



## OPEN ACCESS

## EDITED BY

Yukihiro Yamaguchi,  
University of North Carolina at Chapel Hill,  
United States

## REVIEWED BY

Anto Sam Crosslee Louis Sam Titus,  
University of Houston, United States  
Xiaodong Li,  
The University of Osaka, Japan

## \*CORRESPONDENCE

Najib Maaamer Faed Murshed

✉ najeebmoammer@gmail.com

Kishan Prasad Hosapatna Laxminarayana

✉ kishanprasadh@nitte.edu.in

RECEIVED 15 October 2025

REVISED 22 November 2025

ACCEPTED 03 December 2025

PUBLISHED 02 January 2026



## CITATION

Murshed NMF, Shetty P, Jayaswamy PK,  
Jacob AM, Alawadhi SSA and Hosapatna  
Laxminarayana KP (2026) Annexin A1 and A2  
in inflammatory bowel disease pathogenesis:  
exploring new  
avenues for diagnosis and treatment.  
*Front. Immunol.* 16:1725965.  
doi: 10.3389/fimmu.2025.1725965

## COPYRIGHT

© 2026 Murshed, Shetty, Jayaswamy, Jacob,  
Alawadhi and Hosapatna Laxminarayana. This is  
an open-access article distributed under the  
terms of the [Creative Commons Attribution  
License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/). The use, distribution or  
reproduction in other forums is permitted,  
provided the original author(s) and the  
copyright owner(s) are credited and that the  
original publication in this journal is cited, in  
accordance with accepted academic  
practice. No use, distribution or reproduction  
is permitted which does not comply with  
these terms.

# Annexin A1 and A2 in inflammatory bowel disease pathogenesis: exploring new avenues for diagnosis and treatment

Najib Maaamer Faed Murshed\*, Praveenkumar Shetty ,  
Pavan K. Jayaswamy, Ankeeta Menona Jacob,  
Samah Saleh Ahmed Alawadhi and  
Kishan Prasad Hosapatna Laxminarayana \*

Department of Pathology, KS Hegde Medical Academy, Nitte (Deemed to be University),  
Mangalore, India

Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, is a significant global health burden with gastrointestinal inflammation resulting from dysfunctional immune responses and chronic inflammation. This review synthesizes the roles of annexin A1 (AnxA1) and annexin A2 (AnxA2) in the pathophysiology of IBD, their diagnostic biomarkers, and therapeutic potential. AnxA1 interacts with FPR2/ALX receptors, inhibiting the release of pro-inflammatory cytokines and promoting epithelial cell repair. AnxA2 exhibits dual roles by interacting with S100A10. AnxA2 can induce NF- $\kappa$ B activation, promoting pro-inflammatory cytokine release and plasminogen activation. On the other hand, AnxA2 activates the TRAM-TRIF pathway, inhibiting NF- $\kappa$ B activation, promoting production of anti-inflammatory cytokines, fibrinolysis, and restoring tight junctions. Their modulation of NF- $\kappa$ B pathways shapes the molecular landscape of IBD. AnxA1 and AnxA2 are non-invasive plasma biomarkers that improve subtype-specific diagnostic accuracy compared to C-reactive protein. In the therapeutic context, AnxA1 mimetics and AnxA2 inhibitors reduce inflammation and promote healing, potentially in conjunction with anti-TNF drugs or nanoparticle delivery. Longitudinal studies and clinical trials are essential to identify the gaps in the standardization of testing and cytokine network interactions. AnxA1 and AnxA2 have the potential to transform the development of precise diagnostics and personalized therapies, redefining the management of IBD.

## KEYWORDS

inflammatory bowel disease, annexin A1, annexin A2, biomarker, pathogenesis, Ulcerative Colitis, Crohn's Disease

## 1 Introduction

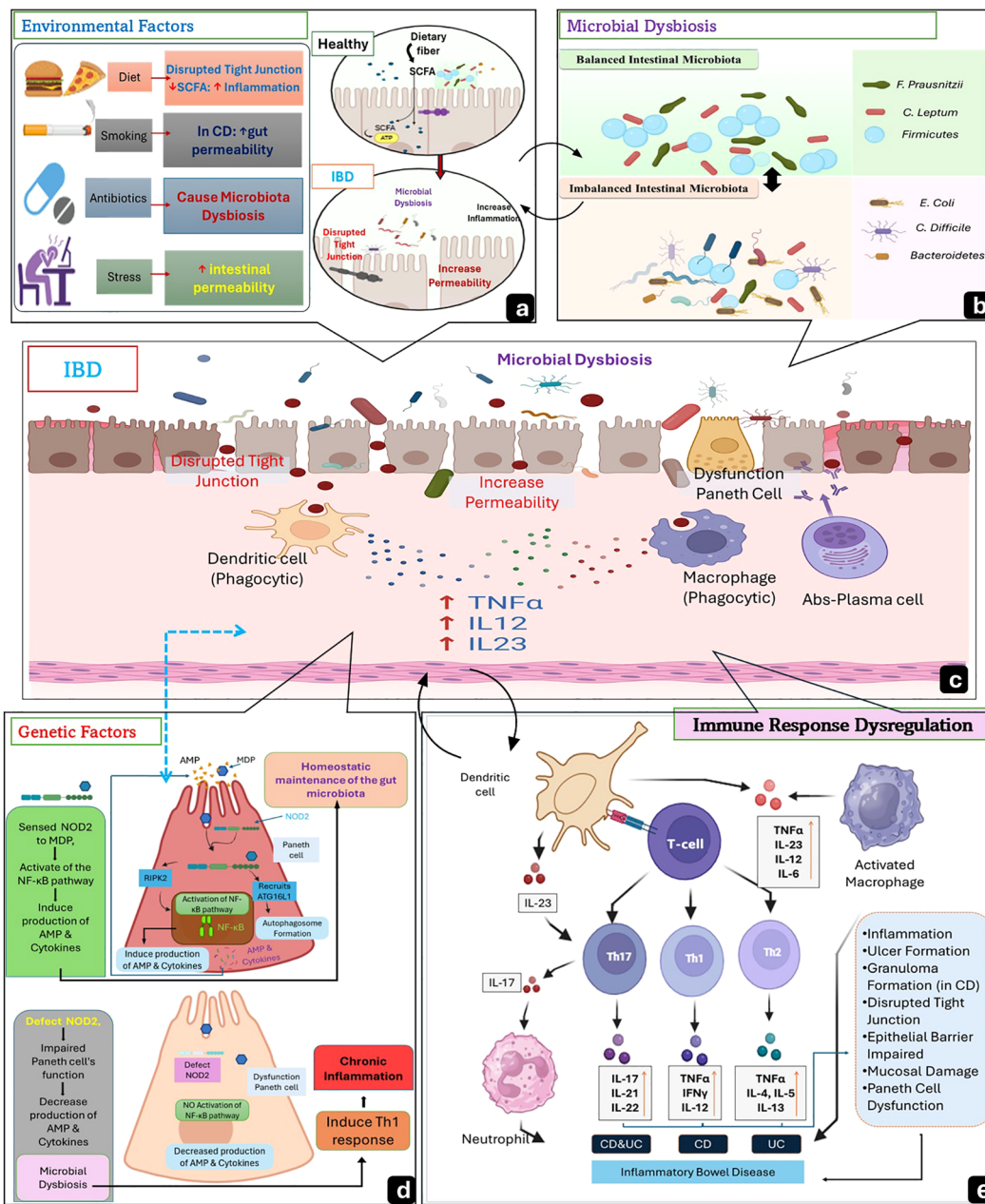
Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory conditions involving the gastrointestinal tract (GIT), especially the lamina propria, characterized by relapses and remission. That has a substantial impact on the health, quality of life, and psychological dimensions of IBD patients and is subclassified into ulcerative colitis (UC) and Crohn's disease (CD) (1, 2). The global prevalence and burden of IBD are rising, with significant regional and national differences in prevalence and trends. As per 2017 data, there were 6.8 million cases of IBD worldwide. The age-standardized prevalence rate increased from 79.5 per 100,000 people in 1990 to 84.3 per 100,000 in 2017 (3). Incidence rates of IBD show significant variation by region. Europe saw rates ranging from 0.97 to 57.9 cases, North America ranged from 8.8 to 23.14, and Asia and the Middle East ranged from 0.15 to 6.5 (4). In India, the incidence and prevalence of IBD are higher than previously believed, with an incidence of 9.3 per 100,000 and nearly 1.5 million cases (5, 6). Due to convergent clinical and pathological characteristics, it can be challenging to distinguish between different IBD subtypes of UC and CD (7, 8). These subtypes of IBD share common symptoms such as abdominal pain, recurrent diarrhea, and rectal bleeding (which occurs more frequently with UC than with CD) (3, 9). Patients with IBD experience a wide range of consequences throughout their condition, such as intestinal bleeding, toxic megacolon, formation of abscesses and constrictions, and fistulizing conditions (4, 5). UC is characterized by persistent inflammation that damages the colon's mucous membrane, which starts at the rectum and frequently causes erosions and ulcers. The CD is featured by patchy, granulomatous inflammation that can affect any part of the digestive tract and is not continuous, often leading to the formation of fistulas (7, 10). The etiology of IBD is not well defined. The etiopathogenesis mechanisms in IBD involve environmental influences, genetic susceptibility, dysregulated immune responses, and microbial dysbiosis, as shown in Figure 1. These factors lead to intestinal barrier dysfunction, resulting in bowel inflammation (11). The diagnosis of IBD is made by physical examination and the patient's history in combination with colonoscopy, histological and radiographic tests, and non-specific tests for biomarkers from blood and/or stools (12). Inflammation in IBD is marked by imbalanced levels of specific molecules, many of which are validated but not routinely tested. These include molecules related to the inflammatory acute-phase response, coagulation and fibrinolysis, proteinase inhibitors, transport proteins, other serum proteins, and cytokines (13).

Dysregulation of immune response characterizes the Pathogenesis of IBS, which compromises the intestinal epithelial barrier integrity, leading to chronic inflammation, by hypersecretion of pro-inflammatory mediators involving Tumor Necrosis factor-alpha (TNF- $\alpha$ ) and Interleukin-6 (IL-6), which release by overactive T-helper-1 (Th1) and T-helper-17 (Th17) cells in CD or T-helper-2 (Th2) cell in UC (14). These cytokines induce nuclear factor-kappa B (NF- $\kappa$ B) activation, which amplifies

the inflammation cascade initiated by immune dysregulation (15). Therefore, in countering the inflammation caused by these pro-inflammatory cytokines, endogenous pro-resolving proteins such as Annexins play critical roles in maintaining epithelial barrier integrity, stabilizing tight junctions, and mitigating barrier disruption (16). Annexin A1 (AnxA1) is a glucocorticoid-regulated protein that promotes inflammation resolution through multiple mechanisms, including inhibition of NF- $\kappa$ B signaling, enhancement of IL-10 production, limitation of neutrophil recruitment, and promotion of macrophage-mediated efferocytosis; these actions support mucosal healing in preclinical colitis models and are associated with mucosal recovery in human samples (9, 17, 18). Annexin A2 (AnxA2) contributes to membrane-cytoskeleton dynamics (exocytosis, endocytosis, phagocytosis), cell migration, and plasminogen activation, and has context-dependent functions in inflammation and tissue repair; in colitic settings, AnxA2 can amplify NF- $\kappa$ B-driven cytokine production and epithelial responses, while in other contexts it supports fibrinolysis and wound closure (19, 20).

To control the disease, IBD frequently requires long-term treatment based on a mix of medications. The range of IBD treatment choices has expanded significantly over the last several years. Medications such as aminosalicylates, Corticosteroids, immunomodulators, and biologics are combined with other general interventions and, in some instances, surgical resection to control symptoms (12). It has been demonstrated that biological therapy, such as Adalimumab, Infliximab, and Certolizumab, improves the quality of life for patients with IBD by blocking the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF- $\alpha$ ). However, some individuals do not react to biological therapy for various reasons, including the immune system state. This variability makes patient monitoring, including measuring medication levels in plasma, essential during treatment (21). When treating IBD in its acute stages, Glucocorticoids (GCs) have been recommended to induce the disease into remission. GCs exhibit significant anti-inflammatory effects by suppressing the migration and proliferation of practically all immune cells, depending on the disease's severity (22). It has been demonstrated that several pro-resolving mediators can control critical phases of inflammation to induce resolution, specialized pro-resolving lipid mediators (SPMs), and proteins such as annexins (23).

Recent single-cell and multi-omics studies refine the cellular map of annexin expression in human IBD: AnxA1 signals are detected in epithelial cells, stromal compartments, and certain T-cell subsets, while AnxA2 transcripts are enriched in macrophage populations in inflamed colonic mucosa (24–26). These datasets indicate cell-type and treatment-context dependence of annexin expression, and they motivate cautious evaluation of annexins as candidate biomarkers or therapeutic targets. Inter-study heterogeneity, driven by patient age, microbiome composition, medication exposure, sample type (biopsy versus blood), and analytic platform (bulk versus single-cell versus proteomics), limits the generalizability of individual reports and underlines the need for standardized assays and larger, longitudinal cohorts (27, 28).



**FIGURE 1** Schematic illustration of the Factors of Etiopathogenesis of IBD. **(a)** Environmental factors, such as a high-fat, high-sugar diet, disrupt tight junctions, while a low-fiber diet reduces short-chain fatty acids (SCFAs), thereby impairing epithelial barrier integrity. Smoking (mainly in CD) increases gut permeability, antibiotics eliminate beneficial bacteria, leading to dysbiosis, and stress disrupts the gut-brain axis, promoting inflammation. **(b)** Microbial dysbiosis occurs when there is an imbalance in gut microbiota, with a decrease in beneficial bacteria and an increase in pathogenic microbes. **(c)** Inflamed intestinal mucosa in IBD shows mucus depletion due to Goblet cell dysfunction, disrupted tight junctions, increased permeability, and microbial translocation into the lamina propria. **(d)** Genetic factors such as NOD2 mutations impair Paneth cell function, reducing antimicrobial peptide (AMP) production and contributing to dysbiosis. **(e)** Immune response dysregulation occurs when CD4+ T cells are activated and then differentiate into Th1 (mainly in CD) cell, Th17 (commonly in CD), and Th2 (mainly in UC), releasing pro-inflammatory cytokines that drive chronic inflammation. Created by the author using BioRender and Microsoft PowerPoint.

### 1.1 Literature search strategy

A targeted literature search was conducted in PubMed, Scopus, and Web of Science for all available years up to 2025, using Annexin-related terms (“Annexin A1”, “AnxA1”, “Annexin A2”, “AnxA2”) combined with inflammatory bowel disease terms

(“inflammatory bowel disease”, “ulcerative colitis”, “Crohn\* disease”, “colitis”). The search retrieved 186 records, comprising 55 PubMed (AnxA1+IBD = 52; AnxA2+IBD = 3), 68 Scopus (AnxA1+IBD = 61; AnxA2+IBD = 7), and 63 Web of Science (AnxA1+IBD = 61; AnxA2+IBD = 2) records. After removing 101 duplicates, 85 unique studies remained. As this is a narrative (non-

systematic) review, broad inclusion criteria were applied, permitting original studies from human IBD cohorts, validated animal colitis models, and *in vitro* mechanistic systems examining annexin signaling, mucosal immunity, epithelial biology, or biomarker development. Review articles and mechanistic overviews were consulted when they contributed relevant conceptual or translational context. Non-peer-reviewed materials, conference abstracts, and articles lacking extractable biological relevance were excluded.

For clarity, evidence was organized into three categories: human clinical evidence (biopsy analyses, circulating biomarkers, proteomics, and single-cell datasets), animal evidence (e.g., DSS, TNBS, IL-10-deficient, and other validated colitis models), and *in vitro* evidence (immune cells, epithelial cells, and intestinal organoids). This framework allows distinction between preclinical mechanistic insights and emerging clinical observations, supporting a coherent and translational interpretation of Annexin biology in IBD. A simplified PRISMA-style flow diagram summarizing the search and screening steps is presented in Figure 2.

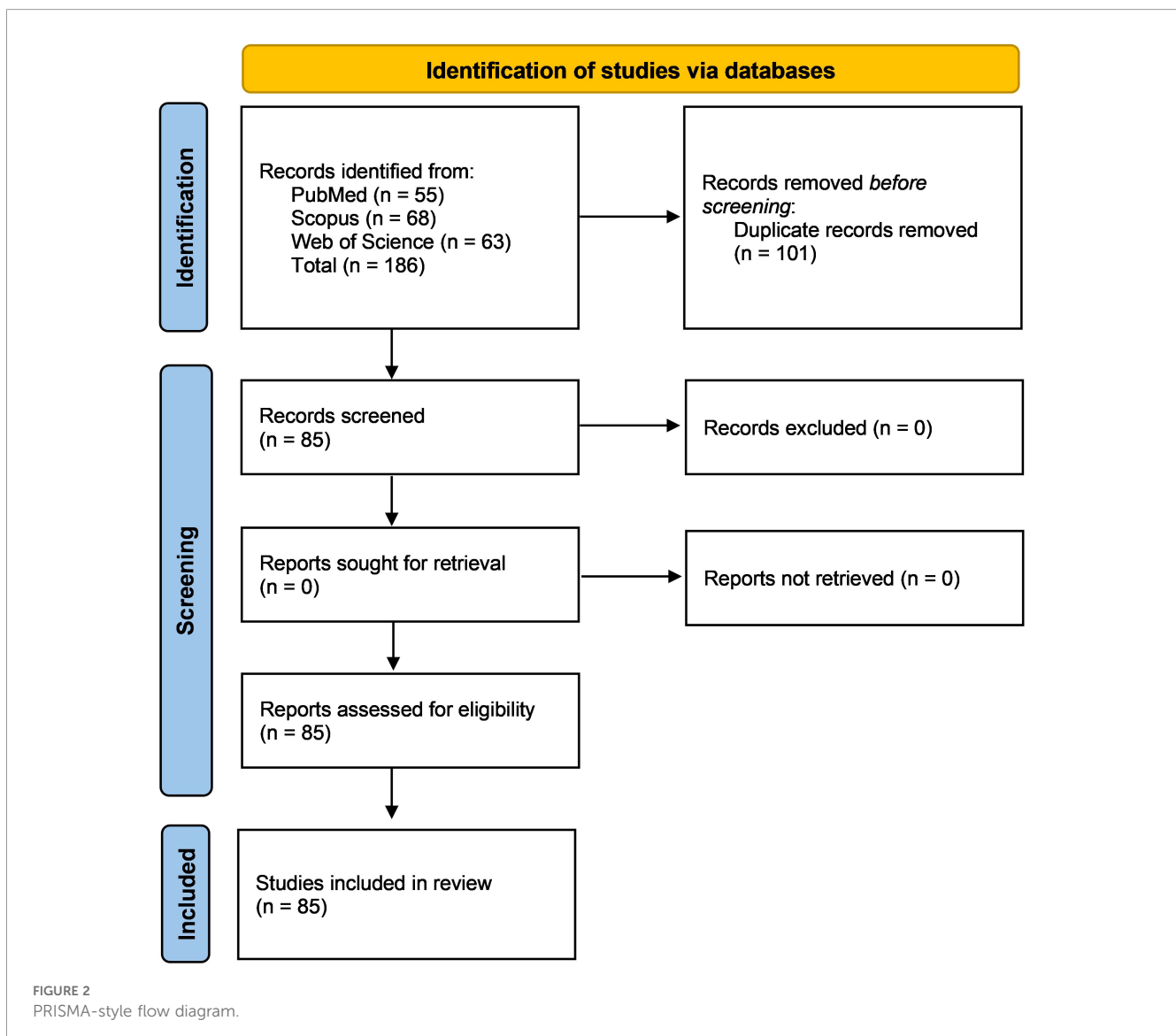
## 2 Etiopathogenesis of IBD

### 2.1 Etiology of IBD

Inflammatory bowel disease develops from a multifactorial interplay involving environmental exposures, microbial dysbiosis, genetic susceptibility, and dysregulated immune responses. Environmental factors, including smoking, diet, medications, antibiotics, and psychosocial stress, influence intestinal permeability, microbiome composition, and mucosal immune function (11). Recent multi-omics studies further confirm that environmental stressors reshape gut microbial metabolites and epithelial-immune communication, influencing disease onset and relapse (29).

#### 2.1.1 Environmental factors

Environmental factors strongly influence the etiopathogenesis of IBD (11), where smoking, food style, medications, stress, and



psychological components are important factors (30, 31). Smoking has a contradictory impact on different types of IBD. In CD conditions, smoking is harmful, raising the risk of disease onset and postoperative complications. Smoking does not improve UC disease progression (32, 33). Diet plays a crucial role in IBD (34). High consumption of total fats, polyunsaturated fatty acids, omega-6 fatty acids, and meat is associated with an increased risk of CD and UC. In contrast, diets rich in fruit, fiber, and vegetables are linked to a reduced risk of both diseases (35). High doses and frequent use of nonsteroidal anti-inflammatory drugs are associated with a higher risk of CD and UC, whereas aspirin has not shown a significant connection (36). Antibiotic intake, mainly in early life, is significantly associated with increased IBD risk due to its effect on the developing intestinal microbiome (37). Other medications, like anti-contraceptives and statins, also raise the IBD risk (38). Psychological stress, including anxiety and depression, can exacerbate IBD by disrupting immune function through mechanisms such as the hypothalamic-pituitary-adrenal axis, bacterial-mucosal interactions, and neuroimmune mucosal mast cell circuits (39). Integrative analyses show that chronic stress reshapes Th17-related cytokines and microbial metabolites, creating a relapse-prone inflammatory state (25).

### 2.1.2 Microbial imbalances factors

The intestinal microbiome plays a crucial role in human health as a key link between the external environment and the intestinal mucosa (40). Microbial dysbiosis, characterized by a decrease in microbiota diversity, significantly impacts health (41). The gut microbiota is essential for balancing T helper (Th) cells and T regulator (Treg) cells, eliciting the body's inflammatory response. When the composition or function of the microbiota is disrupted, it disrupts the mechanism, leading to intestinal inflammation (40). In patients with IBD, there is a significant disruption in gut microbiota, characterized by a decrease in beneficial, anti-inflammatory bacteria like *Faecalibacterium prausnitzii* and *Clostridium leptum*, and an increase in harmful, pro-inflammatory bacteria such as *Escherichia coli* and *Clostridium difficile* (42, 43). This imbalance includes reducing *Firmicutes* and increasing *Proteobacteria* and *Bacteroidetes* (44). The reduced short-chain fatty acid (SCFA)-producing bacteria impact Treg cell differentiation and epithelial growth, contributing to intestinal inflammation (45). Additionally, the gut microbiota in IBD patients exhibits reduced diversity and stability compared to that of healthy individuals, which further exacerbates disease progression and alters the immune environment of the gut (46). Recent spatial multi-omics analyses highlight microbial-immune clustering in inflamed UC mucosa, where certain bacterial taxa colocalize with activated myeloid cells and IL-23-rich niches (47).

### 2.1.3 Genetic factors

Genetic susceptibility plays a crucial role in our understanding of IBD, particularly CD, compared to UC (48). Higher concordance rates in monozygotic twins and a significantly increased risk for

first-degree relatives (49). Rare genetic variants, such as mutations in the XIAP and IL10RA genes, have been associated with severe early-onset IBD (50). Genome-wide association studies have identified 201 genetic loci linked to CD and UC, suggesting shared inflammatory pathways (51). Notable genes include NOD2, ATG16L1, IRGM, and IL23R. However, these loci account for only 20%-25% of the disease's heritability, highlighting a *genetic vacuum* (52). Current long-read transcriptomic research is increasingly focusing on noncoding RNA dysregulation and altered polyadenylation profiles in UC mucosa, indicating that the regulatory RNA architecture contributes substantially to the disease phenotype (53). Epigenetic mechanisms, including DNA methylation and microbiome-responsive chromatin changes are emerging contributors to the unexplained (heritability gap) (31, 54).

### 2.1.4 Immune dysregulation factors

Both innate and adaptive immune mechanisms contribute significantly to IBD pathogenesis (11). A Th1-mediated immune response is the primary driver of CD (55), while an atypical Th2 response is associated with UC (56). Additionally, recent studies have highlighted the crucial role of Th17 cells in the inflammatory processes of IBD, particularly in CD (57). Th1 and Th17 responses are associated with elevated IFN- $\gamma$ , IL-17A, and IL-12 levels. On the other hand, an atypical Th2 response is characterized by reduced IL-4 levels and increased levels of IL-13 and IL-5 (58). IL-23 is crucial for innate and adaptive immunity, with genetic polymorphisms in IL23R associated with CD and UC. IL-23 significantly contributes to chronic intestinal inflammation by promoting Th17 cytokine production (11). Elevated levels of IL-17A are observed in the mucosa of both CD and UC compared to normal gut tissue (59). In CD, IL-17 and IL-23 play crucial pro-inflammatory roles. IL-23, a member of the IL-12 family, stimulates Th17 differentiation by promoting Th17 gene expression. IL-17 and IL-23 signaling cascades produced various pro-inflammatory substances, including TNF, IFN- $\gamma$ , and IL-22 (60). During inflammation, intestinal macrophages produce TNF, which is essential for the development of colitis (61). Increased macrophage infiltration in UC produces several inflammatory cytokines, which could affect carcinogenesis (62). Single-cell studies highlighted that the tissue-resident immune subsets, including TRM cells, inflammatory monocytes, and IL-23-responsive macrophages, are central drivers of chronicity (26, 63).

## 2.2 Normal architecture and disruption of the intestinal epithelial barrier

The intestinal epithelial barrier consists of a single layer of tightly connected intestinal epithelial cells (IECs), forming the frontline between luminal microbes and underlying immune tissues, and maintains homeostasis through essential mechanisms (64). The mucosa separates the intestinal lumen and deeper tissues, which are physically in touch with the gut lumen and comprise a

single layer of polarized epithelial cells (65). Tight junctions between epithelial cells control paracellular permeability, preventing harmful substances from entering underlying tissues (66). Goblet cells secrete mucus that forms a protective layer, blocking pathogens and aiding their removal (67). Paneth cells release antimicrobial peptides (AMPs), controlling microbial populations (68). Dendritic cells and macrophages in the lamina propria produce TGF- $\beta$  and IL-10, fostering Treg-mediated immune homeostasis, as shown in Figure 3 (69). This harmonious system breaks down in IBD, much like a besieged fortress. Dysregulated immunity releases TNF- $\alpha$  and IL-17, which disrupt tight junctions, increase permeability, and permit translocation of microbes (70). Recent organoid-based epithelial injury models confirm that exposure to inflammatory cytokines reduces ZO-1, occludin, and claudin-1 localization, directly demonstrating junctional rearrangement observed in patient tissue (71, 72). In CD, Paneth cell defects, connected to NOD2 mutations, impair AMP production and exacerbate microbial dysbiosis (73). In UC, goblet cell dysfunction thins the mucus layer, exposing the epithelium to pathogens (73). SCFAs are decreased by microbial shifts, in turn impairing epithelial repair and Treg function (74). Microbial shifts modulate bile acid metabolism, altering FXR-dependent epithelial signals and disrupting barrier renewal (28). The barrier defects of CD are exacerbated by dysregulated bile acid metabolism, a novel disruptor that modifies microbial signalling (75). Antibiotics used in early life further disrupt microbiota, which leads to barrier failure (76).

## 2.3 Signaling pathways in inflammation

Intracellular signaling pathways orchestrate the activation, amplification, and chronicity of intestinal inflammation, as illustrated in Figure 4A. NF- $\kappa$ B activation, triggered by pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6, and IL-1 $\beta$ , stimulates the transcription of pro-inflammatory genes, including cyclooxygenase-2 (COX-2), IL-6, and IL-8. These genes, in turn, promote neutrophil infiltration and epithelial damage (77). Mitogen-activated protein kinases (MAPKs), like p38, JNK, and ERK, stimulate Th17 differentiation and neutrophil ROS production through mediating cytokine signalling (51). IL-6 and IL-23 activate the Janus kinase-signal transducer and activator of the transcription (JAK-STAT) signaling pathway, which sustains immune cell survival and cytokine persistence, particularly in CD (78, 79). Multi-omics analyses show that JAK-STAT upregulation co-occurs with metabolic rewiring of inflammatory monocytes in UC, reinforcing cytokine persistence (80). Chronicity is sustained through a feedback loop created by MAPK-driven NF- $\kappa$ B activation or JAK-STAT synergy with IL-23 signaling. While smoking may increase NF- $\kappa$ B in CD, IL23R variants improve Th17 responses (81, 82). Single-cell datasets reveal spatial clustering of NF- $\kappa$ B-high myeloid cells near damaged epithelial zones, clarifying why anti-TNF therapies fail when these niches dominate (47).

## 3 Structure and function of AnxA1 and AnxA2

AnxA1 and AnxA2 are calcium-dependent phospholipid-binding proteins belonging to the annexin superfamily. Currently, 13 common vertebrate annexins have been identified (Annexin A1–A13). AnxA1 and AnxA2 are the first human annexins to be cloned (83, 84).

### 3.1 Structural characteristics of AnxA1 and AnxA2

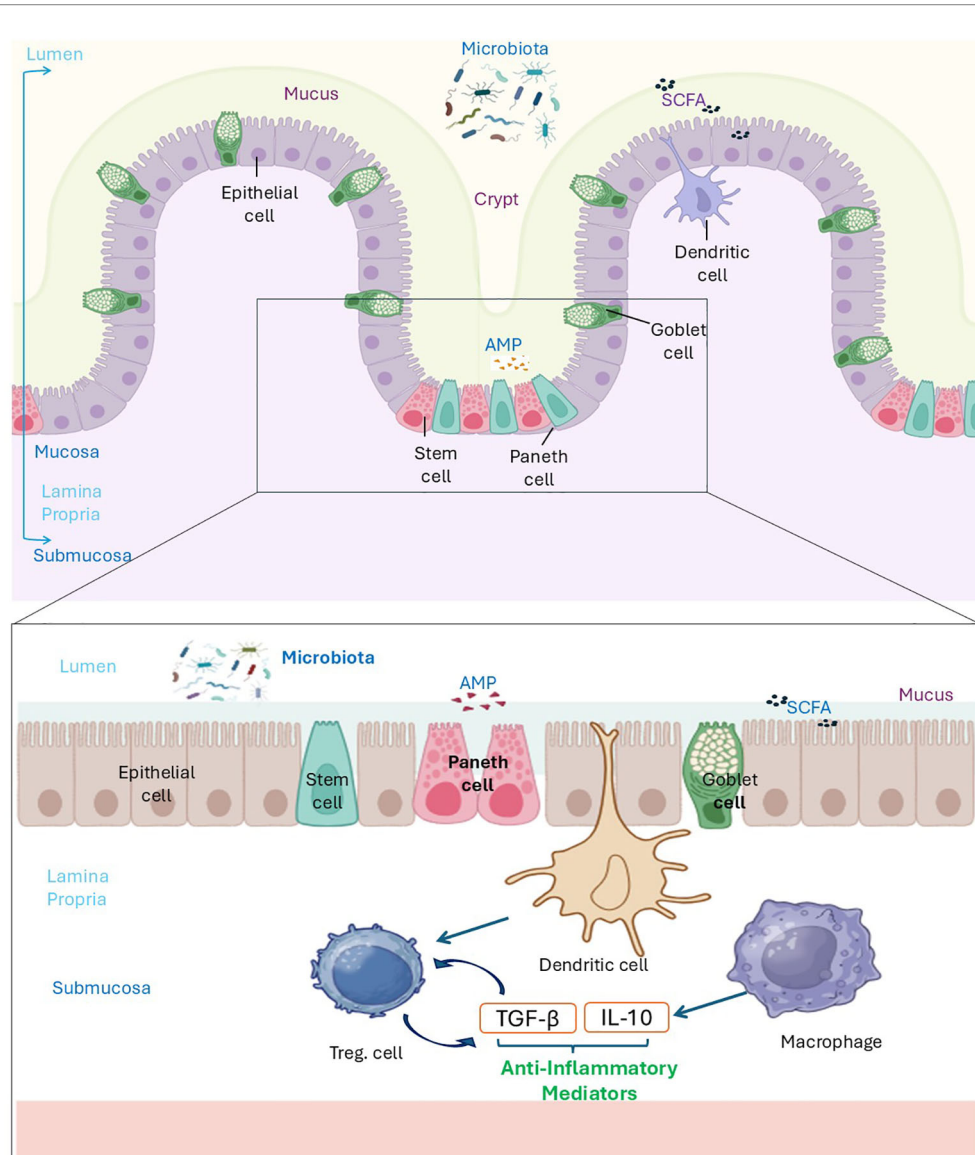
AnxA1 is a 37-kDa phospholipid-binding protein dependent on calcium (85). Formerly referred to as lipocortin-1, renocortin, macrocortin, and lipomodulinb (84). AnxA2 is a 36-kDa phospholipid-binding protein dependent on calcium (19, 86). Formerly referred to as calpactin I, lipocortin II, placental anticoagulant IV, chromobindin VIII, and p36 (87). AnxA1 is a monomeric, amphipathic cytoplasmic protein comprising 346 amino acids. In comparison, AnxA2 is a monomeric protein containing 339 amino acids that binds to calcium and phospholipids (88). Both proteins share a conserved structural organization of two main domains: a protein core domain of the COOH-terminal (C-terminal) that mediates Calcium-dependent phospholipid binding and typically contains four homologous repeats, each consisting of five  $\alpha$ -helices, and a flexible NH<sub>2</sub>-terminal (N-terminal) that confers regulatory functions relevant to inflammation (89, 90).

The length and sequence of the N-terminal domains of AnxA1 and AnxA2 vary and have short tails of 33 and 42 residues, respectively (90). They contain specific binding sites and phosphorylation sites for S100 proteins (S100A11 for AnxA1 and S100A10 for AnxA2). In AnxA1, the N-terminal region interacts with the S100 protein-ligand S100A11 (91). In contrast, AnxA2 interacts with S100A10, forming a heterotetramer that enhances membrane interaction and supports fibrinolysis (92). The N-terminal domain in AnxA1 contains phosphorylation sites (Ser/Thr) and possesses several proteolytic motifs, and a truncated N-terminal fragment is often found in inflammatory fluids (93). In AnxA2, phosphorylation at Tyr23, Ser25, and Ser11 modulates membrane association, nuclear shuttling, and extracellular translocation, functions that are increasingly recognized as context-dependent regulators of inflammation (94).

### 3.2 Distribution and regulation of AnxA1 and AnxA2

#### 3.2.1 AnxA1 distribution and regulation

AnxA1 is distributed and expressed across various organs and tissues, mainly in epithelial and endothelial cells. It is present in all leukocytes except B lymphocytes, with the highest levels in monocytes and neutrophils. AnxA1 is found in plasma, seminal

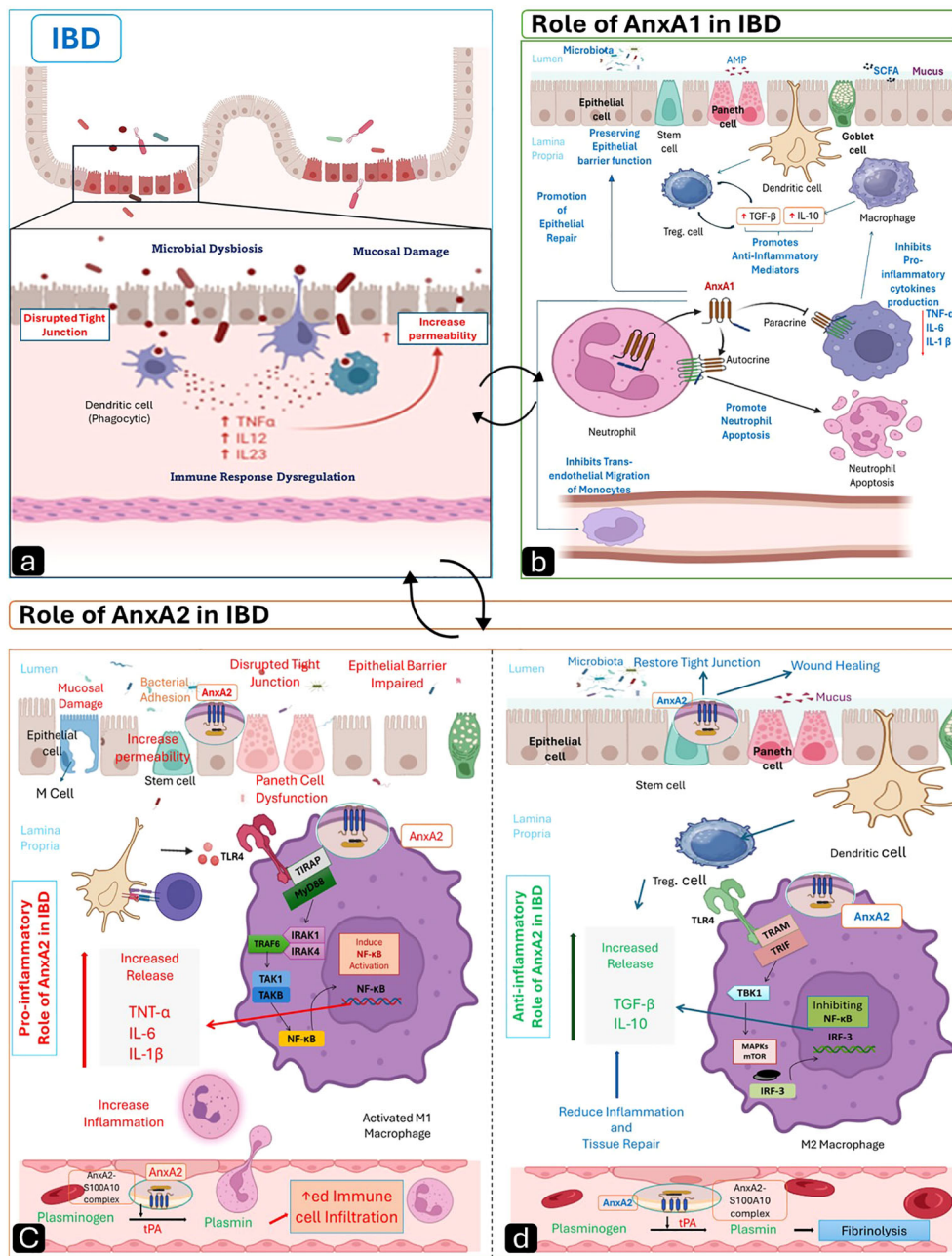


**FIGURE 3** Normal structure of intestinal mucosa in a healthy state. Epithelial cells form the main structural component of the intestinal mucosa, tightly connected by tight junction proteins to regulate permeability. Goblet cells produce mucus, creating a protective layer against microbial invasion. Paneth cells secrete antimicrobial peptides (AMPs) to control microbial populations. Dendritic cells, located between the intestinal epithelium and lamina propria, capture translocated microbiota and produce TGF- $\beta$ , promoting the generation of Tregs. Additionally, macrophages secrete IL-10, an anti-inflammatory cytokine that helps maintain immune homeostasis. These specialized cells preserve barrier integrity and immune balance in the intestinal mucosa. Created by the author using BioRender and Microsoft PowerPoint.

fluid, and intracellular and extracellular locations (95), and can be released into the bloodstream, acting in autocrine and paracrine signalling (96). AnxA1 secretion occurs via non-conventional mechanisms involving ATP-binding cassette (ABC transporter) transport, phosphorylation at serine-27 in Pituitary cells, and gelatinase granules in neutrophils (97). AnxA1 displays an atypical subcellular distribution, primarily found in the cytoplasm, with a smaller but functionally significant fraction found in both the inner and outer plasma membrane leaflets (98, 99).

In its resting state, the AnxA1 N-terminal region is concealed, and its release requires extracellular calcium stimulation (~1 mM), enabling AnxA1 to translocate to the outer leaflet of the plasma membrane, and engage in autocrine and paracrine signaling (17, 100). Recent studies show that membrane-exposed AnxA1 interacts directly with FPR2/ALX to induce efferocytosis, macrophage IL-10 production, and resolution-phase reprogramming (101).

AnxA1 is induced and regulated by glucocorticoids (GCs) (102), AnxA1 acts through the formyl peptide receptor type 2/lipoxin A4 receptor (FPR2/ALX). FPR2/ALX, along with FPR1 and FPR3, belongs



**FIGURE 4**  
 The role of AnxA1 and AnxA2 in IBD. **(A)** Intestinal mucosal alteration and immune response dysregulation in IBD. **(B)** Role of AnxA1 in IBD: AnxA1 plays an anti-inflammatory role by interacting with FPR2 on neutrophils and macrophages, thereby inhibiting pro-inflammatory cytokines, and promoting anti-inflammatory cytokines (TGF- $\beta$ , IL-10), while also inducing neutrophil apoptosis. It maintains epithelial barrier integrity by stabilizing tight junctions and supports epithelial repair through wound healing and reduced monocyte migration. **(C)** Pro-inflammatory role of AnxA2: AnxA2 interacts with S100A10, activating NF- $\kappa$ B, which in turn increases the production of pro-inflammatory cytokines (TNF- $\alpha$ , IL-6, IL-1 $\beta$ ) and promotes plasminogen activation, ultimately leading to immune infiltration, tight junction disruption, and increased epithelial permeability. **(D)** Anti-inflammatory role of AnxA2: AnxA2 inhibits NF- $\kappa$ B, promotes IL-10 and TGF- $\beta$ , enhances fibrinolysis, and aids tight junction restoration and tissue repair. Created by the author using BioRender and Microsoft PowerPoint.

to a family of G-protein-coupled receptors with significant sequence homology (20, 103). During inflammatory disease, GCs regulate AnxA1 levels. In diseases characterized by high cortisol levels, such as Cushing's disease, AnxA1 levels are upregulated. Meanwhile, conditions with low cortisol levels, such as Addison's disease, are associated with reduced AnxA1 levels compared to healthy controls (104).

### 3.2.2 AnxA2 distribution and regulation

AnxA2 is produced by endothelial, trophoblast, epithelial, and tumor cells, macrophages, monocytes, and dendritic cells (105). AnxA2 has diverse subcellular localizations and can be present in the cell membrane, cytoplasm, or nucleus (106, 107). The S100A10–AnxA2 heterotetramer, formed by two AnxA2 subunits bound to an

S100A10 dimer via the first 12 N-terminal amino acids of AnxA2. This heterotetramer is localized to the cell membranes (92, 105). AnxA2 is regulated by post-translational modifications and subcellular localization, influencing extracellular translocation and cellular roles (106); (i) Tyr23 phosphorylation drives extracellular translocation and NF- $\kappa$ B-linked inflammatory signaling (108). (ii) Serine acetylation stabilizes tetramer formation and supports fibrinolytic activity (92, 109).

Recent single-cell and spatial studies have highlight strong enrichment of AnxA2 in epithelial and macrophage populations in active UC, where extracellular AnxA2 correlates with pro-inflammatory cytokine programs (25, 110).

### 3.3 Functional roles of AnxA1

AnxA1 exerts potent anti-inflammatory and pro-resolving actions. It inhibits phospholipase A2 (PLA2) activity, reducing prostaglandin synthesis and macrophage activation, decreasing the acute inflammatory response (111). AnxA1 actions are mediated largely through FPR2/ALX and downstream signaling pathways that regulate innate and adaptive immune responses (112).

In neutrophils, AnxA1 inhibits activation and reduces arachidonate release, enzyme release, and adhesion to endothelial cells (113). It induces transient calcium fluxes and L-selectin shedding, reducing cell transmigration and promoting neutrophil apoptosis, which is vital for controlling inflammation (97, 114). In monocytes and macrophages, exogenous AnxA1 downregulates monocyte accumulation in inflammatory responses, inhibits phagocytic activity, adhesion, and trans-endothelial migration of monocytic cells, and promotes apoptosis (115–117). AnxA1 inhibits nitric oxide production and inducible nitric oxide synthase expression, which leads to an increase in IL-10 protein and reduces IL-12 levels (118). In lymphocytes, AnxA1 has an anti-proliferative effect on T-lymphocytes but not B-lymphocytes, as AnxA1 does not express in B-lymphocytes (111, 119). It suppresses mitogen-stimulated T-cell proliferation and inhibits antigen presentation, interfering with the activation of antigen-specific T-lymphocytes (120–123). Furthermore, AnxA1 is expressed and functions in several inflammation-related cell types, including endothelial cells, epithelial cells, mast cells, and synovocytes (111). Recent evidence shows that AnxA1 also drives macrophage polarization toward pro-resolving M2 phenotypes via STAT3/IL-10 pathways, enhancing tissue repair and epithelial restitution (80, 101). Single-cell profiling in colitis further confirms enrichment of ANXA1 in epithelial and CD4<sup>+</sup> T-cell subsets involved in mucosal healing (124).

AnxA1 is expressed in endothelial cells and localized to the nucleus; however, its mobilization is not evident during short-term neutrophil adhesion assays (125). In epithelial cells like A549, AnxA1 regulates cell proliferation (126). It mediates the anti-proliferative actions of GCs by inhibiting prostaglandin release and affecting cytosolic phospholipase A2 activation through epidermal growth factor signalling (127, 128). In Mast cells,

AnxA1 is found in perivascular tissues, express AnxA1 is expressed, though at lower levels. GCs modulate increased AnxA1 expression in mast cells during inflammation (129). Significantly, AnxA1 in mast cells can inhibit histamine release, contributing to the stabilization effects of interleukin-2 (130). Given the mast cell's role in initiating and potentially resolving inflammation, AnxA1's function in these cells is expected to be significant and warrants further investigation (131).

### 3.4 Functional roles of AnxA2

AnxA2 is involved in membrane trafficking and organization, participating in processes such as exocytosis, endocytosis, and the formation of tight junctions (105, 132). AnxA2 binds with F-actin and plays a role in actin dynamics, organization, and membrane cytoskeletal rearrangement (92, 106). In Fibrinolysis regulation, AnxA2 heterotetramer binds plasminogen and tPA on the cell surface, promoting plasmin generation and regulating fibrinolysis (89, 108). AnxA2 has a well-established dual role in inflammation:

#### 3.4.1 Pro-inflammatory context (extracellular AnxA2)

The externalization of AnxA2/A2t activates the NF- $\kappa$ B signaling pathway, leading to the production of pro-inflammatory cytokines, including TNF- $\alpha$ , IL-6, and IL-1 $\beta$ . This transition is regulated by Tyr23 phosphorylation, which serves as a molecular switch driving its translocation and pro-inflammatory signaling (94). Strongly enriched in epithelial cells during active UC (25, 110). Organoid injury models show that AnxA2 upregulation coincides with tight-junction disruption and epithelial stress responses (133).

#### 3.4.2 Anti-inflammatory/repair context (intracellular AnxA2)

Intracellular AnxA2 performs the opposite function, supporting barrier repair by stabilizing ZO-1, occludin, and claudin-1. It also facilitates fibrinolysis and wound resolution through plasmin generation. Recent organoid studies have further demonstrated that AnxA2 enhances  $\beta$ 1-integrin recycling, thereby promoting epithelial cell migration and tissue repair (47). Whether AnxA2 is protective or inflammatory depends on its subcellular localization, phosphorylation state, and interaction with innate immune pathways, including TRAM–TRIF versus MyD88 signaling biases in macrophages (94).

## 4 Roles of AnxA1 and A2 in IBD pathogenesis

AnxA1 and AnxA2 are key endogenous regulators of inflammation signaling, exhibiting dysregulated expression that contributes to the chronic intestinal inflammation observed in IBD pathogenesis (84). Both proteins influence epithelial integrity, macrophage programming, neutrophil trafficking, and cytokine amplification loops that are relevant to UC and CD.

Their context-dependent actions in inflammation, immunity, and tissue repair position them at the intersection of molecular pathways central to IBD pathogenesis, as supported by classical and modern mechanistic studies (134, 135). A comparative overview of AnxA1 and AnxA2 expression patterns and functional roles is summarized in Table 1.

## 4.1 AnxA1 and AnxA2 in inflammatory diseases

Inflammation is generally a protective immune response; however, when it becomes uncontrolled or untreatable, it can cause further damage and lead to chronic diseases, including asthma, lung injuries, multiple sclerosis, rheumatoid arthritis, rhinitis, chronic obstructive pulmonary disease, Crohn's disease, ulcerative colitis, prostatitis, endocrine disorders, psoriasis, vasculitis, and a range of autoimmune and degenerative disorders such as obesity, Alzheimer's disease, and atherosclerosis (84, 139). Annexins serve as endogenous inflammation-limiting mediators, counterbalancing pro-inflammatory signaling and helping to restore homeostasis (112). AnxA1 is well-established as a

glucocorticoid-induced pro-resolving mediator (122, 140). It suppresses macrophage pro-inflammatory cytokine release, promotes IL-10 production, and inhibits PLA2 activity (141).

In Asthma, AnxA1 and SPMs levels are lower in wheezy newborns than in controls, with higher serum IgE levels and eosinophilia (142). AnxA1-derived peptides, such as Ac2-26, reduce CRTH2 expression, PGD2 levels, and eosinophil accumulation (143, 144). In respiratory illness, AnxA1 is decreased in lung tissue and bronchoalveolar lavage fluid (145), and proteolytic degradation during lung injury further decreases its availability (146).

In multiple sclerosis (MS), high-dose GCs and immunomodulatory therapies are the gold-standard approaches for managing acute relapses and promoting recovery (147). AnxA1 was elevated in treatment-naive relapsing/remitting MS (RRMS) patients, with a negative correlation to disease severity and progression, suggesting a compensatory inflammatory control mechanism (148). In rheumatoid arthritis (RA), AnxA1 is key in regulating inflammation, primarily through GC treatment. In treatment-naive RA patients, lower AnxA1 levels are associated with reduced Foxp3 expression and increased IL-17 production, underscoring the importance of AnxA1 in immune regulation and

TABLE 1 Comparative patterns of AnxA1 and AnxA2 across IBD stages & models.

Disease stage/ model	AnxA1 expression & functional pattern	AnxA2 expression & functional pattern
Active ulcerative colitis (human mucosa, biopsies)	Frequently elevated in epithelium and lamina propria in several transcriptomic/proteomic studies; linked to epithelial signals and pro-resolution pathways (FPR2/ALX/IL-10) in some cohorts (24, 53, 94).	Upregulated in UC mucosa in proteomic/transcriptomic datasets; A2t externalization / S100A10 interactions are associated with NF- $\kappa$ B activation and higher local cytokines in UC (25, 94).
Ulcerative colitis remission/healing (human)	Partial restoration of AnxA1 expression, when measured, was associated with improved clinical/endoscopic scores in small cohorts (24, 133).	Often reduced vs active disease, though some samples retain elevated A2 in areas prone to relapses (limited human longitudinal data) (24, 25).
Active Crohn's disease (human mucosa, biopsies)	Mixed reports: several studies identify increased ANXA1 transcripts in CD lesion panels and as part of diagnostic gene sets; functional work suggests defective AnxA1 secretion (non-conventional/ABC transporter) in CD that impairs FPR2 signaling (94, 124).	Variable — moderate expression in inflamed segments in some datasets; may show reparative roles in fistula/repair contexts (mechanistic, limited human validation) (72, 94).
Crohn's remission/healing (human)	Reports of restored AnxA1 activity in limited samples linked to repair; human longitudinal data are limited (72, 124).	AnxA2 may participate in epithelial restitution via integrin trafficking in repair models; human confirmation is scarce (72).
DSS colitis (mouse, acute chemical model)	Protective role: AnxA1 deficiency worsens colitis; Ac2-26 or AnxA1 nanoparticles improve histology, $\uparrow$ IL-10 and efferocytosis, $\downarrow$ inflammation (94, 101, 133).	Often upregulated in inflamed tissue; can contribute to both inflammation (NF- $\kappa$ B axis) and repair depending on cell type and timing (94, 136).
TNBS / Th1-skewed colitis models	AnxA1/Ac2-26 reduces Th1/Th17 inflammation and mucosal damage in several preclinical studies (94, 101).	AnxA2 effects are model-dependent; reported roles include matrix remodeling and modulation of inflammation (94).
Intestinal organoids / epithelial-repair models ( <i>in vitro</i> / organoid)	Promotes wound closure and tight-junction integrity (ZO-1/occludin/cludins) in inflamed epithelium models; AnxA1 influence tested in stem-cell epithelium assays (71, 72, 133).	Regulates $\beta$ 1-integrin internalization and epithelial migration — organoid and cell studies validate role for AnxA2 in epithelial resealing (71, 72).
Single-cell / spatial transcriptomics (scRNA, spatial) findings	Detected in epithelial compartments and immune subsets (e.g., some CD4 <sup>+</sup> T-cell populations, Tregs), depending on the dataset and disease context (26, 124).	Enriched in macrophage clusters and certain stromal/epithelial cells in UC atlases; ligand-receptor analyses show ANXA1-FPR interactions across fibroblast-macrophage axes (25, 26, 137).
Proteomics/serum / fecal biomarker studies	Included in multi-gene expression panels (e.g., 3-gene panel discriminating CD vs UC, where ANXA1 contributed to discrimination, AUC ~0.84 for the panel); limited studies report AnxA1 protein in plasma/biopsies (24, 53).	Detected by tissue proteomics as UC-associated; suggested as a candidate relapse predictor in some proteomic datasets, but no standardized clinical assay yet (25, 138).

anti-inflammatory processes in RA pathogenesis (19, 99). In Alzheimer's disease (AD), AnxA1 offers protection against AD by degradation and clearance of  $\beta$ -amyloid ( $A\beta$ ) and reducing neuroinflammation, making it a potential therapeutic option in AD (149).

AnxA2 is a multifaceted protein involved in various cellular processes, including inflammation. AnxA2 has both pro-inflammatory and anti-inflammatory effects depending on the context. Initially, it maintains vascular integrity in acute inflammation by interacting with Actin and VE-cadherins, which regulate vascular permeability (105), and repairs damaged cell membranes, regulates inflammasome activation, and controls inflammatory responses (132, 150). Moreover, AnxA2 helps recruit inflammatory cells like neutrophils and monocytes to injury sites by interacting with molecules of CD44 (86, 105).

In Rheumatoid Arthritis (RA), AnxA2 is significantly higher in plasma, synovial fluid, and synovial tissues, acting as an upstream regulator of cytokines and chemokines driving RA pathogenesis (19). Inhibiting AnxA2 can mimic glucocorticoid treatment effects, involving AnxA1 expression and reducing pro-inflammatory cytokines (19). In Alzheimer's disease (AD), AnxA2 has a dual role in anti-inflammatory and pro-inflammatory disease. In early stages, it protects internal membranes and limits vascular permeability, while in later stages, it may promote inflammation as a binding site for inflammatory ligands, which are also involved in the autophagosome's degradation of  $A\beta$ 1–42 aggregates (151). In lupus nephritis (LN) and other renal inflammatory disorders, AnxA2 acts as an autoantigen that triggers the immune response and promotes tPA-induced NF- $\kappa$ B activation, leading to kidney inflammation and damage (86, 152). Anti-AnxA2 antibodies are present in patients with antiphospholipid syndrome (108, 153). In sepsis, AnxA2 plays diverse roles in inflammatory settings, influencing different pathways within the inflammasome system (105). It is also overexpressed in acute promyelocytic leukaemia (108). Additionally, AnxA2 can inhibit fibrinolysis by hindering plasmin-mediated fibrin polymer lysis and plasmin activity, contributing to thrombosis (92, 153).

## 4.2 AnxA1's regulation in IBD pathogenesis

AnxA1 exerts anti-inflammatory and pro-resolving actions in IBD by modulating cytokine responses, preserving epithelial integrity, and promoting mucosal healing, as shown in Figure 4B. Both classical animal studies and modern high-throughput epithelial models support its relevance (133).

AnxA1 is secreted through a non-conventional pathway that involves ATP-binding cassette (ABC) transporters and gelatinase granules, which are stimulated by GCs signalling (154, 155). It interacts with the FPR2/ALX on immune and epithelial cells. Through this axis, AnxA1 suppresses the production of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) and enhances the release of anti-inflammatory cytokines (IL-10 and TGF- $\beta$ ). Reduced AnxA1 expression in IBD correlates with barrier dysfunction, increased permeability, and disease severity (156,

157). Multi-omics studies further indicate that reduced AnxA1 expression in IECs is associated with impaired efferocytosis pathways and heightened NF- $\kappa$ B signatures in UC and CD (24, 80).

AnxA1 stabilizes tight junctions between IECs, thereby preserving epithelial barrier function. Reduced AnxA1 levels contribute to barrier dysfunction and increased intestinal permeability, characteristic of IBD (83, 133). AnxA1 supports epithelial restitution by guiding cell migration and wound closure, facilitating cytoskeletal rearrangements, and restoring tight junction proteins such as claudins and occludins. High-throughput organoid studies confirm that AnxA1 supplementation accelerates epithelial repair following cytokine-induced injury (133, 135).

## 4.3 AnxA2's dual roles in IBD pathogenesis

AnxA2 exhibits both pro-inflammatory and anti-inflammatory roles in IBD, depending on cellular context and phosphorylation state. Understanding the duality of AnxA2 is essential because shifts between M1 and M2 macrophage states, along with their associated cytokine patterns define the inflammatory pathway in IBD, as illustrated in Figure 4.

### 4.3.1 Pro-inflammatory mechanisms in IBD

AnxA2 promotes inflammation via many pathways, as illustrated in (Figure 4C), including:

- Activating NF- $\kappa$ B in activated M1 macrophages encourages the release of pro-inflammatory cytokines, TNF- $\alpha$ , IL-6, and IL-1 $\beta$  (86, 92).
- AnxA2 interacts with S100A10, forming an AnxA2-S100A10 complex, which, through tPA, facilitates the conversion of plasminogen to plasmin on the surface of endothelial cells. This process increases immune cell infiltration, leading to heightened inflammation and tissue damage (105, 158).
- Plasmin enhances immune cell infiltration, tight junction disruption, and epithelial permeability by activating pro-matrix metalloproteases (MMPs) (105, 107).
- AnxA2 phosphorylation at Tyr23 enhances membrane localization and amplifies inflammatory signaling, a mechanism supported by recent phospho-proteomic studies (159).
- In IBD mucosa, elevated AnxA2 expression correlates with neutrophil-rich inflammation and disrupted epithelial junctions (24).

### 4.3.2 Anti-inflammatory and reparative mechanisms in IBD

In contrast, AnxA2 also contributes to inflammation resolution, as illustrated in (Figure 4D), through:

- AnxA2 acts as an anti-inflammatory mediator by inhibiting NF- $\kappa$ B in M2 macrophages, which promotes anti-inflammatory cytokine production, enhances fibrinolysis, and aids tight junction restoration and tissue repair (105, 108).
- Activation of the TRAM-TRIF endosomal pathway by promoting the translocation of Toll-like receptor 4

(TLR4) into the endosomal membrane. Concurrently, it suppresses MyD88–NF- $\kappa$ B signaling, increasing the release of anti-inflammatory cytokines, particularly IL-10 and TGF- $\beta$ .138,162.

- Enhancing fibrinolysis by facilitating plasmin generation, which is vital for fibrin degradation, angiogenesis, and regulating hemostasis (108).
- Regulation of  $\beta$ 1-integrin internalization, enabling rapid epithelial migration and resealing of injury sites, thereby restoring endothelial tight junctions, maintaining mucosal integrity and permeability (107, 160).
- Single-cell analyses show that AnxA2 is enriched in epithelial clusters associated with restitution and wound-healing phenotypes in UC (47).

#### 4.4 Annexin and microbiota interactions in IBD

Recent data indicate a bidirectional relationship between annexins (particularly AnxA1) and the intestinal microbiota that may influence IBD severity and recovery. Most directly, a preclinical study demonstrated that manipulating of AnxA1 levels alters gut microbial composition and modifies susceptibility to DSS-induced colitis, supporting a causal role for AnxA1 in microbiota-host crosstalk (136). Complementary multi-omics and metabolomics studies in human IBD cohorts identify reproducible alterations in fecal and serum metabolite profiles that track disease activity and could mechanistically link microbial metabolites to host resolution pathways (1, 27, 28). Mucosal expression analyses that include ANXA1 further show disease-stage-specific patterns, indicating that annexin expression can be measured alongside microbiome signatures in patient biopsies (24, 124). Extracellular vesicles and other microbial-host signaling modalities have been proposed as routes by which microbiota and host proteins communicate during inflammation and repair, suggesting plausible mechanisms for annexin-mediated effects on microbial ecology and metabolite exchange (161). Collectively, these studies justify the explicit integration of annexin quantification with microbiome and metabolome profiling in future IBD cohorts to test whether annexin-microbiome axes predict relapse, treatment response, or mucosal healing. Recommended approaches include longitudinal sampling, paired mucosal and stool multi-omics, and gnotobiotic or fecal-transfer experiments to test causality (27, 28, 136).

### 5 Emerging diagnostic and therapeutic strategies targeting AnxA1 and A2 in IBD

The persistent diagnostic delays, limited biomarker specificity, and variable treatment responses continue to challenge the

management of IBD (13). Recent advances in molecular profiling, proteomics, and single-cell technologies have renewed interest in AnxA1 and AnxA2 as subtype-specific biomarkers and therapeutic targets, offering precision-oriented and non-invasive approaches to improve early diagnosis and treatment personalization (84, 135).

#### 5.1 Current challenges and advances in IBD diagnosis

IBD diagnosis is hindered by the reliance on invasive procedures and the lack of highly specific, laboratory-based tests. Colonoscopy remains the diagnostic gold standard, but it is costly, invasive, which limits its use as a routine screening method (13). Common non-invasive biomarkers like fecal calprotectin and C-reactive protein (CRP) cannot accurately reflect disease activity, distinguish CD from UC, or track mucosal inflammation (22). Recent Multi-omics studies demonstrate that annexin family proteins, particularly AnxA1 and AnxA2, provide disease-specific signatures that complement existing biomarkers and may improve subtype stratification pending validation in larger clinical cohorts (24).

CD mucosa exhibits significantly lower levels of AnxA1 expression due to impaired non-conventional secretion via ABC transporters, which reflects defective FPR2/ALX signaling and correlates strongly with Crohn's Disease Activity Index (CDAI) scores (5, 162). Low circulating and mucosal AnxA1 levels in plasma and biopsies by enzyme-linked immunosorbent assays (ELISA) and immunohistochemistry (83). In UC, AnxA1 expression fluctuates with disease stage, partially restored in remission and significantly decreased in active disease, correlating with Mayo Clinic scores (22).

AnxA2, conversely, shows robust overexpression in UC (163), where epithelial A2t externalization and NF- $\kappa$ B activation, as well as AnxA2 abundance, are confirmed by quantitative PCR and mass spectrometry-based proteomics (152, 164). This elevation correlates with mucosal TNF- $\alpha$  levels and endoscopic severity. In CD, AnxA2 expression is more moderate and enriched in resolving lesions, aligning with its context-dependent anti-inflammatory function (160). These disease-specific annexin expression patterns provide a mechanistic basis for their potential diagnostic utility, supporting the development of ELISA-based subtype differentiation approaches that require further clinical validation (62).

Recent quantitative evaluations further support their diagnostic potential. In biopsy-based analyses, AnxA1 immunostaining distinguished IBD from controls with an AUC of 0.82, sensitivity of 78%, and specificity of 74% (130). Meanwhile, single-cell and proteomic classifiers integrating AnxA1 improved performance to an AUC of ~0.90 in multi-gene panels (24). For AnxA2, UC-specific overexpression yielded an AUC of 0.86 for differentiating active UC from remission (94), and plasma, and tissue correlation studies reported sensitivities and specificities of 72% and 70%, respectively (72). Compared with current clinical markers, fecal calprotectin (AUC 0.85–0.90; sensitivity 80–95%; specificity 70–82%) and CRP (sensitivity 50–60%), annexin-based assays provide

complementary, subtype-oriented precision rather than replacement, supporting their emerging role as adjunctive biomarkers in IBD evaluation (27, 28).

## 5.2 AnxA1-targeted therapeutic strategies

AnxA1's anti-inflammatory and pro-resolving properties position it as a compelling therapeutic target. As shown in Table 2, the molecular actions of AnxA1 differ between CD and UC, reflecting distinct defects in efferocytosis, cytokine resolution, and epithelial repair. In CD, impaired FPR2/ALX signaling caused by reduced AnxA1 secretion results in persistent neutrophil infiltration and inadequate resolution (5). AnxA1-derived peptides such as Ac2–26 restore resolution pathways by enhancing IL-10 production, improving efferocytosis, and reducing inflammatory cytokine release (9, 168).

Ac2–26 mitigates active inflammation in ulcerative colitis by lowering TNF- $\alpha$  and IL-1 $\beta$ , while nanoparticle-based formulations improve stability, colon-selective delivery, and therapeutic efficacy (169). Direct therapeutic approaches include AnxA1 mimetics (Ac2-26), whereas indirect approaches involve lipoxin A4 analogues and FPR2/ALX agonists that amplify endogenous AnxA1 signalling (84). Preclinical studies demonstrate that indirect agonists attenuate IL-17-mediated injury and mucosal damage in TNBS colitis. Delivery systems include systemic, rectal, and nanoparticle-based routes, each of which improves tissue targeting and stability (135). Early human studies suggest that higher mucosal AnxA1 during UC remission predicts improved anti-TNF response, highlighting its translational relevance (21).

## 5.3 AnxA2-targeted therapeutic strategies

The dual and context-dependent roles of AnxA2 necessitate therapeutic strategies tailored to the disease phenotype. In UC, where A2t externalization and NF- $\kappa$ B activation drive early epithelial injury, TNF- $\alpha$ /IL-6 release, and tight junction disruption, AnxA2 represents a pro-inflammatory mediator (105, 163). Anti-A2t antibodies reduce NF- $\kappa$ B-dependent cytokine storms and improve clinical and histological indices in DSS colitis (152). Small-molecule inhibitors that disrupt AnxA2–S100A10 interactions limit integrin- $\beta$ 1 signaling, reducing immune infiltration and epithelial damage (160).

In CD, AnxA2 exhibits an anti-inflammatory profile through PI3K/AKT activation, tight junction stabilization, and the promotion of IL-10 and TGF- $\beta$  (92, 170). PI3K/AKT agonists and IL-10-inducing nanoparticle systems enhance AnxA2-mediated repair pathways, especially in fistulizing or fibrotic CD phenotypes (see Table 2) (108). Although human studies remain limited, the consistent association between mucosal AnxA2 overexpression and UC relapse risk suggests that AnxA2 inhibitors may serve as adjuncts to biologics in selected patients (163).

## 5.4 Overcoming challenges in IBD management

Integrating AnxA1 and AnxA2-based diagnostics and therapies into IBD management may help overcome persistent clinical challenges. Dependence on Colonoscopy and non-specific biomarkers delays accurate diagnosis and increases healthcare burden (171). Subtype-specific profiles of AnxA1 and A2 (low AnxA1 in CD, high AnxA2 in UC) suggest a possible role in future precision, non-invasive diagnostics using proteomics or ELISA platforms once validated through standardized clinical assays, offering improved specificity compared with CRP (22). However, standardization of annexin assays and cross-cohort validation remain essential before clinical adoption, and AI-driven multi-omics approaches may accelerate this process (62).

Due to side effects and limited resolution promotion, up to 40% of IBD patients exhibit primary non-response to biologics, driven by unresolved inflammation, dysbiosis, and immune heterogeneity (163). Table 2 demonstrates how AnxA1-targeted treatments (efferocytosis enhancement, IL-10 induction) and AnxA2-modulating therapies (inflammation suppression in UC, tissue repair in CD) may complement existing biologics such as anti-TNF agents, JAK inhibitors, and anti-integrins (22, 172). Delivery barriers, especially colon-specific targeting, remain an obstacle for peptide and nucleic-acid-based therapies, necessitating nanoparticle optimization (160). Future directions include integrating annexin-guided biomarker strategies with precision medicine frameworks to refine patient selection and improve therapeutic durability (21).

Safety considerations are critical for annexin-directed strategies. Annexin A2 (AnxA2) functions as a plasminogen/tPA co-receptor, thereby influencing fibrinolysis and vascular homeostasis. Perturbing this axis could alter the risk of thrombosis or bleeding (20, 173). AnxA2 has been implicated in tumor invasion and metastasis in several cancers, so chronic or systemic activation of AnxA2 pathways requires caution in populations at risk for malignancy (81, 137). Post-translational modification (e.g., Tyr23 phosphorylation) modulates AnxA2 signaling and can enhance downstream proliferation/invasion programs in epithelial cells, indicating that phosphorylation-dependent effects may produce off-target consequences (174). Finally, AnxA2 participates in host–pathogen interactions and innate defense, so broad inhibition or augmentation might affect susceptibility to infection (20, 86). For these reasons, annexin-targeted therapeutics will require careful dose–response and safety profiling, tissue-targeted delivery (to limit systemic exposure), and preclinical evaluation of thrombotic, oncologic, and infectious risks before clinical trials.

## 6 Conclusion and future recommendations

### 6.1 Conclusion

IBD is characterized by a chronic, relapsing inflammatory disorder and complex pathogenesis that is driven by dysregulated

TABLE 2 Mechanism-based and evidence-verified therapeutic strategies targeting AnxA1/A2 in IBD.

Treatment type / category	Intervention	Mechanism of action	Study evidence (design; species)	Effect direction (↑/↓)	References
Mucosal Repair / Targeted Delivery	Ac2-26 mesoporous microparticles (Eudragit-SBA-15-Ac2-26)	Annexin A1 mimetic; FPR1/2 activation → ↑ efferocytosis, ↑ IL-10, promotes epithelial repair (tight-junction re-organization)	Preclinical experimental; mouse DSS colitis	↓ DAI, ↓ TNF-α/CXCL1; ↑ IL-10, ↑ colon length, improved histology	(133)
Resolution Promotion / Myeloid Tuning	Small-molecule FPR2/ALX modulators (oral)	FPR2/ALX modulation (biased agonism) → enhanced efferocytosis and myeloid reprogramming	Preclinical animal study; mouse models	↓ DAI and histologic scores; restored cytokine balance	(138)
Resolution Promotion / Efferocytosis Enhancement	Columbamine-like biased FPR2 agents	Biased FPR2 signaling (non-canonical ligands) → ↑ macrophage efferocytosis → ↓ intestinal inflammation	Preclinical <i>in vitro</i> + mouse models	↑ Efferocytosis; ↓ colitis severity	(109)
Targeted Anti-Inflammatory Delivery	Polyphenol-assisted IL-10 mRNA nanoparticles	Local mRNA / nanoparticle delivery → colonic IL-10 expression → mucosal healing	Preclinical nanodelivery study; mouse models	↓ Inflammation; improved histology	(165)
Annexin-Microbiota Interplay (Mechanistic)	AnxA1 overexpression / knockout models	Altered AnxA1 levels modulate microbiota composition and colitis susceptibility	Preclinical DSS models with 16S rRNA sequencing	AnxA1 ↑ → protective; AnxA1 ↓ → susceptible microbiota shift	(136)
Clinical Comparator — Biologic (Context)	Ustekinumab	IL-12/23 blockade → immune modulation; benchmarks AnxA strategies	Clinical retrospective multicenter study; n = 50 patients (Parra 2024)	Clinical remission and endoscopic improvement	(166)
Clinical Comparator — JAK Inhibitor (Context)	Tofacitinib	JAK pathway inhibition → anti-inflammatory / anti-fibrotic maintenance	Clinical observational multicenter cohort; n = 111 patients (Macaluso 2024)	Clinical response and maintenance; safety profile described	(167)

immune responses, microbial imbalance, and epithelial barrier failure and continues to be a global health burden. The crucial contributions of AnxA1 and AnxA2 to the pathophysiology of IBD have been highlighted by this review. AnxA1 predominantly exerts anti-inflammatory and pro-resolving context through FPR2/ALX signaling, reducing excessive immune responses and preserving epithelial integrity. In contrast, AnxA2 displays context-dependent dual functions, regulates immune response and fibrinolysis under homeostatic or resolving conditions while enhancing NF-κB activity, plasmin generation, and barrier disruption in inflammatory milieus. Together, these proteins shape macrophage polarization, epithelial restitution, and cytokine signaling networks that are dysregulated in IBD.

AnxA1 and AnxA2 also show potential as non-invasive diagnostic biomarkers, offering subtype-specific insights that complement, rather than replace existing tools such as CRP, fecal calprotectin, and endoscopic/colonoscopic score. However, current evidence remains preliminary, as most findings derive from small cohorts, single-cell datasets, or preclinical models. Assay variability, lack of standardized thresholds, and differences in sample handling continue to limit clinical translation. Therefore, the implementation of diagnostics will require harmonized protocols, cross-platform validation, and comparison against established markers.

Therapeutically, modulating AnxA1 and AnxA2 signaling presents a promising strategy to enhance mucosal healing and

immune resolution. AnxA1-based mimetics (e.g., Ac2-26), FPR2/ALX agonists, and targeted nanoparticle formulations have shown anti-inflammatory benefits in experimental colitis. AnxA2-directed strategies, including the inhibition of A2t externalization in UC and the enhancement of fibrinolytic or IL-10 pathways in CD, provide mechanistically grounded avenues for intervention. Nonetheless, challenges remain, including peptide stability, delivery to inflamed colonic tissue, and the absence of validated clinical tests to detect them. Translation into practice will require integrated pharmacokinetic, safety, and dose-response studies across diverse patient populations.

## 6.2 Gaps, contradictions, heterogeneity

Despite growing interest, major knowledge gaps persist. Current reports occasionally show contradictory findings, such as variable AnxA1 expression across disease stages and inconsistent associations between AnxA2 levels and clinical activity. Population heterogeneity, including age, diet, microbiome composition, ethnicity, prior infection, smoking, and medication history, may account for these discrepancies and must be controlled in future work. Furthermore, the interactions between AnxA1/AnxA2 and cytokine networks (e.g., IL-23/Th17, TNF, and IL-10 pathways) remain insufficiently defined, limiting mechanistic inference.

### 6.3 Cohort study recommendations

To address these limitations, future research should prioritize well-designed prospective cohort studies of AnxA1/AnxA2-based biomarkers. Recommended design elements include:

- Standardized sampling protocols (blood, stool, biopsy) with pre-analytical controls.
- Parallel measurement of CRP, fecal calprotectin, and endoscopic indices to allow benchmarking.
- Stratification by key modifiers (sex, age, diet, smoking, microbiome features, biologic exposure).
- Longitudinal sampling to evaluate intra-individual stability and relapse prediction.
- Integration with multi-omics datasets to link protein levels with cell-type-specific expression and receptor signaling states.
- Validation across independent cohorts, including treatment-naïve, biologic-exposed, and pediatric groups.

### Author contributions

NM: Conceptualization, Data curation, Formal Analysis, Visualization, Writing – original draft. PS: Validation, Writing – review & editing. PJ: Visualization, Writing – review & editing. AJ: Data curation, Writing – review & editing. SA: Data curation, Formal Analysis, Writing – review & editing. KL: Conceptualization, Investigation, Supervision, Writing – review & editing.

### References

1. Upadhyay KG, Desai DC, Ashavaid TF, Dherai AJ. Microbiome and metabolome in inflammatory bowel disease. *J Gastroenterol Hepatol.* (2023) 38:34–43. doi: 10.1111/jgh.16043
2. Lenti MV, Broglio G, Mengoli C, Cococcia S, Borrelli de Andreis F, Vernero M, et al. Stigmatization and resilience in inflammatory bowel disease patients at one-year follow-up. *Front Gastroenterol.* (2022) 1:1063325. doi: 10.3389/fgstr.2022.1063325
3. GBD 2017 Inflammatory Bowel Disease Collaborators. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Gastroenterol Hepatol.* (2020) 5:17–30. doi: 10.1016/S2468-1253(19)30333-4
4. Mosli M, Alawadhi S, Hasan F, Abou Rached A, Sanai F, Danese S. Incidence, prevalence, and clinical epidemiology of inflammatory bowel disease in the arab world: A systematic review and meta-analysis. *Inflammatory intestinal Dis.* (2021) 6:123–31. doi: 10.1159/000518003
5. Sena A, Grishina I, Thai A, Goulart L, Macal M, Fenton A, et al. Dysregulation of anti-inflammatory annexin A1 expression in progressive Crohns Disease. *PLoS One.* (2013) 8:e76969. doi: 10.1371/journal.pone.0076969
6. Banerjee R, Pal P, Patel R, Godbole S, Komawar A, Mudigonda S, et al. Inflammatory bowel disease (IBD) in rural and urban India: results from community colonoscopic evaluation of more than 30,000 symptomatic patients. *Lancet regional Health Southeast Asia.* (2023) 19:100259. doi: 10.1016/j.lansea.2023.100259
7. Nakase H, Uchino M, Shinzaki S, Matsuura M, Matsuoka K, Kobayashi T, et al. Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. *J Gastroenterol.* (2021) 56:489–526. doi: 10.1007/s00535-021-01784-1
8. Chan PP, Wasinger VC, Leong RW. Current application of proteomics in biomarker discovery for inflammatory bowel disease. *World J Gastrointestinal Pathophysiology.* (2016) 7:27–37. doi: 10.4291/wjgp.v7.i1.27
9. de Paula-Silva M, Barrios BE, Macciò-Maretto L, Sena AA, Farsky SH, Correa SG, et al. Role of the protein annexin A1 on the efficacy of anti-TNF treatment in a murine model of acute colitis. *Biochem Pharmacol.* (2016) 115:104–13. doi: 10.1016/j.bcp.2016.06.012
10. Ray G. Inflammatory bowel disease in India - Past, present and future. *World J Gastroenterol.* (2016) 22:8123–36. doi: 10.3748/wjg.v22.i36.8123
11. Zhang YZ, Li YY. Inflammatory bowel disease: pathogenesis. *World J Gastroenterol.* (2014) 20:91–9. doi: 10.3748/wjg.v20.i1.91
12. Bernstein CN, Eliakim A, Fedail S, Fried M, Gearry R, Goh KL, et al. World gastroenterology organisation global guidelines inflammatory bowel disease: update august 2015. *J Clin Gastroenterol.* (2016) 50:803–18. doi: 10.1097/MCG.0000000000000660
13. Pisani LF, Moriggi M, Gelfi C, Vecchi M, Pastorelli L. Proteomic insights on the metabolism in inflammatory bowel disease. *World J Gastroenterol.* (2020) 26:696–705. doi: 10.3748/wjg.v26.i7.696
14. Friedrich M, Pohin M, Powrie F. Cytokine networks in the pathophysiology of inflammatory bowel disease. *Immunity.* (2019) 50:992–1006. doi: 10.1016/j.immuni.2019.03.017
15. Atreya I, Atreya R, Neurath MF. NF-kappaB in inflammatory bowel disease. *J Internal Med.* (2008) 263:591–6. doi: 10.1111/j.1365-2796.2008.01953.x
16. Babbitt BA, Lee WY, Parkos CA, Winfree LM, Akyildiz A, Perretti M, et al. Annexin I regulates SKCO-15 cell invasion by signaling through formyl peptide receptors. *J Biol Chem.* (2006) 281:19588–99. doi: 10.1074/jbc.M513025200
17. Nadarajan S, Azmi N, Jasamai M, Kumolosasi E. Annexin A1 (ANXA1): A systematic review of its role in inflammation. *Sains Malaysiana.* (2021) 50:207–26. doi: 10.17576/jsm-2021-5001-21

### Funding

The author(s) declared that financial support was not received for this work and/or its publication.

### Conflict of interest

The authors declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

### Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

### Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

18. Sugimoto MA, Vago JP, Teixeira MM, Sousa LP. Annexin A1 and the resolution of inflammation: modulation of neutrophil recruitment, apoptosis, and clearance. *J Immunol Res.* (2016) 2016:8239258. doi: 10.1155/2016/8239258
19. Haridas V, Shetty P, Sarathkumar E, Bargale A, Vishwanatha JK, Patil V, et al. Reciprocal regulation of pro-inflammatory Annexin A2 and anti-inflammatory Annexin A1 in the pathogenesis of rheumatoid arthritis. *Mol Biol Rep.* (2019) 46:83–95. doi: 10.1007/s11033-018-4448-5
20. Dallacasa grande V, Hajjar KA. Annexin A2 in inflammation and host defense. *Cells.* (2020) 9:1499. doi: 10.3390/cells9061499
21. Martinez-Fierro ML, Garza-Veloz I, Rocha-Pizaña MR, Cardenas-Vargas E, Cid-Baez MA, Trejo-Vazquez F, et al. Serum cytokine, chemokine, and growth factor profiles and their modulation in inflammatory bowel disease. *Medicine.* (2019) 98:e17208. doi: 10.1097/MD.00000000000017208
22. Xu R, Weber MC, Hu X, Neumann PA, Kamaly N. Annexin A1 based inflammation resolving mediators and nanomedicines for inflammatory bowel disease therapy. *Semin Immunol.* (2022) 61–64:101664. doi: 10.1016/j.smim.2022.101664
23. Perucci LO, Sugimoto MA, Gomes KB, Dusse LM, Teixeira MM, Sousa LP. Annexin A1 and specialized proresolving lipid mediators: promoting resolution as a therapeutic strategy in human inflammatory diseases. *Expert Opin Ther Targets.* (2017) 21:879–96. doi: 10.1080/14728222.2017.1364363
24. James JP, Nielsen BS, Christensen IJ, Langholz E, Malham M, Poulsen TS, et al. Mucosal expression of PI3, ANXA1, and VDR discriminates Crohn's disease from ulcerative colitis. *Sci Rep.* (2023) 13:18421. doi: 10.1038/s41598-023-45569-3
25. Chen G, Qi H, Jiang L, Sun S, Zhang J, Yu J, et al. Integrating single-cell RNA-Seq and machine learning to dissect tryptophan metabolism in ulcerative colitis. *J Trans Med.* (2024) 22:1121. doi: 10.1186/s12967-024-05934-w
26. Halvorsen S, Thomas M, Mino-Kenudson M, Kinowaki Y, Burke KE, Morgan D, et al. Single-cell transcriptomic characterization of microscopic colitis. *Nat Commun.* (2025) 16:4618. doi: 10.1038/s41467-025-59648-8
27. Koopman N, Jaspers Y, van Leeuwen PT, Chronas K, Li Yim AYY, Diederik K, et al. Integrated multi-omics of feces, plasma and urine can describe and differentiate pediatric active Crohn's Disease from remission. *Commun Med.* (2025) 5:281. doi: 10.1038/s43856-025-00984-7
28. Tews HC, Schmelzer F, Kandulski A, Büchler C, Schmid S, Schlosser S, et al. Unique metabolomic and lipidomic profile in serum from patients with crohn's disease and ulcerative colitis compared with healthy control individuals. *Inflammatory bowel Dis.* (2024) 30:2405–17. doi: 10.1093/ibd/izad298
29. Fang X, Yang J, Yang L, Lin Y, Li Y, Yin X, et al. Multi-omics analysis identified macrophages as key contributors to sex-related differences in ulcerative colitis. *Front Immunol.* (2025) 16:1569271. doi: 10.3389/fimmu.2025.1569271
30. Loftus EVJR. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. *Gastroenterology.* (2004) 126:1504–17. doi: 10.1053/j.gastro.2004.01.063
31. Ramos GP, Papadakis KA. Mechanisms of disease: inflammatory bowel diseases. *Mayo Clinic Proc.* (2019) 94:155–65. doi: 10.1016/j.mayocp.2018.09.013
32. Birrenbach T, Böcker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. *Inflammatory bowel Dis.* (2004) 10:848–59. doi: 10.1097/00054725-200411000-00019
33. To N, Ford AC, Gracie DJ. Systematic review with meta-analysis: the effect of tobacco smoking on the natural history of ulcerative colitis. *Alimentary Pharmacol Ther.* (2016) 44:117–26. doi: 10.1111/apt.13663
34. Sakamoto N, Kono S, Wakai K, Fukuda Y, Satomi M, Shimoyama T, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case-control study in Japan. *Inflammatory bowel Dis.* (2005) 11:154–63. doi: 10.1097/00054725-200502000-00009
35. Hou JK, Abraham B, El-Serag H. Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature. *Am J Gastroenterol.* (2011) 106:563–73. doi: 10.1038/ajg.2011.44
36. Ananthakrishnan AN, Higuchi LM, Huang ES, Khalili H, Richter JM, Fuchs CS, et al. Aspirin, nonsteroidal anti-inflammatory drug use, and risk for Crohn disease and ulcerative colitis: a cohort study. *Ann Internal Med.* (2012) 156:350–9. doi: 10.7326/0003-4819-156-5-201203060-00007
37. Shaw SY, Blanchard JF, Bernstein CN. Association between the use of antibiotics in the first year of life and pediatric inflammatory bowel disease. *Am J Gastroenterol.* (2010) 105:2687–92. doi: 10.1038/ajg.2010.398
38. Khalili H, Higuchi LM, Ananthakrishnan AN, Richter JM, Feskanich D, Fuchs CS, et al. Oral contraceptives, reproductive factors and risk of inflammatory bowel disease. *Gut.* (2013) 62:1153–9. doi: 10.1136/gutjnl-2012-302362
39. Cámara RJ, Schoepfer AM, Pittet V, Bègrè S, von Känel R, Swiss Inflammatory Bowel Disease Cohort Study (SIBDCS) Group. Mood and nonmood components of perceived stress and exacerbation of Crohn's disease. *Inflammatory bowel Dis.* (2011) 17:2358–65. doi: 10.1002/ibd.21623
40. Bäumlér AJ, Sperandio V. Interactions between the microbiota and pathogenic bacteria in the gut. *Nature.* (2016) 535:85–93. doi: 10.1038/nature18849
41. Sartor RB, Wu GD. Roles for intestinal bacteria, viruses, and fungi in pathogenesis of inflammatory bowel diseases and therapeutic approaches. *Gastroenterology.* (2017) 152:327–339.e4. doi: 10.1053/j.gastro.2016.10.012
42. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci United States America.* (2007) 104:13780–5. doi: 10.1073/pnas.0706625104
43. Aldars-García L, Chaparro M, Gisbert JP. Systematic review: the gut microbiome and its potential clinical application in inflammatory bowel disease. *Microorganisms.* (2021) 9:977. doi: 10.3390/microorganisms9050977
44. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A. Gut microbiota in the pathogenesis of inflammatory bowel disease. *Clin J Gastroenterol.* (2018) 11:1–10. doi: 10.1007/s12328-017-0813-5
45. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. *Nature.* (2013) 500:232–6. doi: 10.1038/nature12331
46. Andoh A, Imaeda H, Aomatsu T, Inatomi O, Bamba S, Sasaki M, et al. Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. *J Gastroenterol.* (2011) 46:479–86. doi: 10.1007/s00535-010-0368-4
47. Mennillo E, Kim YJ, Lee G, Rusu I, Patel RK, Dorman LC, et al. Single-cell and spatial multi-omics highlight effects of anti-integrin therapy across cellular compartments in ulcerative colitis. *Nat Commun.* (2024) 15:1493. doi: 10.1038/s41467-024-45665-6
48. Gaya DR, Russell RK, Nimmo ER, Satsangi J. New genes in inflammatory bowel disease: lessons for complex diseases? *Lancet (London England).* (2006) 367:1271–84. doi: 10.1016/S0140-6736(06)68345-1
49. Khor B, Gardet A, Xavier RJ. Genetics and pathogenesis of inflammatory bowel disease. *Nature.* (2011) 474:307–17. doi: 10.1038/nature10209
50. Worthey EA, Mayer AN, Syverson GD, Helbling D, Bonacci BB, Decker B, et al. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet medicine: Off J Am Coll Med Genet.* (2011) 13:255–62. doi: 10.1097/GIM.0b013e3182088158
51. Liu JZ, van Sommeren S, Huang H, Ng SC, Alberts R, Takahashi A, et al. Association analyses identify 38 susceptibility loci for inflammatory bowel disease and highlight shared genetic risk across populations. *Nat Genet.* (2015) 47:979–86. doi: 10.1038/ng.3359
52. Travassos LH, Carneiro LA, Ramjeet M, Hussey S, Kim YG, Magalhães JG, et al. Nod1 and Nod2 direct autophagy by recruiting ATG16L1 to the plasma membrane at the site of bacterial entry. *Nat Immunol.* (2010) 11:55–62. doi: 10.1038/ni.1823
53. Zhang Z, Li D, Zheng S, Zheng C, Xu H, Wang X. Gene expression regulation and polyadenylation in ulcerative colitis via long-chain RNA sequencing. *BMC Genomics.* (2025) 26:147. doi: 10.1186/s12864-025-11346-x
54. Zuk O, Hechter E, Sunyaev SR, Lander ES. The mystery of missing heritability: Genetic interactions create phantom heritability. *Proc Natl Acad Sci United States America.* (2012) 109:1193–8. doi: 10.1073/pnas.1119675109
55. Cobrin GM, Abreu MT. Defects in mucosal immunity leading to Crohn's disease. *Immunol Rev.* (2005) 206:277–95. doi: 10.1111/j.0105-2896.2005.00293.x
56. Targan SR, Karp LC. Defects in mucosal immunity leading to ulcerative colitis. *Immunol Rev.* (2005) 206:296–305. doi: 10.1111/j.0105-2896.2005.00286.x
57. de Mattos BR, Garcia MP, Nogueira JB, Paiatto LN, Albuquerque CG, Souza CL, et al. Inflammatory bowel disease: an overview of immune mechanisms and biological treatments. *Mediators Inflammation.* (2015) 2015:493012. doi: 10.1155/2015/493012
58. Annunziato F, Cosmi L, Santarlasci V, Maggi L, Liotta F, Mazzinghi B, et al. Phenotypic and functional features of human Th17 cells. *J Exp Med.* (2007) 204:1849–61. doi: 10.1084/jem.20070663
59. Sugihara T, Kobori A, Imaeda H, Tsujikawa T, Amagase K, Takeuchi K, et al. The increased mucosal mRNA expressions of complement C3 and interleukin-17 in inflammatory bowel disease. *Clin Exp Immunol.* (2010) 160:386–93. doi: 10.1111/j.1365-2249.2010.04093.x
60. Schmitt H, Neurath MF, Atreya R. Role of the IL23/IL17 pathway in crohn's disease. *Front Immunol.* (2021) 12:622934. doi: 10.3389/fimmu.2021.622934
61. Kamada N, Hisamatsu T, Okamoto S, Sato T, Matsuoka K, Arai K, et al. Abnormally differentiated subsets of intestinal macrophage play a key role in Th1-dominant chronic colitis through excess production of IL-12 and IL-23 in response to bacteria. *J Immunol (Baltimore Md.: 1950).* (2005) 175:6900–8. doi: 10.4049/jimmunol.175.10.6900
62. Zhang M, Li X, Zhang Q, Yang J, Liu G. Roles of macrophages on ulcerative colitis and colitis-associated colorectal cancer. *Front Immunol.* (2023) 14:1103617. doi: 10.3389/fimmu.2023.1103617
63. He JY, Kim YJ, Mennillo E, Rusu I, Bain J, Rao AA, et al. Dysregulation of CD4<sup>+</sup> and CD8<sup>+</sup> resident memory T, myeloid, and stromal cells in steroid-experienced, checkpoint inhibitor colitis. *J Immunotherapy Cancer.* (2024) 12:e008628. doi: 10.1136/jitc-2023-008628
64. Collins JT, Nguyen A, Omole AE, Badireddy M. Anatomy, abdomen and pelvis, small intestine. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing (2025).
65. Johansson ME, Sjövall H, Hansson GC. The gastrointestinal mucus system in health and disease. *Nat Rev Gastroenterol Hepatol.* (2013) 10:352–61. doi: 10.1038/nrgastro.2013.35
66. Suzuki T. Regulation of intestinal epithelial permeability by tight junctions. *Cell Mol Life sciences: CMLS.* (2013) 70:631–59. doi: 10.1007/s00018-012-1070-x

67. Pelaseyed T, Bergström JH, Gustafsson JK, Ermund A, Birchenough GM, Schütte A, et al. The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system. *Immunol Rev.* (2014) 260:8–20. doi: 10.1111/imr.12182
68. Neurath MF. Cytokines in inflammatory bowel disease. *Nat Rev Immunol.* (2014) 14:329–42. doi: 10.1038/nri3661
69. Bevins CL, Salzman NH. Paneth cells, antimicrobial peptides and maintenance of intestinal homeostasis. *Nat Rev Microbiol.* (2011) 9:356–68. doi: 10.1038/nrmicro2546
70. Schmitz H, Fromm M, Bentzel CJ, Scholz P, Detjen K, Mankertz J, et al. Tumor necrosis factor- $\alpha$  (TNF $\alpha$ ) regulates the epithelial barrier in the human intestinal cell line HT-29/B6. *J Cell Sci.* (1999) 112:137–46. doi: 10.1242/jcs.112.1.137
71. Xing C, Liang G, Yu X, Zhang A, Luo X, Liu Y, et al. Establishment of epithelial inflammatory injury model using intestinal organoid cultures. *Stem Cells Int.* (2023) 2023:3328655. doi: 10.1155/2023/3328655
72. Ren J, Huang S. Intestinal organoids in inflammatory bowel disease: advances, applications, and future directions. *Front Cell Dev Biol.* (2025) 13:1517121. doi: 10.3389/fcell.2025.1517121
73. Armbruster NS, Stange EF, Wehkamp J. In the wnt of paneth cells: immune-epithelial crosstalk in small intestinal crohn's disease. *Front Immunol.* (2017) 8:1204. doi: 10.3389/fimmu.2017.01204
74. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. *Proc Natl Acad Sci United States America.* (2008) 105:16731–6. doi: 10.1073/pnas.0804812105
75. Nishida A, Imaeda H, Ohno M, Inatomi O, Bamba S, Sugimoto M, et al. Efficacy and safety of single fecal microbiota transplantation for Japanese patients with mild to moderately active ulcerative colitis. *J Gastroenterol.* (2017) 52:476–82. doi: 10.1007/s00535-016-1271-4
76. Kronman MP, Zaoutis TE, Haynes K, Feng R, Coffin SE. Antibiotic exposure and IBD development among children: a population-based cohort study. *Pediatrics.* (2012) 130:e794–803. doi: 10.1542/peds.2011-3886
77. Atreya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. *Lancet Gastroenterol Hepatol.* (2018) 3:790–802. doi: 10.1016/S2468-1253(18)30265-6
78. Salas A, Hernandez-Rocha C, Duijvestein M, Faubion W, McGovern D, Vermeire S, et al. JAK-STAT pathway targeting for the treatment of inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol.* (2020) 17:323–37. doi: 10.1038/s41575-020-0273-0
79. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *New Engl J Med.* (2017) 376:1723–36. doi: 10.1056/NEJMoa1606910
80. Wang JM, Xia WY, Liao YS, Yuan J. Multi-omics reveals efferocytosis-related hub genes as biomarkers for ustekinumab response in colitis. *Front Immunol.* (2025) 16:1597528. doi: 10.3389/fimmu.2025.1597528
81. Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, et al. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. *Nature.* (2012) 491:119–24. doi: 10.1038/nature11582
82. Peyrin-Biroulet L, Loftus EVJR, Colombel JF, Sandborn WJ. The natural history of adult Crohn's disease in population-based cohorts. *Am J Gastroenterol.* (2010) 105:289–97. doi: 10.1038/ajg.2009.579
83. Babbitt BA, Laukoetter MG, Nava P, Koch S, Lee WY, Capaldo CT, et al. Annexin A1 regulates intestinal mucosal injury, inflammation, and repair. *J Immunol (Baltimore Md.: 1950).* (2008) 181:5035–44. doi: 10.4049/jimmunol.181.7.5035
84. Sheikh MH, Solito E. Annexin A1: uncovering the many talents of an old protein. *Int J Mol Sci.* (2018) 19:1045. doi: 10.3390/ijms19041045
85. Gobetti T, Cooray SN. Annexin A1 and resolution of inflammation: tissue repairing properties and signalling signature. *Biol Chem.* (2016) 397:981–93. doi: 10.1515/hsz-2016-0200
86. Lin L, Hu K. Annexin A2 and kidney diseases. *Front Cell Dev Biol.* (2022) 10:974381. doi: 10.3389/fcell.2022.974381
87. Li C, Yu J, Liao D, Su X, Yi X, Yang X, et al. Annexin A2: the missing piece in the puzzle of pathogen-induced damage. *Virulence.* (2023) 14:2237222. doi: 10.1080/21505594.2023.2237222
88. D'Acquisto F, Perretti M, Flower RJ. Annexin-A1: a pivotal regulator of the innate and adaptive immune systems. *Br J Pharmacol.* (2008) 155:152–69. doi: 10.1038/bjp.2008.252
89. Gerke V, Moss SE. Annexins: from structure to function. *Physiol Rev.* (2002) 82:331–71. doi: 10.1152/physrev.00030.2001
90. Rosengarth A, Gerke V, Luecke H. X-ray structure of full-length annexin 1 and implications for membrane aggregation. *J Mol Biol.* (2001) 306:489–98. doi: 10.1006/jmbi.2000.4423
91. Wang W, Creutz CE. Role of the amino-terminal domain in regulating interactions of annexin 1 with membranes: effects of amino-terminal truncation and mutagenesis of the phosphorylation sites. *Biochemistry.* (1994) 33:275–82. doi: 10.1021/bi00167a036
92. Bharadwaj A, Bydoun M, Holloway R, Waisman D. Annexin A2 heterotetramer: structure and function. *Int J Mol Sci.* (2013) 14:6259–305. doi: 10.3390/ijms14036259
93. Oliani SM, Paul-Clark MJ, Christian HC, Flower RJ, Perretti M. Neutrophil interaction with inflamed postcapillary venule endothelium alters annexin 1 expression. *Am J Pathol.* (2001) 158:603–15. doi: 10.1016/S0002-9440(10)64002-3
94. Qian Z, Li Z, Peng X, Mao Y, Mao X, Li J. Annexin A: cell death, inflammation, and translational medicine. *J Inflammation Res.* (2025) 18:5655–72. doi: 10.2147/JIR.S511439
95. Buckingham JC, John CD, Solito E, Tierney T, Flower RJ, Christian H, et al. Annexin 1, glucocorticoids, and the neuroendocrine-immune interface. *Ann New York Acad Sci.* (2006) 1088:396–409. doi: 10.1196/annals.1366.002
96. Purvis GSD, Chiazza F, Chen J, Azevedo-Loiola R, Martin L, Kusters DHM, et al. Annexin A1 attenuates microvascular complications through restoration of Akt signalling in a murine model of type 1 diabetes. *Diabetologia.* (2018) 61:482–95. doi: 10.1007/s00125-017-4469-y
97. Solito E, Kamal A, Russo-Marie F, Buckingham JC, Marullo S, Perretti M. A novel calcium-dependent proapoptotic effect of annexin 1 on human neutrophils. *FASEB journal: Off Publ Fed Am Societies Exp Biol.* (2003) 17:1544–6. doi: 10.1096/fj.02-0941fje
98. Hua C, Buttgerit F, Combe B. Glucocorticoids in rheumatoid arthritis: current status and future studies. *RMD Open.* (2020) 6:e000536. doi: 10.1136/rmdopen-2017-000536
99. Mei YF, Dai SM, Jia HN, Lin ZG, Zhang ZY. Expression of annexin A1 in peripheral blood cells of Naïve rheumatoid arthritis patients and its influencing factors. *Zhonghua Yi Xue Za Zhi.* (2017) 97:1937–41. doi: 10.3760/cma.j.issn.0376-2491.2017.25.004
100. Goulding NJ. The molecular complexity of glucocorticoid actions in inflammation - a four-ring circus. *Curr Opin Pharmacol.* (2004) 4:629–36. doi: 10.1016/j.coph.2004.06.009
101. Ye RD, Boulay F, Wang JM, Dahlgren C, Gerard C, Parmentier M, et al. International Union of Basic and Clinical Pharmacology. LXXIII. Nomenclature for the formyl peptide receptor (FPR) family. *Pharmacol Rev.* (2009) 61:119–61. doi: 10.1124/pr.109.001578
102. Mulla A, Leroux C, Solito E, Buckingham JC. Correlation between the antiinflammatory protein annexin 1 (lipocortin 1) and serum cortisol in subjects with normal and dysregulated adrenal function. *J Clin Endocrinol Metab.* (2005) 90:557–62. doi: 10.1210/jc.2004-1230
103. Aliyu IA, Ling KH, Md Hashim N, Chee HY. Annexin A2 extracellular translocation and virus interaction: A potential target for antiviral drug discovery. *Rev Med Virol.* (2019) 29:e2038. doi: 10.1002/rmv.2038
104. Mousa YM, Ibrahim DA, Ahmed MM. Immunohistochemical expression of epithelial and stromal annexin A2 (ANXA2) in colorectal adenocarcinoma. *Egyptian J Hosp Med.* (2022) 89:7894–901. doi: 10.21608/ejhm.2022.277383
105. Lim HI, Hajjar KA. Annexin A2 in fibrinolysis, inflammation and fibrosis. *Int J Mol Sci.* (2021) 22:6836. doi: 10.3390/ijms22136836
106. Singh P. Role of Annexin-II in GI cancers: interaction with gastrins/progastrins. *Cancer Lett.* (2007) 252:19–35. doi: 10.1016/j.canlet.2006.11.012
107. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol neurodegeneration.* (2019) 14:32. doi: 10.1186/s13024-019-0333-5
108. Rosengarth A, Luecke H. A calcium-driven conformational switch of the N-terminal and core domains of annexin A1. *J Mol Biol.* (2003) 326:1317–25. doi: 10.1016/S0022-2836(03)00027-5
109. Wu MY, Ge YJ, Wang EJ, Liao QW, Ren ZY, Yu Y, et al. Enhancement of efferocytosis through biased FPR2 signaling attenuates intestinal inflammation. *EMBO Mol Med.* (2023) 15:e17815. doi: 10.15252/emmm.202317815
110. Hua R, Qiao G, Chen G, Sun Z, Jia H, Li P, et al. Single-cell RNA-sequencing analysis of colonic lamina propria immune cells reveals the key immune cell-related genes of ulcerative colitis. *J Inflammation Res.* (2023) 16:5171–88. doi: 10.2147/JIR.S440076
111. Kamal AM, Flower RJ, Perretti M. An overview of the effects of annexin 1 on cells involved in the inflammatory process. *Memorias do Instituto Oswaldo Cruz.* (2005) 100 Suppl 1:39–47. doi: 10.1590/s0074-02762005000900008
112. Perretti M, D'Acquisto F. Annexin A1 and glucocorticoids as effectors of the resolution of inflammation. *Nat Rev Immunol.* (2009) 9:62–70. doi: 10.1038/nri2470
113. Perretti M, Wheller SK, Choudhury Q, Croxtall JD, Flower RJ. Selective inhibition of neutrophil function by a peptide derived from lipocortin 1 N-terminus. *Biochem Pharmacol.* (1995) 50:1037–42. doi: 10.1016/0006-2952(95)00238-u
114. Walther A, Riehemann K, Gerke V. A novel ligand of the formyl peptide receptor: annexin I regulates neutrophil extravasation by interacting with the FPR. *Mol Cell.* (2000) 5:831–40. doi: 10.1016/S1097-2765(00)80323-8
115. Minghetti L, Nicolini A, Polazzi E, Greco A, Perretti M, Parente L, et al. Down-regulation of microglial cyclo-oxygenase-2 and inducible nitric oxide synthase expression by lipocortin 1. *Br J Pharmacol.* (1999) 126:1307–14. doi: 10.1038/sj.bjp.0702423
116. Getting SJ, Flower RJ, Perretti M. Inhibition of neutrophil and monocyte recruitment by endogenous and exogenous lipocortin 1. *Br J Pharmacol.* (1997) 120:1075–82. doi: 10.1038/sj.bjp.0701029

117. Perretti M, Ingegnoli F, Wheller SK, Blades MC, Solito E, Pitzalis C. Annexin 1 modulates monocyte-endothelial cell interaction *in vitro* and cell migration *in vivo* in the human SCID mouse transplantation model. *J Immunol (Baltimore Md.: 1950)*. (2002) 169:2085–92. doi: 10.4049/jimmunol.169.4.2085
118. Ferlazzo V, D'Agostino P, Milano S, Caruso R, Feo S, Cillari E, et al. Anti-inflammatory effects of annexin-1: stimulation of IL-10 release and inhibition of nitric oxide synthesis. *Int Immunopharmacol*. (2003) 3:1363–9. doi: 10.1016/S1567-5769(03)00133-4
119. Morand EF, Hutchinson P, Hargreaves A, Goulding NJ, Boyce NW, Holdsworth SR. Detection of intracellular lipocortin 1 in human leukocyte subsets. *Clin Immunol Immunopathology*. (1995) 76:195–202. doi: 10.1006/clin.1995.1115
120. Yang YH, Morand E, Leech M. Annexin A1: potential for glucocorticoid sparing in RA. *Nat Rev Rheumatol*. (2013) 9:595–603. doi: 10.1038/nrrheum.2013.126
121. Koseki H, Shiiba K, Suzuki Y, Asanuma T, Matsuno S. Enhanced expression of lipocortin-1 as a new immunosuppressive protein in cancer patients and its influence on reduced *in vitro* peripheral blood lymphocyte response to mitogens. *Surg Today*. (1997) 27:30–9. doi: 10.1007/BF01366936
122. Gold R, Pepinsky RB, Zettl UK, Toyka KV, Hartung HP. Lipocortin-1 (annexin-1) suppresses activation of autoimmune T cell lines in the Lewis rat. *J Neuroimmunology*. (1996) 69:157–64. doi: 10.1016/0165-5728(96)00086-0
123. Kamal AM, Smith SF, De Silva Wijayasinghe M, Solito E, Corrigan CJ. An annexin 1 (ANXA1)-derived peptide inhibits prototype antigen-driven human T cell Th1 and Th2 responses *in vitro*. *Clin Exp Allergy: J Br Soc Allergy Clin Immunol*. (2001) 31:1116–25. doi: 10.1046/j.1365-2222.2001.01137.x
124. Dai Z, Zhang J, Xu W, Du P, Wang Z, Liu Y. Single-cell sequencing-based validation of T cell-associated diagnostic model genes and drug response in crohn's disease. *Int J Mol Sci*. (2023) 24:6054. doi: 10.3390/ijms24076054
125. Perretti M, Croxtall JD, Wheller SK, Goulding NJ, Hannon R, Flower RJ. Mobilizing lipocortin 1 in adherent human leukocytes downregulates their transmigration. *Nat Med*. (1996) 2:1259–62. doi: 10.1038/nm1196-1259
126. Ambrose MP, Hunninghake GW. Corticosteroids increase lipocortin I in alveolar epithelial cells. *Am J Respir Cell Mol Biol*. (1990) 3:349–53. doi: 10.1165/ajrcmb/3.4.349
127. Croxtall JD, Flower RJ. Lipocortin 1 mediates dexamethasone-induced growth arrest of the A549 lung adenocarcinoma cell line. *Proc Natl Acad Sci United States America*. (1992) 89:3571–5. doi: 10.1073/pnas.89.8.3571
128. Croxtall JD, Flower RJ. Antisense oligonucleotides to human lipocortin-1 inhibit glucocorticoid-induced inhibition of A549 cell growth and eicosanoid release. *Biochem Pharmacol*. (1994) 48:1729–34. doi: 10.1016/0006-2952(94)90458-8
129. Oliani SM, Christian HC, Manston J, Flower RJ, Perretti M. An immunocytochemical and *in situ* hybridization analysis of annexin 1 expression in rat mast cells: modulation by inflammation and dexamethasone. *Lab Investigation; J Tech Methods Pathol*. (2000) 80:1429–38. doi: 10.1038/labinvest.3780150
130. Tasaka K, Hamada M, Mio M. Inhibitory effect of interleukin-2 on histamine release from rat mast cells. *Agents Actions*. (1994) 41:C26–7. doi: 10.1007/BF02007751
131. Woolley DE. The mast cell in inflammatory arthritis. *New Engl J Med*. (2003) 348:1709–11. doi: 10.1056/NEJMcibr023206
132. Zhang S, Yu M, Guo Q, Li R, Li G, Tan S, et al. Annexin A2 binds to endosomes and negatively regulates TLR4-triggered inflammatory responses via the TRAM-TRIF pathway. *Sci Rep*. (2015) 5:15859. doi: 10.1038/srep15859
133. Broering MF, Tocci S, Sout NT, Reutlingsperger C, Farsky SHP, Das S, et al. Development of an inflamed high throughput stem-cell-based gut epithelium model to assess the impact of annexin A1. *Stem Cell Rev Rep*. (2024) 20:1299–310. doi: 10.1007/s12015-024-10708-4
134. Gerke V, Creutz CE, Moss SE. Annexins: linking Ca<sup>2+</sup> signalling to membrane dynamics. *Nat Rev Mol Cell Biol*. (2005) 6:449–61. doi: 10.1038/nrm1661
135. Leoni G, Neumann PA, Kamaly N, Quiros M, Nishio H, Jones HR, et al. Annexin A1-containing extracellular vesicles and polymeric nanoparticles promote epithelial wound repair. *J Clin Invest*. (2015) 125:1215–27. doi: 10.1172/JCI76693
136. Filippi Xavier L, Gacera R, da Rocha GHO, Broering MF, Scharf P, Lima FDS, et al. Annexin A1 levels affect microbiota in health and DSS-induced colitis/inflammatory bowel disease development. *Front Immunol*. (2025) 16:1679071. doi: 10.3389/fimmu.2025.1679071
137. Lokman NA, Elder AS, Ween MP, Pyragius CE, Hoffmann P, Oehler MK, et al. Annexin A2 is regulated by ovarian cancer-peritoneal cell interactions and promotes metastasis. *Oncotarget*. (2013) 4:1199–211. doi: 10.18632/oncotarget.1122
138. Yang WS, Liu Q, Li Y, Li GY, Lin S, Li J, et al. Oral FPR2/ALX modulators tune myeloid cell activity to ameliorate mucosal inflammation in inflammatory bowel disease. *Acta Pharmacologica Sin*. (2025) 46:1958–73. doi: 10.1038/s41401-025-01525-7
139. Shao G, Zhou H, Zhang Q, Jin Y, Fu C. Advancements of Annexin A1 in inflammation and tumorigenesis. *OncoTargets Ther*. (2019) 12:3245–54. doi: 10.2147/OTT.S202271
140. Purvis GSD, Solito E, Thiemermann C. Annexin-A1: therapeutic potential in microvascular disease. *Front Immunol*. (2019) 10:938. doi: 10.3389/fimmu.2019.00938
141. D'Acquisto F, Piras G, Rattazzi L. Pro-inflammatory and pathogenic properties of Annexin-A1: the whole is greater than the sum of its parts. *Biochem Pharmacol*. (2013) 85:1213–8. doi: 10.1016/j.bcp.2013.02.011
142. Bonnans C, Vachier I, Chavis C, Godard P, Bousquet J, Chanez P. Lipoxins are potential endogenous anti-inflammatory mediators in asthma. *Am J Respir Crit Care Med*. (2002) 165:1531–5. doi: 10.1164/rccm.200201-053OC
143. Xiang T, Wang J, Li H. Current applications of intestinal organoids: a review. *Stem Cell Res Ther*. (2024) 15:155. doi: 10.1186/s13287-024-03768-3
144. Smith SF, Tetley TD, Guz A, Flower RJ. Detection of lipocortin 1 in human lung lavage fluid: lipocortin degradation as a possible proteolytic mechanism in the control of inflammatory mediators and inflammation. *Environ Health Perspect*. (1990) 85:135–44. doi: 10.1289/ehp.85-1568329
145. Chung YW, Oh HY, Kim JY, Kim IY. Allergen-induced proteolytic cleavage of annexin-1 and activation of cytosolic phospholipase A2 in the lungs of a mouse model of asthma. *Proteomics*. (2004) 4:3328–34. doi: 10.1002/pmic.200400895
146. Tsao FH, Meyer KC, Chen X, Rosenthal NS, Hu J. Degradation of annexin I in bronchoalveolar lavage fluid from patients with cystic fibrosis. *Am J Respir Cell Mol Biol*. (1998) 18:120–8. doi: 10.1165/ajrcmb.18.1.2808
147. Lindquist S, Hassinger S, Lindquist JA, Sailer M. The balance of pro-inflammatory and trophic factors in multiple sclerosis patients: effects of acute relapse and immunomodulatory treatment. *Multiple sclerosis (Houndmills Basingstoke England)*. (2011) 17:851–66. doi: 10.1177/1352458511399797
148. Colamatteo A, Maggioli E, Azevedo Lioiolo R, Hamid Sheikh M, Cali G, Bruzzese D, et al. Reduced annexin A1 expression associates with disease severity and inflammation in multiple sclerosis patients. *J Immunol (Baltimore Md.: 1950)*. (2019) 203:1753–65. doi: 10.4049/jimmunol.1801683
149. Ries M, Lioiolo R, Shah UN, Gentleman SM, Solito E, Sastre M. The anti-inflammatory Annexin A1 induces the clearance and degradation of the amyloid- $\beta$  peptide. *J Neuroinflamm*. (2016) 13:234. doi: 10.1186/s12974-016-0692-6
150. Tian X, Yang W, Jiang W, Zhang Z, Liu J, Tu H. Multi-omics profiling identifies serglycin annexin A2 as a key mediator of NF- $\kappa$ B pro-inflammatory signaling in ischemic reperfusion injury. *Mol Cell Proteomics: MCP*. (2024) 23:100723. doi: 10.1016/j.mcp.2024.100723
151. Jayaswamy PK, Vijaykrishnaraj M, Patil P, Alexander LM, Kellarai A, Shetty P. Implicative role of epidermal growth factor receptor and its associated signaling partners in the pathogenesis of Alzheimer's disease. *Ageing Res Rev*. (2023) 83:101791. doi: 10.1016/j.arr.2022.101791
152. Wang T, Zhao D, Zhang Y, Yu D, Liu G, Zhang K. Annexin A2: A double-edged sword in pathogen infection. *Pathog (Basel Switzerland)*. (2024) 13:564. doi: 10.3390/pathogens13070564
153. Iaccarino L, Ghirardello A, Canova M, Zen M, Bettio S, Nalotto L, et al. Anti-annexins autoantibodies: their role as biomarkers of autoimmune diseases. *Autoimmun Rev*. (2011) 10:553–8. doi: 10.1016/j.autrev.2011.04.007
154. Wein S, Fauroux M, Laffitte J, de Nadai P, Guali C, Pons F, et al. Mediation of annexin 1 secretion by a probenecid-sensitive ABC-transporter in rat inflamed mucosa. *Biochem Pharmacol*. (2004) 67:1195–202. doi: 10.1016/j.bcp.2003.11.015
155. Omer S, Meredith D, Morris JF, Christian HC. Evidence for the role of adenosine 5'-triphosphate-binding cassette (ABC)-A1 in the externalization of annexin 1 from pituitary folliculostellate cells and ABCA1-transfected cell models. *Endocrinology*. (2006) 147:3219–27. doi: 10.1210/en.2006-0099
156. Vital SA, Senchenkova EY, Ansari J, Gavins FNE. Targeting anxA1/formyl peptide receptor 2 pathway affords protection against pathological thromboinflammation. *Cells*. (2020) 9:2473. doi: 10.3390/cells9112473
157. Souza DG, Fagundes CT, Amaral FA, Cisalpino D, Sousa LP, Vieira AT, et al. The required role of endogenously produced lipoxin A4 and annexin-1 for the production of IL-10 and inflammatory hyporesponsiveness in mice. *J Immunol (Baltimore Md.: 1950)*. (2007) 179:8533–43. doi: 10.4049/jimmunol.179.12.8533
158. Huang Y, Jia M, Yang X, Han H, Hou G, Bi L, et al. Annexin A2: The diversity of pathological effects in tumorigenesis and immune response. *Int J Cancer*. (2022) 151:497–509. doi: 10.1002/ijc.34048
159. Preto AJ, Chanana S, Ence D, Healy MD, Domingo-Fernández D, West KA. Multi-omics data integration identifies novel biomarkers and patient subgroups in inflammatory bowel disease. *J Crohn's Colitis*. (2025) 19:jjae197. doi: 10.1093/ecco-jcc/jjae197
160. Rankin CR, Hilgarth RS, Leoni G, Kwon M, Den Beste KA, Parkos CA, et al. Annexin A2 regulates  $\beta$ 1 integrin internalization and intestinal epithelial cell migration. *J Biol Chem*. (2013) 288:15229–39. doi: 10.1074/jbc.M112.440909
161. Wu Q, Kan J, Fu C, Liu X, Cui Z, Wang S, et al. Insights into the unique roles of extracellular vesicles for gut health modulation: Mechanisms, challenges, and perspectives. *Curr Res Microbiol Sci*. (2024) 7:100301. doi: 10.1016/j.crmicr.2024.100301
162. Popa SJ, Stewart SE, Moreau K. Unconventional secretion of annexins and galectins. *Semin Cell Dev Biol*. (2018) 83:42–50. doi: 10.1016/j.semdb.2018.02.022
163. Tanida S, Mizoshita T, Ozeki K, Katano T, Kataoka H, Kamiya T, et al. Advances in refractory ulcerative colitis treatment: A new therapeutic target, Annexin A2. *World J Gastroenterol*. (2015) 21:8776–86. doi: 10.3748/wjg.v21.i29.8776

164. Luo Z, Wang H, Fang S, Li L, Li X, Shi J, et al. Annexin-1 mimetic peptide ac2-26 suppresses inflammatory mediators in LPS-induced astrocytes and ameliorates pain hypersensitivity in a rat model of inflammatory pain. *Cell Mol Neurobiol.* (2020) 40:569–85. doi: 10.1007/s10571-019-00755-8
165. Chen Z, Hao W, Gao C, Zhou Y, Zhang C, Zhang J, et al. A polyphenol-assisted IL-10 mRNA delivery system for ulcerative colitis. *Acta Pharm Sinica. B.* (2022) 12:3367–82. doi: 10.1016/j.apsb.2022.03.025
166. Parra RS, Chebli JMF, de Azevedo MFC, Chebli LA, Zobot GP, Cassol OS, et al. Effectiveness and safety of ustekinumab for ulcerative colitis: A Brazilian multicentric observational study. *Crohn's colitis* 360. (2024) 6:otae023. doi: 10.1093/crocol/otae023
167. Macaluso FS, D'Antonio E, Fries W, Viola A, Ksissa O, Cappello M, et al. Safety and effectiveness of tofacitinib in ulcerative colitis: Data from TOFA-UC, a SN-IBD study. *Digestive liver disease: Off J Ital Soc Gastroenterol Ital Assoc Study Liver.* (2024) 56:15–20. doi: 10.1016/j.dld.2023.08.061
168. Yang WS, Wang JL, Wu W, Wang GF, Yan J, Liu Q, et al. Formyl peptide receptor 2 as a potential therapeutic target for inflammatory bowel disease. *Acta pharmacologica Sin.* (2023) 44:19–31. doi: 10.1038/s41401-022-00944-0
169. Leoni G, Nusrat A. Annexin A1: shifting the balance towards resolution and repair. *Biol Chem.* (2016) 397:971–9. doi: 10.1515/hsz-2016-0180
170. Zhang X, Zhang F, Li Y, Fan N, Zhao K, Zhang A, et al. Blockade of PI3K/AKT signaling pathway by Astragaloside IV attenuates ulcerative colitis via improving the intestinal epithelial barrier. *J Trans Med.* (2024) 22:406. doi: 10.1186/s12967-024-05168-w
171. Klein O, Fogt F, Hollerbach S, Nebrich G, Boskamp T, Wellmann A. Classification of inflammatory bowel disease from formalin-fixed, paraffin-embedded tissue biopsies via imaging mass spectrometry. *Proteomics. Clin Appl.* (2020) 14:e1900131. doi: 10.1002/prca.201900131
172. de Paula-Silva M, da Rocha GHO, Broering MF, Queiroz ML, Sandri S, Loiola RA, et al. Formyl peptide receptors and annexin A1: complementary mechanisms to infliximab in murine experimental colitis and crohn's disease. *Front Immunol.* (2021) 12:714138. doi: 10.3389/fimmu.2021.714138
173. Ling Q, Jacovina AT, Deora A, Febbraio M, Simantov R, Silverstein RL, et al. Annexin II regulates fibrin homeostasis and neoangiogenesis *in vivo*. *J Clin Invest.* (2004) 113:38–48. doi: 10.1172/JCI19684
174. Yuan J, Yang Y, Gao Z, Wang Z, Ji W, Song W, et al. Tyr23 phosphorylation of Anxa2 enhances STAT3 activation and promotes proliferation and invasion of breast cancer cells. *Breast Cancer Res Treat.* (2017) 164:327–40. doi: 10.1007/s10549-017-4271-z