bouhuys M et al., PR3-ANCA and NET markers were detected simultaneously in the patient's lesion tissue, further confirming this mechanism [34].

In general, ANCA can significantly amplify intestinal inflammation in UC patients by inducing NET release and may lead to the occurrence of extraintestinal complications. Therefore, intervening in the interaction between ANCA and NETs, such as targeted inhibition of FcRn to accelerate ANCA clearance, is expected to fundamentally alleviate inflammation in UC patients and improve disease prognosis. In the future, further exploring the role of NETs in the pathogenesis of UC and developing targeted therapeutic strategies against NETs will provide new research directions for precise treatment of UC.

3.2 Genetic and Immune Regulation

Genetic factors play a key role in the occurrence and development of ANCA-positive UC by affecting the regulatory balance of the immune system, indirectly changing disease susceptibility, phenotypic characteristics, and progression trajectory. Studies focusing on the association between *TNFRSF1B* gene polymorphism and ANCA-positive UC have found a significant correlation between them [13]. *TNFRSF1B* encodes tumor necrosis factor receptor superfamily member 1B (TNFRSF1B), a cell-surface receptor that plays an indispensable role in regulating immune responses and inflammatory processes.

The study further pointed out that specific *TNFRSF1B* gene variants (such as rs1861513) were significantly more frequent in ANCA-positive UC patients than in the control group, suggesting that these gene variants may affect ANCA production and disease phenotype. Specific data confirm this: genetic variants in *TNFRSF1B* are more frequent among ANCA-positive IBD patients. Carriers of the risk allele displayed lower circulating soluble TNFR2 protein levels, which may partly explain elevated ANCA levels and potential differences in anti-TNF therapeutic response.This clearly indicates that *TNFRSF1B* gene polymorphism not only affects ANCA production but may also exacerbate UC inflammation and increase disease severity [13].

From the perspective of immune regulation, *TNFRSF1B* gene polymorphism may regulate immune cell function and inflammatory factor release by affecting the activation of cell signaling pathways. For example, abnormal activation of TNFRSF1B receptors may lead to excessive production of pro-inflammatory cytokines (such as TNF-α), which further aggravate intestinal mucosal inflammation. In addition, *TNFRSF1B* gene variants may affect the activation state of neutrophils, making them more likely to release NETs and thus aggravating inflammatory damage [13].

Animal model studies further revealed the potential link between TNFRSF1B and ANCA. The study found that targeted inhibition of neonatal Fc receptor (FcRn) can accelerate ANCA clearance, reduce NET formation, and alleviate experimental colitis [12]. This finding suggests that *TNFRSF1B* gene variants may indirectly regulate NET release and inflammatory intensity by affecting ANCA metabolism and clearance efficiency.

In addition, studies on combined detection of PR3-ANCA and *TNFRSF1B* gene variants may help improve the prediction of anti-TNF therapeutic response in IBD patients [13], further highlighting the important value of genetic factors in immune regulation and treatment response prediction. In addition to *TNFRSF1B*, Deutschmann C et al. also found that chitinase-3-like protein 1 (CHI3L1) is a novel neutrophil antigen target in CD [33], and the gene polymorphism of this protein is also related to ANCA expression in UC patients, suggesting that more immune-related genes are involved in the pathogenesis regulation of ANCA-positive UC.

In summary, *TNFRSF1B* gene polymorphism has important significance in the pathogenesis of ANCA-positive UC. Future research can further explore the specific molecular mechanism between *TNFRSF1B* gene variants and ANCA production, and how to regulate immune responses by targeting the TNFRSF1B pathway, so as to provide new targets and strategies for the treatment of UC. At the same time, exploring the association between other immune-related genes and ANCA will help to comprehensively reveal the genetic regulatory network of ANCA-positive UC.

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4. Advances and Challenges in ANCA Detection Technology

4.1 Novel Detection Methods

Traditional indirect immunofluorescence (IIF) has certain subjectivity in ANCA detection, which may affect the accuracy and repeatability of results. In recent years, with the continuous progress of technology, novel detection methods have emerged, bringing new breakthroughs for ANCA detection.

As mentioned earlier, Roitsch S et al. established a proof-of-concept flow-cytometry-based assay that uses neutrophil extracellular traps (NET-coated microbeads) for ANCA detection [23]. This novel approach may mitigate the subjective interpretation limitations of conventional indirect immunofluorescence, although clinical cut-off values and formal diagnostic performance metrics have not yet been established for routine laboratory application. This improvement not only reduces the incidence of false positive and false negative results but also provides a more reliable basis for clinical diagnosis.

In addition, Rodrigues AV et al. optimized the IIF protocol for the Indian population [18]. The study found that adjusting IIF detection conditions and antibody dilution can better meet the detection needs of local populations, highlighting the necessity of establishing population-adapted indirect immunofluorescence assay parameters. Zarur EB et al. further improved the IIF technique by optimizing fluorescently labeled antibodies and incubation conditions, significantly increasing the positive rate of ANCA detection and greatly improving the repeatability of results [35]. This improvement is applicable to ANCA detection in different populations and facilitates detection in primary medical institutions. This result indicates that the establishment of localized detection standards is of great significance for improving detection accuracy, especially in populations affected by different genetic backgrounds and environmental factors.

4.2 Multi-marker Combined Diagnosis

A single marker may have limitations in the diagnosis of UC, while multi-marker combined diagnosis can provide more comprehensive disease information and improve the accuracy of diagnosis and early screening ability. Torres J et al. proposed that combined detection of ANCA with other serological markers, such as anti-glycoprotein 2 antibody (anti-gp2), can predict the occurrence of inflammatory bowel disease (IBD) up to 5 years before symptom onset [36]. Multi-marker serological panels including anti-GP2 can identify individuals at future risk of developing IBD years before clinical symptom onset. This early screening ability is of great significance for early intervention and treatment, which can effectively delay disease progression and improve patient prognosis. Zhang S et al. confirmed that anti-zymogen granule glycoprotein 2 antibody (anti-GP2) has a high positive rate in CD patients, and combined detection with ANCA can further improve the accuracy of IBD subtype differentiation [37].

In addition, multi-marker combined diagnosis can optimize treatment strategies. For example, combined assessment of PR3-ANCA serostatus and *TNFRSF1B* genetic variants may help improve the prediction of anti-TNF therapeutic response in UC patients[13]. This indicates that combined detection of multiple markers can provide more personalized treatment plans for UC patients, improve treatment effects, and reduce unnecessary drug use and side effects. Kim JM et al. also found in a pediatric IBD study that combined detection of PR3-ANCA with other markers (such as ASCA) can more accurately distinguish UC from Crohn's disease (CD), with a significantly higher positive rate of PR3-ANCA in pediatric UC patients than in pediatric CD patients (42% vs. 8%, $P<0.001$) [22].

The application of machine learning technology provides a new idea for multi-marker combined diagnosis. Sokollik C et al used machine learning algorithms to integrate ANCA subtypes, ASCA, and clinical indicators to construct an IBD subtype classification model, with a diagnostic accuracy of 85%, significantly higher than traditional combined detection methods [25]; Wei Y et al. discovered a novel antigen target for CD [38], which further enriches the marker combination when combined with ANCA, providing a new direction for improving diagnostic efficiency.

In general, multi-marker combined diagnosis significantly improves the accuracy of UC diagnosis and early screening ability, can comprehensively assess disease risk and severity, optimize treatment strategies, and guide individualized treatment. In the future, with the discovery of more biomarkers and the progress of detection technology, multi-marker combined diagnosis combined with machine learning will play a greater role in the clinical management of UC.

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5. Therapeutic Implications and Future Directions

5.1 ANCA-Targeted Therapeutic Strategies

ANCA-targeted therapeutic strategies provide new ideas for the treatment of UC, with the core mechanism of blocking its driving effect on intestinal inflammation by regulating ANCA production, clearance, or action pathways. Taking animal studies on neonatal Fc receptor (FcRn) inhibitors as an example, the study focused on the key role of FcRn in ANCA metabolism. By specifically inhibiting FcRn function, accelerated ANCA clearance was achieved. The results showed that experimental colitis model animals treated with FcRn inhibitors had significantly improved colonic histopathological changes—the comprehensive score reflecting mucosal injury, inflammatory cell infiltration, and tissue structure destruction decreased significantly from an average of 8.5 to 4.2 ($P<0.001$), which intuitively proved the reduction of intestinal inflammation, further revealing the molecular logic of FcRn inhibitors exerting anti-inflammatory effects by reducing ANCA levels, providing animal experimental evidence for subsequent clinical application [12].

In addition to targeted biologics such as FcRn inhibitors, the anti-inflammatory and antioxidant properties of natural products also provide potential therapeutic directions for ANCA-related inflammatory pathways, with the advantages of multi-target regulation and low toxic and side effects. Taking studies on *Musa acuminata* waste extract and *Thuja occidentalis* mother tincture as examples, these two studies explored the intervention effects of plant-derived components on intestinal inflammation [39][40]. Among them, the study on *Musa acuminata* waste extract found that its rich polyphenols and other antioxidants can reduce the excessive activation of neutrophils by scavenging reactive oxygen free radicals and inhibiting oxidative stress pathways, and neutrophils are important target cells for ANCA production and action; at the same time, the extract significantly inhibited the release of pro-inflammatory cytokines such as TNF-α and IL-6 in vitro experiments. These cytokines are not only key mediators of intestinal inflammation but may also indirectly enhance the pathogenic effect of ANCA by upregulating the expression of ANCA target antigens (such as PR3). In animal models, colonic inflammation scores decreased significantly from an average of 7.8 to 5.1 ($P=0.01$) after intervention with *Musa acuminata* waste extract, verifying its in vivo anti-inflammatory activity [40]. Another study on *Thuja occidentalis* mother tincture showed that its volatile oil components can regulate the balance of immune cells, reduce the infiltration of pro-inflammatory macrophages, and reduce ANCA-mediated immune damage to intestinal epithelium by enhancing the antioxidant barrier function of intestinal mucosa, providing new candidate substances for adjuvant treatment of ANCA-positive UC [39].

Attention should be paid to potential adverse reactions of biologic therapy in ANCA-positive UC. Rivera-Burgos I et al. reported a UC patient who developed severe antiphospholipid syndrome and diffuse glomerulonephritis after adalimumab use [41], suggesting that ANCA-positive UC patients should be closely monitored for autoimmune complications when using TNF inhibitors; for severe ANCA-positive UC patients unresponsive to drug therapy, surgical treatment is still an important option. A prospective study by Habeeb TAAM et al. showed that laparoscopic restorative proctocolectomy has a good curative effect on ANCA-positive UC patients with extraintestinal manifestations, and the incidence of postoperative hepatobiliary complications is not significantly different from that of negative patients [42].

These findings collectively reveal the diverse potential of ANCA pathway-targeted therapeutic strategies: FcRn inhibitors represent a cutting-edge direction for precise targeted antibody clearance, suitable for patients with high ANCA titers and high inflammatory activity; natural products provide a mild and effective option for mild patients or combined therapy. Future research can further verify the efficacy differences of FcRn inhibitors in UC patients with different ANCA subtypes (such as PR3-ANCA, pANCA) through clinical cohorts, and in-depth analyze the interaction mechanism between active ingredients in natural products and ANCA-related immune pathways. In addition, individualized treatment plans combining ANCA dynamic monitoring and drug dose adjustment will significantly improve the precision and long-term prognosis of UC treatment, providing more safe and effective treatment options for patients.

5.2 Individualized Treatment

Due to their unique immunopathological characteristics, ANCA-positive UC patients often have different responses to conventional treatment, requiring more refined personalized treatment plans.

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Taking the stratified management of pediatric inflammatory bowel disease (IBD) as an example, the study emphasizes the inclusion of ANCA detection results in the clinical decision-making system, especially in optimizing the timing of tumor necrosis factor (TNF) inhibitor use [43]. Accumulated clinical observations indicate that ANCA-positive pediatric IBD patients tend to have poorer responses to glucocorticoid therapy. This difference may be related to the continuous activation of neutrophils mediated by ANCA, making the inflammatory pathway difficult to be completely inhibited by hormones. Based on this, for ANCA-positive UC patients, especially the pediatric population, early introduction of biologics (such as TNF inhibitors) may control inflammation progression more quickly and avoid disease progression caused by hormone resistance. In clinical practice, a multi-dimensional efficacy prediction model can be constructed by combining ANCA detection results with patients' clinical symptoms (such as diarrhea frequency, bloody stool degree), disease activity scores (such as Mayo score), and other serological markers (such as C-reactive protein, fecal calprotectin), so as to more accurately judge the patient's response potential to hormones or biologics and provide a scientific basis for formulating individualized treatment plans.

In addition, the implementation of individualized treatment requires in-depth analysis of the impact of patients' genetic background and immune status on ANCA expression and disease phenotype. Taking the study on the association between *TNFRSF1B* gene polymorphism and ANCA-positive UC as an example, the study found that specific variants of the *TNFRSF1B* gene are closely related to the clinical characteristics of ANCA-positive UC patients—patients carrying this variant not only have higher disease activity scores but also significantly higher serum ANCA titers, indicating that their immune system is in a more active pro-inflammatory state [13]. This finding provides an important clue for optimizing treatment strategies at the genetic level: for ANCA-positive UC patients carrying such gene variants, conventional doses of immunosuppressants may be difficult to effectively control inflammation, and more aggressive immunoregulatory schemes are needed, such as combined use of biologics with different mechanisms of action or adjustment of immunosuppressant doses, to specifically inhibit excessive immune responses driven by gene variants, delay disease progression, and reduce the risk of complications such as intestinal fibrosis and intestinal perforation. For ANCA-positive UC patients with special complications, individualized symptomatic treatment plans need to be formulated. For example, Ohta R et al. reported patients with cytomegalovirus infection complicated with fulminant UC, who need timely antiviral treatment while receiving immunosuppressive therapy [45]; for patients with mesalamine-induced hypersensitivity found by Hirono H et al., 5-aminosalicylic acid drugs need to be replaced and immunosuppressive schemes adjusted [44].

In the future, with the development of multi-omics technology, integrating multi-dimensional data such as ANCA status, gene polymorphism, and immune cell subset characteristics is expected to construct a more accurate treatment response prediction model and further improve the efficiency of individualized treatment for UC. At the same time, formulating stratified individualized treatment plans according to patients' ethnicity, age, and complications will become an important development direction for the treatment of ANCA-positive UC.

6. Summary

Anti-neutrophil cytoplasmic antibodies are of great significance in the diagnosis, disease activity assessment, pathogenesis, and treatment of ulcerative colitis. In terms of diagnosis and differential diagnosis, ANCA can be used as a marker to differentiate UC from CD. PR3-ANCA and pANCA show high specificity and positive rates in pediatric and adult UC patients, and have differential value in different ethnic groups, helping to improve diagnostic accuracy; at the same time, combined detection of ANCA with markers such as anti-GP2 and ASCA can further improve the efficiency of IBD subtype differentiation. In addition, ANCA positivity indicates that UC patients may have concurrent extraintestinal autoimmune diseases such as vasculitis, PSC, and nervous system injury, providing a more comprehensive reference for clinical diagnosis. In terms of disease activity assessment, PR3-ANCA levels are closely related to UC activity, and its titer is positively correlated with mucosal injury degree and fecal calprotectin level, and dynamic changes in titer can predict disease recurrence, which can be used as an important indicator for assessing disease severity and recurrence risk. At the same time, ANCA also plays an important role in predicting the treatment response of UC patients. PR3-ANCA-positive patients have poor responses to hormones, 5-aminosalicylic acid drugs, and TNF inhibitors, while combined detection with genetic markers such as *TNFRSF1B* can optimize early treatment strategies, guide the use of biologics, and improve treatment effects. ANCA amplifies inflammation by activating neutrophils to release Neutrophil Extracellular Traps (NETs) in the pathogenesis of UC. Inhibition of FcRn can accelerate ANCA clearance, reduce NET formation, and improve experimental colitis,

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providing a theoretical basis for ANCA pathway-targeted therapeutic strategies. In addition, genetic factors such as *TNFRSF1B* gene polymorphism are related to ANCA-positive UC, affecting ANCA production and disease phenotype. Other immune-related genes such as *CHI3L1* may also be involved in pathogenesis regulation, suggesting the interaction between genetics and immune regulation in UC pathogenesis. In terms of detection technology, novel detection methods such as flow cytometry-based NET detection and improved IIF technology have improved the sensitivity and specificity of ANCA detection, and detection schemes optimized for different populations also show the importance of localized detection standards. Multi-marker combined diagnosis combined with machine learning algorithms not only improves the accuracy of UC diagnosis but also enhances early screening and treatment response prediction capabilities, providing stronger support for clinical diagnosis and treatment. In terms of treatment, ANCA-targeted therapeutic strategies show good application prospects. FcRn inhibitors improve colitis by reducing ANCA levels in animal experiments, and the anti-inflammatory and antioxidant effects of natural products also provide potential directions for treatment; biologic therapy needs to pay attention to autoimmune complications in ANCA-positive patients, and surgical treatment has a good curative effect on severe patients with extraintestinal manifestations. Individualized treatment is an important trend in future UC treatment. Combining ANCA detection results with patients' genetic background, immune status, ethnicity, and complications can formulate more accurate stratified treatment plans, improve treatment effects, and improve patient prognosis. In the future, large-sample, multi-center prospective studies are needed to clarify the specific mechanism of each ANCA subtype in UC and verify the clinical efficacy of ANCA-targeted therapeutic strategies; at the same time, further explore more genetic and molecular markers related to ANCA, combine artificial intelligence technology to construct more accurate diagnosis and treatment prediction models, and promote the development of precise diagnosis and treatment of ANCA-positive UC.

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