Journal of Inflammation Research

Dovepress
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REVIEW

Impact of Neutrophils on the Tissue Microenvironment During Intestinal Inflammation

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Abstract: Neutrophils (polymorphonuclear leukocytes, PMN) are abundant innate immune cells that rapidly accumulate at mucosal surfaces during inflammation. While their antimicrobial functions are essential for host defense, sustained PMN activation profoundly alters the tissue microenvironment, driving epithelial barrier disruption, ECM remodeling, metabolic imbalance, and microbiome dysbiosis. In chronic inflammatory diseases such as inflammatory bowel disease (IBD), these processes contribute to persistent tissue injury and therapeutic resistance. In this review, we synthesize evidence from human mucosal biopsies, experimental models of intestinal inflammation, and emerging single-cell, spatial, and metabolic approaches to define how PMN shape the inflamed mucosal microenvironment. We highlight mechanisms governing PMN recruitment, retention, and survival; effector programs including reactive oxygen species production, protease release, and PMN extracellular trap formation; and bidirectional crosstalk with epithelial, stromal, and immune cell compartments. We further discuss how PMN-driven metabolic and microbiome alterations reinforce chronic inflammation and influence responses to biologic therapy. Collectively, these insights reframe PMN as context-dependent regulators of mucosal pathology and repair and identify PMN-centered pathways as promising targets for precision therapies aimed at restoring barrier function and promoting durable inflammatory resolution.

Keywords: neutrophil, PMN, mucosal inflammation, innate immunity, barrier function, NETosis, microbiome, inflammatory disease

Introduction

Neutrophils (polymorphonuclear leukocytes, PMN) are the most abundant circulating leukocytes and among the first responders to sites of mucosal injury and infection. Traditionally viewed as short-lived effector cells specialized in microbial killing, they are now recognized as dynamic regulators of the tissue microenvironment. At mucosal barriers—including the gastrointestinal tract, lung, and genitourinary system—PMN not only combat pathogens but also profoundly influence barrier function, ECM remodeling, and immune signaling cascades.[1,2]

The mucosal immune system is uniquely poised at the interface between the external environment and host tissues, where epithelial surfaces are exposed to a constant flux of microbial and dietary antigens. Disruption of homeostatic immune regulation at these surfaces can lead to uncontrolled PMN infiltration and activation, a hallmark of chronic inflammatory diseases such as inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), and asthma.[3,4] In these contexts, PMN act as a "double-edged sword": they provide critical antimicrobial defense but simultaneously release reactive oxygen species (ROS), proteases, and PMN extracellular traps (NETs) that exacerbate tissue injury.[5,6]

Emerging evidence underscores the heterogeneity of PMN functional states. High-dimensional single-cell RNA sequencing (scRNA-seq), mass cytometry, and spatial transcriptomics have identified PMN subsets with divergent transcriptional programs, some skewed toward pro-inflammatory or tissue-destructive functions and others linked to pro-resolving and repair phenotypes.[7,8] Such diversity suggests that PMN activity is shaped not only by pathogen-associated molecular patterns and damage-associated molecular patterns, but also by tissue-specific cues, microbiota-derived metabolites, and cytokine gradients present in the inflamed microenvironment.[9,]

https://doi.org/10.2147/JIR.S540855
Received: 20 November 2025
Accepted: 15 April 2026
Published: 1 May 2026

Within the gastrointestinal tract, particularly in ulcerative colitis (UC) and Crohn's disease (CD), PMN infiltration into the lamina propria and across the epithelium correlates strongly with disease activity and tissue damage.[10,11] PMN-derived biomarkers, including fecal calprotectin and circulating myeloperoxidase-DNA (MPO-DNA) complexes, are now standard tools for clinical disease monitoring.[12,13] Despite this, the mechanisms governing PMN persistence, tissue remodeling, and interactions with other immune and stromal cells remain incompletely defined.

Although this review focuses primarily on the gastrointestinal tract, many of the principles governing PMN-driven tissue remodeling extend to other organ systems characterized by barrier surfaces and chronic inflammation. In chronic airway diseases such as chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis, excessive PMN recruitment, protease release, and PMN extracellular trap (NET) formation contribute to epithelial injury, mucus hypersecretion, and airway remodeling.[14] Similarly, in inflammatory skin diseases such as psoriasis, aberrant PMN activation and degranulation amplify local inflammation through increased release of cytotoxic enzymes and NET-associated mediators.[15] PMN are also implicated in liver pathology, where recruitment to sites of injury and release of reactive species and cytokines promote hepatocellular damage and fibrotic responses in viral hepatitis, steatohepatitis, and ischemia-reperfusion injury.[16] Furthermore, PMN contribute to kidney inflammation and tissue damage in acute and chronic renal diseases, reflecting their broader role in organ-specific inflammatory pathology.[17] Collectively, these observations underscore that PMN-driven remodeling of tissue microenvironments represents a conserved pathological axis across organ systems, with insights gained from intestinal inflammation informing broader inflammatory disease biology.

This review will discuss how PMN shape the mucosal microenvironment during active inflammation, with a focus on their recruitment and retention, effector programs, impact on barrier and (ECM) integrity, microbiome interactions, and crosstalk with innate and adaptive immune cells. We synthesize evidence from complementary experimental and clinical approaches, including human mucosal biopsies, murine models of intestinal inflammation, in vitro epithelial–PMN co-culture systems, and emerging high-dimensional methodologies such as single-cell RNA sequencing, spatial transcriptomics, and metabolic profiling. Together, these approaches provide a framework for understanding how context-dependent PMN programs drive either tissue injury or resolution. We will also highlight their roles in chronic mucosal inflammation, particularly IBD, and explore therapeutic strategies that target PMN trafficking, activation, and survival.

PMN Recruitment and Retention

Chemokine-Driven Trafficking

To understand how PMN shape the inflamed mucosal microenvironment, it is first necessary to consider the mechanisms governing their recruitment to mucosal tissues and the signals that promote their persistence once inflammation is established. PMN recruitment to inflamed mucosal sites is orchestrated by a chemokine network that integrates signals from epithelial, stromal, and immune cells. The CXC chemokines CXCL8 (IL-8) in humans and CXCL1/2 (KC/Gro) in mice bind CXCR1 and CXCR2 on PMN, initiating directed migration from the vasculature into tissues.[2,18] In the intestine, epithelial cells and lamina propria macrophages upregulate Il-8 in response to microbial products and pro-inflammatory cytokines such as IL-1β and TNFα[19,20] (Figure 1). Enhanced chemokine gradients in UC and CD lesions correlate with massive PMN influx into the mucosa and crypt abscesses.[10] In the lung, PMN-dominant diseases like cystic fibrosis and acute respiratory distress syndrome (ARDS) show similar CXCR2-dependent recruitment, underscoring the conserved role of CXC chemokines across mucosal tissues.[21]

Therapeutically, CXCR2 antagonists have been explored in clinical trials for COPD and IBD, with partial success, highlighting the translational potential of targeting chemokine-driven trafficking.[22,23] However, redundancy in the chemokine system often limits the efficacy of single-target blockade.

Integrin-Mediated Adhesion

Once PMN are primed by chemokines, firm adhesion to endothelial cells is mediated by β2 integrins (LFA-1/CD11a-CD18 and Mac-1/CD11b-CD18) binding to ICAM-1 and ICAM-2.[24] At gut-associated endothelium, MAdCAM-1—primarily known for lymphocyte homing—also contributes to PMN adhesion during intestinal inflammation.[25,26] Rolling interactions

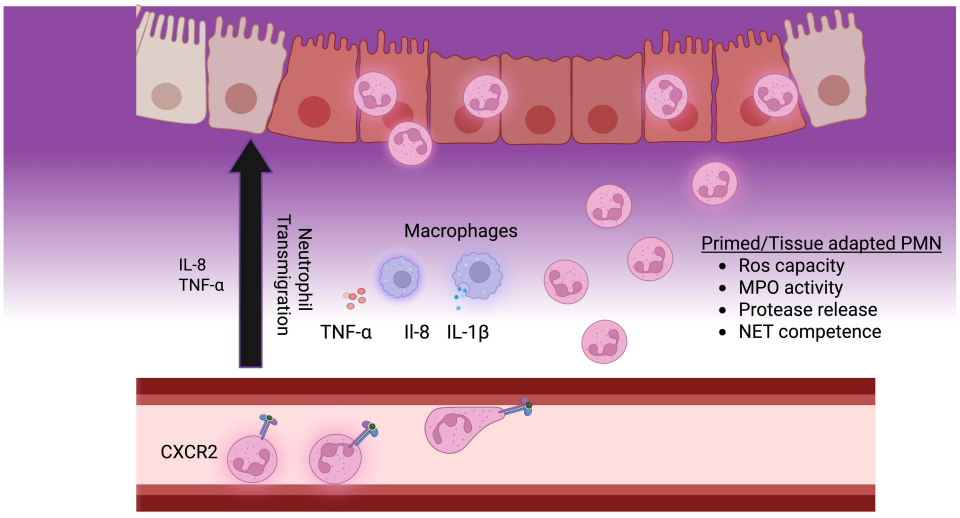

Figure 1 Chemokine- and cytokine-driven recruitment and activation of PMN in intestinal inflammation. This schematic illustrates the sequential steps governing PMN recruitment from the circulation into inflamed intestinal tissue. Epithelial cells and lamina propria macrophages produce CXC chemokines (e.g., CXCL8/IL-8) and pro-inflammatory cytokines (TNF-α, IL-1β), establishing gradients that promote PMN adhesion to activated endothelium, transendothelial migration, and accumulation within the lamina propria and epithelial compartment. These signals not only direct PMN trafficking but also prime PMNs for enhanced effector responses once within the tissue microenvironment.

mediated by selectins (E- and P-selectin) transition to firm adhesion through integrin activation triggered by chemokine receptor signaling.[27]

In IBD, endothelial ICAM-1 and VCAM-1 are markedly upregulated, promoting exaggerated PMN entry into tissues.[28] Antibody blockade of adhesion molecules, including anti-ICAM-1 and anti-α4β7 integrin therapies, have been evaluated for colitis, though safety and efficacy vary. Natalizumab (anti-α4 integrin) and vedolizumab (anti-α4β7) primarily target lymphocyte trafficking but highlight the therapeutic relevance of adhesion pathways.[29]

Signals Driving Prolonged Retention

While PMN are classically short-lived (half-lives of 6–12 hours in circulation), retention within inflamed mucosal tissues can extend their lifespan to several days.[30,31] Cytokines such as GM-CSF, G-CSF, TNFα, and IL-1β activate survival pathways via STAT3 and NF-κB, delaying apoptosis.[32,33] Hypoxia, acidosis, and microbial signals within inflamed mucosa further prolong PMN survival.[34,35] Reverse migration—where PMN exit tissues and re-enter circulation—has also been described, potentially contributing to systemic inflammation and distant organ injury.[36]

In IBD, defective clearance of apoptotic PMN by macrophages exacerbates tissue damage, perpetuating cycles of inflammation.[37] Transcriptional profiling has identified "tissue-persistent" PMN subsets in colonic lesions with enriched expression of anti-apoptotic genes.[38] This persistence promotes chronic tissue injury and fibrosis.

PMN Functional Programs in Inflamed Mucosa

Reactive Oxygen Species (ROS) Production

Once recruited and retained within inflamed mucosal tissues, PMN engage distinct effector programs that extend well beyond microbial killing and directly remodel the local tissue environment. PMN-derived superoxide anion, hydrogen peroxide and MPO combine to catalyze the ultimate formation of HOCl, a highly reactive oxidant that can directly modify proteins, lipids, and nucleic acids.[39,40] Recent studies highlight that MPO not only generates oxidants but also participates in remodeling epithelial barriers. Specifically, MPO-mediated chlorination of extracellular tight junction tyrosines—including occludin, ZO-1, and claudins—leading to altered localization and impaired barrier integrity.[41] These modifications illustrate how PMN oxidative products extend beyond microbial killing to active tissue remodeling, driving persistent permeability defects observed in IBD lesions.

https://doi.org/10.2147/JIR.S540855

In UC, excessive MPO activity correlates with disease severity, and fecal MPO serves as a clinical biomarker.[13,42] Genetic deficiencies in NADPH oxidase components (eg., chronic granulomatous disease) illustrate the importance of ROS for antimicrobial defense, as patients suffer from recurrent mucosal infections.[43,44] Conversely, pharmacologic MPO inhibitors are under investigation for IBD to mitigate oxidative damage.[45]

Degranulation and Protease Release

PMN release proteolytic enzymes stored in primary (azurophilic), secondary (specific), and tertiary (gelatinase) granules. Key proteases include PMN elastase (NE), cathepsin G, and proteinase 3, which degrade microbial proteins but also damage epithelial junctional complexes and ECM components.[46] Matrix metalloproteinases (MMP-8, MMP-9) further amplify tissue breakdown.[47]

In the colon, uncontrolled protease activity contributes to ulceration and loss of epithelial barrier integrity.[48] Elevated MMP-9 levels in IBD correlate with disease activity and predict poor response to anti-TNF therapy.[49] Protease inhibitors, including α1-antitrypsin and synthetic NE inhibitors, are being explored as adjunctive therapies.[50]

NETosis and Extracellular Traps

PMN NETs are web-like structures composed of decondensed chromatin decorated with histones, MPO, NE, and antimicrobial peptides.[5,6] While NETs immobilize and kill microbes, their persistence drives mucosal damage by exposing epithelial cells to cytotoxic histones and proteases. NETs have been detected in intestinal biopsies and feces of IBD patients, correlating with active disease.[51] Impaired clearance of NETs, due to reduced DNase activity, exacerbates tissue injury and perpetuates inflammation.[52]

NETosis also links PMN to thrombosis, as NETs provide scaffolds for platelet adhesion and coagulation factor activation. This may partly explain the increased risk of thromboembolic complications in IBD.[53] Therapeutic strategies include DNase supplementation and PAD4 inhibitors to block NET formation.[54,55]

Cytokine Crosstalk

PMN both respond to and produce cytokines that shape mucosal inflammation. IL-1β, TNFα, and IL-6 amplify PMN recruitment and survival.[56] In turn, activated PMN release IL-1β, amplifying feed-forward loops that sustain inflammation.[57] PMN-derived TNFα contributes to epithelial apoptosis and barrier dysfunction.[58]

Importantly, PMN are also sources of IL-17 and oncostatin M (OSM), cytokines linked to therapy resistance in IBD.[59,60] IL-17 is central to both recruitment and activation of PMN at mucosal sites.[61] OSM has recently emerged as a predictor of anti-TNF non-response, highlighting a PMN-driven signature that shapes therapeutic outcomes.[59]

PMN Metabolic Reprogramming in Inflamed Mucosa

In addition to canonical effector mechanisms such as oxidative burst, degranulation, and NET formation, PMN function in inflamed mucosa is tightly coupled to metabolic reprogramming imposed by hypoxia, nutrient availability, and inflammatory cues. PMN rely primarily on glycolysis for ATP (adenosine triphosphate) generation, a metabolic strategy that supports rapid effector responses even under hypoxic conditions. In mucosal inflammation, hypoxia-inducible factors (HIF-1α and HIF-2α) reinforce glycolytic programming and prolonged PMN survival.[34,35] In parallel, pro-inflammatory cytokines and microbial ligands enhance glucose uptake and lactate release, creating localized acidosis that influences epithelial and stromal cell function.[62] Metabolic checkpoints also tune effector outputs: HIF-1α–driven glycolysis augments ROS generation, whereas inhibition of mitochondrial oxidative phosphorylation can limit degranulation and NET formation.[63] These insights suggest that PMN metabolism is not merely permissive but actively shapes effector programs, positioning metabolic interventions (eg., glycolysis inhibitors, HIF stabilizers) as potential strategies to modulate PMN activity in IBD.

PMN-Derived Purines and Metabolic Crosstalk

PMN play a central role not only as effector cells but also as key regulators of the local inflammatory milieu through the generation of extracellular purine nucleosides, particularly adenosine. As PMN infiltrate the inflamed mucosa, they release ATP[64] and other nucleotides (eg. diadenosine phosphates),[65] into the extracellular space, either via degranulation,

pannexin channels, or cell lysis. This ATP is rapidly metabolized by a coordinated cascade of ectonucleotidases—principally CD39 (ENTPD1)[64] and ENTPD8,[66] which convert ATP/ADP to AMP, and CD73 (NT5E), which dephosphorylates AMP to adenosine.[67] Hypoxia and HIF-1α activation within the inflamed mucosa strongly upregulate both enzymes on intestinal epithelial,[68] amplifying adenosine production under conditions of limited oxygenation. Adenosine, in turn, engages specific G-protein–coupled adenosine receptors (A2A and A2B subtypes) on PMN, epithelial cells, and endothelial cells to dampen inflammation. Through these receptors, adenosine suppresses PMN oxidative burst, limits proinflammatory cytokine release, enhances epithelial barrier function, and promotes inflammatory resolution.[69] Thus, PMN-derived nucleotides and extracellular metabolism to adenosine constitutes an endogenous negative feedback mechanism that restrains excessive tissue injury in acute colitis. However, prolonged or dysregulated adenosine signaling can also contribute to tissue hypo-responsiveness and fibrosis,[70] underscoring its dual role as both a resolution mediator and potential driver of chronic disease.

Remodeling the Mucosal Microenvironment

Barrier Function: Tight Junctions, Adherens Junctions, and Mucus Layers

The cumulative impact of PMN effector programs is not confined to individual target cells but manifests as broad remodeling of the mucosal microenvironment, encompassing epithelial barrier integrity, ECM architecture, and local metabolic niches. PMN influx into mucosal tissues perturbs epithelial architecture at multiple levels. At the apical junctional complex, ROS (notably MPO-derived HOCl) oxidizes and chlorinates junctional proteins (occludin, claudins, ZO-1), weakening the actin cytoskeleton and increasing paracellular permeability[39,71] (Figure 2). Proteases released during degranulation (PMN elastase, proteinase-3, MMP-9) cleave extracellular domains of E-cadherin and occludin, further destabilizing tight and adherens junctions and promoting drop-outs in transepithelial electrical resistance.[46–48] Epithelial cytoskeletal remodeling downstream of p38 MAPK and MLCK activation increases actomyosin contraction, opening the paracellular space.[72]

During transepithelial migration, PMN transiently unzip tricellular junctions and displace mucins, a process facilitated by junctional adhesion molecule (JAM-A) and CD11b/CD18–ICAM-1 interactions on the apical surface.[24,27] Mucus architecture is also altered: PMN proteases thin the MUC2 gel and disrupt goblet-cell function, exposing the epithelium to luminal antigens and bacteria.[73] In IBD, these mechanisms converge to drive "leaky" barrier phenotypes that correlate with disease activity and relapse risk; clinically, fecal calprotectin and MPO reflect ongoing PMN–epithelial engagement and barrier disruption.[12,13] Therapeutically, barrier-protective strategies (eg., myosin light chain kinase (MLCK) inhibition, protease inhibitors, and mucin-stabilizing approaches) are being explored to restore epithelial integrity.[50,72]

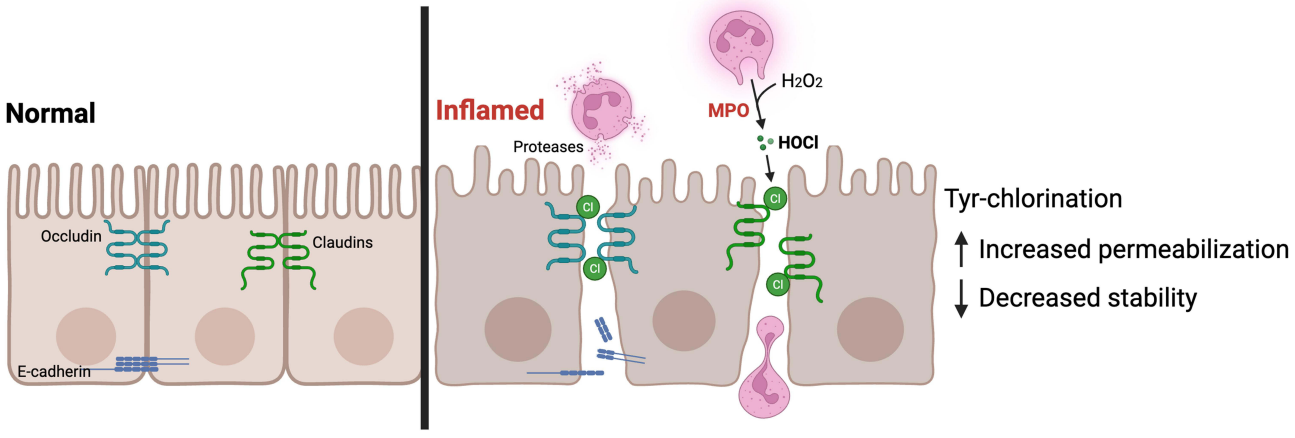

Figure 2 PMN-mediated disruption of epithelial barrier integrity. Under homeostatic conditions, epithelial barrier function is maintained by tight and adherens junction complexes, including occludin, claudins, E-cadherin, and associated scaffolding proteins. During inflammation, infiltrating PMNs release MPO–derived HOCl and granule-derived proteases that chemically modify and proteolytically cleave extracellular junctional domains. These processes destabilize junctional architecture, weaken cytoskeletal anchoring, and increase paracellular permeability, thereby amplifying microbial translocation and sustaining mucosal inflammation.

https://doi.org/10.2147/JIR.S540855

Matrix Degradation: MMPs and ECM Remodeling

PMN orchestrate potent ECM remodeling programs. Granule-derived proteases (NE, cathepsin G, proteinase-3) and gelatinases (MMP-8/9) degrade collagens I/III/IV and laminins, widen interstitial spaces, and facilitate additional leukocyte trafficking.[46,47] NET-bound proteases remain catalytically active and are physically retained in the tissue, prolonging proteolysis and exposing bioactive matrix fragments ("matrikines") that engage TLRs and integrins on epithelial and stromal cells.[5] MMP-9 upregulation in IBD correlates with endoscopic severity, predicts anti-TNF nonresponse, and associates with non-healing ulcers, implicating PMN-dominant ECM circuits in refractory disease.[49]

Crosstalk with stromal cells amplifies remodeling: IL-1β/TNFα from PMN induces fibroblast MMPs and suppresses TIMPs, shifting the balance toward net matrix loss, while ROS modify ECM epitopes and promote fibroblast activation.[56,57,74] Over time, cycles of acute degradation and maladaptive repair favor fibrotic remodeling in CD, where PMN persistence and protease/NET signatures are enriched in stricturing segments.[38] Translationally, selective MMP-9 inhibition and combined protease blockade (including NE inhibitors) are being evaluated as adjuncts to biologics to enhance mucosal healing.[49,50]

Metabolite Shaping: Short-Chain Fatty Acid Depletion, Tryptophan Catabolism, HOCl-Driven Chemistry

PMN significantly reshape the mucosal metabolic landscape during active inflammation. In the inflamed bowel, for example, short-chain fatty acid (SCFA)-producing commensal microbes decline, lowering butyrate and acetate that normally promote epithelial barrier function and Treg differentiation via GPR43/109A and histone deacetylase inhibition.[75] Simultaneously, inflammatory cytokines and IDO/TDO activity drive tryptophan catabolism away from AhR ligands, diminishing IL-22-dependent epithelial repair and antimicrobial peptide induction.[76]

Oxidative chemistry adds a distinct layer: MPO-derived HOCl modifies lipids and amino acids to generate chlorinated species (eg., 2-chloro-adipic acid, chlorotyrosine), which perturbs epithelial bioenergetics, inactivates protease inhibitors, and stiffens local ECM.[39,71] These oxidative adducts and altered metabolite profiles are detectable in stool and serum, suggesting their utility as "liquid biopsy" readouts of PMN activity. In parallel, oxygen consumption by infiltrating PMN and microvascular dysfunction increase luminal oxidative stress, favoring outgrowth of facultative anaerobes (eg., Enterobacteriaceae) and perpetuating a dysbiotic, inflammation-sustaining state.[40,77,78] Restoring SCFAs (dietary fiber, butyrate enemas), supporting AhR signaling, and limiting chlorinating stress (MPO inhibition) represent complementary strategies to normalize the metabolite landscape.[75,79,80]

Beyond proteases and ROS, PMN alter the mucosal metabolite and ionic landscape. During transepithelial migration, PMN release lactic acid and adenosine, inducing localized acidosis that directly impacts epithelial transporter activity.[38,76] Cartwright and colleagues demonstrated that PMN transmigration creates polarized acidification zones that trigger adaptive epithelial programs, including SLC26A3-mediated chloride/bicarbonate exchange.[62] Furthermore, PMN-derived adenosine serves as a buffering mechanism, linking purinergic signaling to epithelial protection during inflammatory acidity.[81] These findings support a model where PMN are not only damage effectors but also architects of a distinct metabolic microenvironment. Epithelial barrier disruption and metabolic perturbations directly influence microbial community structure, PMN-driven tissue remodeling has profound downstream consequences for the intestinal microbiota.

Microbiome Interactions: Pathogen Overgrowth and Commensal Depletion

PMN and the intestinal microbiota maintain a dynamic and reciprocal relationship that profoundly influences mucosal outcomes. Dysbiosis in IBD is typified by reduced levels of obligate anaerobes, such as *Faecalibacterium prausnitzii* and members of the Lachnospiraceae, and expansion of pathobionts, including adherent-invasive *Escherichia coli*.[10] PMN effector responses reinforce these shifts: production of reactive oxygen and nitrogen species elevates luminal oxygen and nitrate, creating niches that favor facultative anaerobes such as Enterobacteriaceae.[77] In parallel, NET-bound proteases and histones degrade mucins, disrupt the protective MUC2 barrier, and reduce colonization resistance, further exposing the epithelium to luminal microbes.[5,73]

Microbiota-derived metabolites also modulate PMN function. SCFA, including butyrate and acetate, normally constrain PMN chemotaxis and oxidative burst, while simultaneously promoting epithelial integrity and Treg differentiation.[75] Conversely, microbiota-derived indole derivatives have recently been shown to function as selective MPO inhibitors that drive PMN toward reparative programs,[41,82] suggesting that metabolite niches critically shape PMN functional responses (Figure 3).

Therapeutically, microbiome-directed strategies—such as dietary fiber supplementation, probiotics, prebiotics, and fecal microbiota transplantation—aim to restore commensal-derived signals. These approaches may be most effective when coupled with interventions that temper PMN-derived damage, such as MPO or protease inhibitors, thereby enabling commensals to re-engraft and reinforce barrier function.[50,80] Future directions include combining metabolic supplementation (eg., butyrate, indole derivatives) with PMN reprogramming agents to re-establish a homeostatic PMN–microbiota dialogue.

PMN and Immune Crosstalk

Effects on Dendritic Cells and Macrophages

Beyond their direct effects on epithelial and stromal compartments, PMN exert substantial influence over innate and adaptive immune responses through sustained crosstalk with myeloid and lymphoid cell populations. PMN shape innate immunity by delivering "immunoregulatory cargo" to dendritic cells (DCs) and macrophages. Uptake of apoptotic PMN by macrophages normally promotes resolution, inducing IL-10 and TGFβ secretion via efferocytosis.[79] In chronic inflammation, however, delayed PMN apoptosis and persistence of necrotic PMN release danger signals (HMGB1, S100A8/9), skewing macrophages toward pro-inflammatory M1-like phenotypes.[37,83] NETs are taken up by DCs, triggering type I interferon production and priming autoreactive T cell responses.[52] PMN-derived IL-1β and TNFα activate DCs and enhance antigen presentation capacity, linking innate sensing to adaptive immunity.[56]

A therapeutic approach currently under investigation examines how macrophage autophagy and its ability to phagocytose dead cells like PMN in the inflammatory environment can be utilized to promote resolution, as macrophages suppress colitis

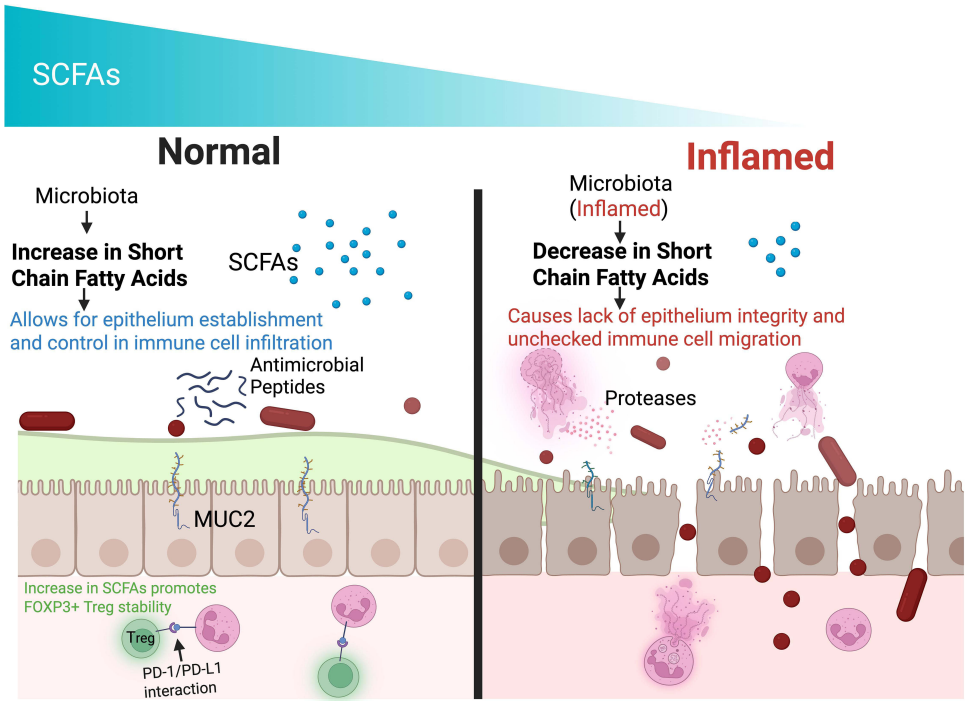

Figure 3 Reciprocal interactions between PMN, epithelial barrier function, and the intestinal microbiota. In the healthy intestine, intact mucus layers (MUC2), antimicrobial peptide production, and regulatory immune networks maintain microbial compartmentalization and support metabolite production, including SCFA that reinforce epithelial integrity and immune tolerance. During inflammation, PMN-driven oxidative and proteolytic stress disrupts mucus architecture and epithelial defenses, promoting loss of colonization resistance, depletion of SCFA-producing commensals, and expansion of inflammatory microbial communities. These changes reinforce PMN recruitment and activation, establishing a feed-forward loop between dysbiosis and tissue injury.

https://doi.org/10.2147/JIR.S540855

symptoms.[84,85] Driving intestinal macrophages towards the anti-inflammatory M2 phenotype, as opposed to the pro-inflammatory M1 phenotype, allows for enhanced resolution in the setting of colitis, indicated by markers like reduced peritoneal PMN and a reduction in cytokines IL-6 and IL-8.[86,87] Anti-TNF treatment for IBD has been shown to increase the proportion of M2-like macrophages that support immunosuppression and wound repair.[88]

Impact on T Cell Polarization

PMN exert strong influence over T cell fate. In inflamed mucosa, they provide IL-1β, IL-6, and IL-23 that drive Th17 polarization, reinforcing PMN recruitment through IL-17–CXCL8 loops.[89] At the same time, excessive PMN-derived ROS and proteases impair Treg stability, tipping the Th17/Treg balance toward chronic inflammation.[38] Recent data demonstrates that PMN-derived arginase and ROS can suppress local T cell proliferation, creating immune-suppressive niches akin to tumor-associated PMN.[90] Furthermore, PMN have also been shown to play a immunoregulatory role, through the promotion of FOXP3+ Tregs by means of PDL-1.[91] In IBD, PMN-rich lesions show transcriptional signatures of IL-17 and IFNγ, underscoring their role in shaping effector T cell responses.[60]

The histone component of NETs contributes to the activation and recruitment of Th17 cells and their associated signals, which drive various inflammatory pathologies. Some ongoing studies suggest the development of a NET-specific histone inhibitor as a means of alleviating some of the harmful effects associated with NET-associated histones.[92] Pharmacological inhibitors of histones are currently being studied in various pathologies, including sepsis, COVID-19 and ARDS.[93,94]

B Cell and Plasma Cell Niche Alterations

PMN also impact humoral immunity. In mucosal tissues, PMN-derived BAFF (B cell activating factor) and APRIL promote B cell survival and class-switching.[95] PMN migrating into Peyer's patches and mesenteric lymph nodes modulate germinal center responses and IgA production.[96] In chronic colitis, PMN accumulation in tertiary lymphoid structures alters plasma cell niches and disrupts local antibody repertoires, potentially influencing microbial containment.[11] Moreover, PMN proteases degrade IgA and IgG at inflamed sites, undermining effective humoral responses.[97]

Over activation of B cells by NETs can cause an excessive immune response leading to the progression of chronic inflammatory disorders.[98] Extracellular DNA from PMN, in the form of LL37-DNA complexes from NETs are able to enter B cells and activate TLR9 signaling, initiating the activation of polyclonal B cells. This is accompanied with an increase in memory B cells, which produce antibodies to target the PMN derived LL37 molecule, leading to IFN production, contributing to chronic inflammatory effects.[99]

Recruitment of PMN to inflamed mucosal surfaces influences plasma cell niches in nearby lymphoid tissue. Inflammation activated PMN are recruited to the epithelium of the GI tract and release APRIL into the villi of the lamina propria, allowing for IgA and IgG producing plasma cell niches to survive and establish in the upper and lower mucosal-associated lymphoid tissue by upregulating antiapoptotic genes.[100,101]

PMN-Driven Therapy Resistance: The M4/M5 Signature and OSM

Transcriptomic profiling in refractory IBD has revealed PMN-enriched modules associated with nonresponse to anti-TNF therapy. Prominently, the M4/M5 inflammatory macrophage signature—driven in part by PMN–macrophage interactions—associates with persistent inflammation despite TNF blockade.[60] PMN themselves are sources of oncostatin M (OSM), a cytokine that activates stromal cells and has emerged as a predictive biomarker of anti-TNF nonresponse.[102] Elevated OSM expression in colonic lesions correlates with poor therapeutic outcomes and failure to achieve mucosal healing. These findings suggest that PMN-derived signals may reprogram the tissue microenvironment to resist biologic therapy. Translationally, targeting PMN–stromal crosstalk, OSM signaling, or PMN persistence may augment existing biologic efficacy and reduce refractory disease.

PMN in IBD Pathogenesis

Spatial Mapping of PMN in UC vs CD Lesions

These PMN-centered interactions converge most prominently in chronic inflammatory diseases of the intestine, where dysregulated recruitment, persistence, and effector activity contribute directly to disease pathogenesis. In UC, PMN

infiltrate diffusely across the lamina propria and accumulate in crypt abscesses, a histological hallmark of active disease.[10] By contrast, CD exhibits patchy PMN infiltration, often at the ulcer margins or within transmural lesions.[11] Multiplex imaging and spatial transcriptomics have revealed PMN clusters at the leading edge of mucosal damage, in close association with epithelial stem/progenitor compartments and activated fibroblasts.[38] PMN positioning within crypts is linked to barrier breakdown and microbial translocation, while perivascular clustering correlates with sustained chemokine gradients.

Persistent Activation and Chronic Damage

Acute PMN responses are normally self-limiting, resolving as efferocytosis clears apoptotic PMN. In IBD, however, persistent PMN activation is driven by ongoing microbial stimulation, pro-inflammatory cytokine networks (IL-1β, TNFα, IL-6), and hypoxic stress.[34,56] Transcriptional profiling of colonic PMN from IBD patients reveals enrichment of NF-κB, STAT3, and HIF-1α target genes, sustaining ROS production, protease release, and NETosis.[38] These effector functions accelerate barrier dysfunction, ECM destruction, and fibroblast activation, promoting ulceration and fibrosis.

Prolonged PMN survival—mediated by GM-CSF, G-CSF, and microbial signals—further amplifies mucosal injury.[30] Defective efferocytosis by macrophages exacerbates PMN persistence, generating necrotic PMN debris that fuels sterile inflammation.[37] This creates a feed-forward loop wherein PMN sustain the very environment that retains and reactivates them.

PMN-Derived Biomarkers

Clinical translation of PMN biology has yielded reliable biomarkers for IBD activity. Fecal calprotectin, a heterodimer of S100A8/S100A9 released by activated PMN, is widely used to monitor disease activity and predict relapse.[12] Elevated levels correlate with endoscopic severity and histological inflammation, providing a non-invasive tool superior to C-reactive protein in mucosal disease.[13] Fecal and serum MPO levels, as well as circulating MPO-DNA complexes reflecting NETosis, have been proposed as additional biomarkers of PMN activity.[51,52]

PMN-derived transcripts, including OSM and IL-1β, stratify anti-TNF responders vs. non-responders.[59] Integrating these markers with spatial transcriptomic data may allow predictive modeling of therapeutic outcomes. Moreover, metabolic readouts such as chlorinated tyrosine adducts in stool or plasma represent emerging signatures of PMN oxidative stress in IBD.[80]

Translational Implications

The pathogenesis of IBD illustrates the dual nature of PMN: essential for microbial defense but pathogenic when chronically activated. Therapies targeting PMN trafficking (CXCR2 antagonists, anti-adhesion molecules), effector pathways (MPO inhibitors, protease inhibitors, PAD4 inhibitors for NETosis), and persistence (modulation of GM-CSF or efferocytosis enhancers) are under investigation.[23,50,54] Understanding how PMN spatially and temporally integrate into mucosal lesions is crucial for designing precision interventions that temper their pathogenic activities without compromising host defense.

Therapeutic Implications

Targeting Recruitment and Trafficking

Recognition of the multifaceted roles PMN play in sustaining mucosal inflammation has prompted the development of therapeutic strategies aimed at modulating their recruitment, effector functions, and survival. Given the centrality of chemokines in PMN recruitment, blocking CXCR2 signaling has been pursued in both preclinical models and early clinical trials. CXCR2 antagonists reduce PMN infiltration and attenuate colitis severity in mice,[18] and in COPD patients they lower neutrophilic airway inflammation. However, redundancy in chemokine networks limits efficacy, as alternative ligands and receptors can compensate.[23] Adhesion molecule targeting provides another avenue: monoclonal antibodies against ICAM-1 and integrins reduce leukocyte trafficking, while clinically approved vedolizumab (anti-α4β7) demonstrates the translational success of trafficking blockade, albeit primarily directed at lymphocytes.[29] As such, extending such strategies to PMN requires precision to avoid impairing host defense and immunosuppression.

Modulating Effector Functions

Directly tempering PMN effector functions is an active area of therapeutic exploration. MPO inhibitors mitigate oxidative tissue damage and are advancing in IBD clinical trials.[80] Protease inhibitors, including NE and MMP-9 blockade, reduce barrier injury and fibrosis in animal models.[49,50] Targeting NETosis with PAD4 inhibitors or DNase supplementation prevents accumulation of cytotoxic NET structures and has shown promise in autoimmune and thrombotic contexts.[54] The challenge remains to selectively suppress pathogenic outputs without undermining microbial clearance.

Barrier-Protective and Microbiome-Directed Strategies

Because PMN-derived ROS and proteases compromise epithelial junctions and mucus layers, barrier-protective agents represent a complementary therapeutic direction. Small-molecule inhibitors of MLCK and stabilizers of tight junction complexes enhance barrier integrity and reduce colitis severity.[72] Mucin supplementation and goblet cell–supporting therapies are under investigation for restoring mucus layers.[73]

Microbiome-directed strategies—dietary fiber enrichment, probiotics, FMT, and postbiotics (SCFAs, tryptophan metabolites)—restore commensal niches and rebalance PMN–microbiota interactions.[75,76] Combining these with PMN-targeted interventions may synergize by simultaneously restoring tolerogenic signals and reducing PMN-driven dysbiosis.

Addressing Therapy Resistance

The recognition of PMN-derived OSM as a mediator of anti-TNF resistance has translational implications.[59] Patients with high OSM expression in colonic lesions are less likely to respond to TNF blockade, suggesting that OSM-targeting approaches or combined PMN-stromal disruption may improve outcomes. More broadly, identifying PMN-driven transcriptional modules that predict nonresponse to biologics could inform precision medicine in IBD.[60]

Balancing Host Defense and Inflammation

A central challenge in PMN-targeted therapy is maintaining antimicrobial defense while limiting tissue damage. PMN-depleting strategies, although effective in dampening inflammation in preclinical models, are not viable clinically due to infection risk.[1] Precision targeting of effector pathways, spatially restricted drug delivery (eg., colonic-release formulations), and temporal modulation (targeting peak inflammation phases) represent approaches to navigate this therapeutic trade-off.

Emerging Therapeutic Strategies: Reprogramming and Resolution

Beyond blocking recruitment or dampening effector functions, future therapies may focus on *reprogramming* PMN toward resolution. Specialized pro-resolving mediators (SPMs), including resolvins, protectins, and maresins, promote efferocytosis-competent, non–NET-forming PMN states that terminate inflammation without compromising host defense.[79,103] Similarly, CXCR4 antagonists that disrupt retention signals may prevent accumulation of tissue-persistent PMN enriched for pro-fibrotic and pro-inflammatory signatures (Hidalgo & Frenette, 2019). Another frontier is the modulation of PMN checkpoint pathways: PD-L1–expressing PMN, identified in mucosal and tumor contexts, can suppress local T cell proliferation, potentially contributing to immune evasion and therapy resistance.[90] These innovations suggest that PMN-directed therapy may evolve from suppression to context-aware reprogramming, with the goal of restoring balance between antimicrobial defense and tissue protection.

Future Perspectives

Spatial and Single-Cell Approaches to Dissect PMN States

While current therapeutic approaches largely focus on attenuating PMN-driven injury, emerging technologies now offer unprecedented opportunities to resolve PMN heterogeneity and identify context-dependent programs that may be selectively targeted or reprogrammed. Recent single-cell atlases and spatial technologies are resolving PMN heterogeneity in inflamed mucosa, revealing transcriptional programs that correlate with position, microenvironmental cues, and treatment response.[38,104] scRNA-seq overcomes historical challenges of PMN RNA capture by optimizing nuclei-based protocols and immediate fixation, enabling detection of activation modules (NF-κB, HIF-1α, STAT3), oxidative/

NETosis signatures, and reparative modules linked to lipid mediator biosynthesis.[38] Spatial transcriptomics and multiplex imaging extend this by mapping PMN states to discrete niches—crypt abscesses, ulcer margins, subepithelial capillaries, and fibroblast-rich zones—clarifying how local gradients of oxygen, metabolites, and cytokines coordinate survival and effector outputs.[104] Longitudinal sampling during flares and remission will determine whether PMN states cycle predictably and whether "pre-relapse" states can be prospectively identified.

Functionally, coupling single-cell modalities to ex vivo perturbations (eg., cytokine, metabolite, and microbial ligand panels) and CRISPR perturb-seq can causally assign regulators to pathogenic vs. reparative programs. Priority readouts include oxidative and chlorinating capacity, NET competence, protease release thresholds, and cytokine output (IL-1β, OSM), each tied to tissue position and clinical status.[5,59] Integrating these datasets with matched microbiome/metabolome profiles will illuminate feed-forward loops between dysbiosis, PMN metabolism, and barrier failure.[75,76]

Defining "Beneficial" vs "Pathogenic" PMN Subsets

A central goal is to distinguish PMN states that promote resolution from those that perpetuate injury. On the pathogenic end, states marked by high MPO/NE, PAD4 (NETosis competence), and OSM expression track with persistent ulceration, ECM destruction, and anti-TNF nonresponse.[5,49,59] Conversely, pro-resolving phenotypes may feature enhanced efferocytosis readiness, lipid mediator class switching (resolvins/protectins/maresins), reduced protease release, and metabolic shifts toward oxidative phosphorylation with restrained NOX2 activity.[105] Tissue context likely governs these fates: hypoxia and acidic pH prolong survival and favor NETosis-prone programs, whereas SCFA- and tryptophan–IL-22–rich environments bias toward barrier protection and controlled degranulation[35,75,76] (Figure 4).

Establishing robust markers that are detectable in routine specimens (whole blood, stool, formalin-fixed biopsies) will be key. Candidates include NET-associated histone modifications, chlorotyrosine adducts (MPO activity), transcriptional OSM/IL1B modules, and surface patterns indicative of reverse migration or tissue retention (eg., CXCR4^hi^ signatures).[38,52,80] Validating these panels against clinical outcomes will enable actionable subclassification.

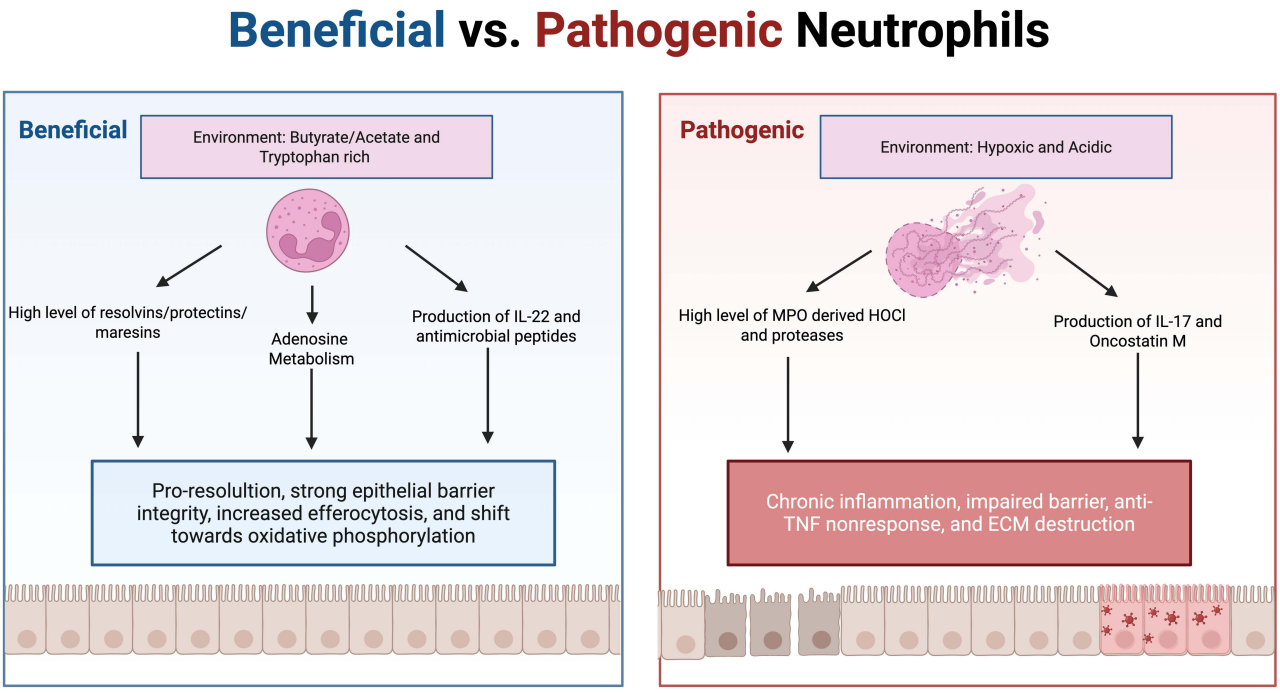

Figure 4 Context-dependent PMN functional states within inflamed mucosal tissue. This conceptual model illustrates how local tissue microenvironments shape distinct PMN functional programs. In metabolite-rich, oxygenated niches characterized by abundant SCFA and tryptophan derivatives, PMN adopt restrained, pro-resolving states that support epithelial barrier maintenance and tissue repair. In contrast, hypoxic, acidic microenvironments enriched for inflammatory cytokines promote PMN programs characterized by heightened oxidative burst, protease release, and extracellular trap formation, leading to barrier disruption and chronic tissue injury. These divergent states highlight how spatial and metabolic context governs PMN contributions to either resolution or pathology.

https://doi.org/10.2147/JIR.S540855

Therapeutic Innovation: Reprogramming Rather Than Depleting

Given the indispensable role of PMN in mucosal defense, future therapies should shift from broad suppression to reprogramming pathogenic states. Three complementary avenues are emerging:

1. Context-aware effector modulation. Local MPO inhibition (colonic-release formulations) and selective protease blockade (NE/MMP-9) can dampen tissue-damaging chemistry while preserving core antimicrobial functions, potentially in time-limited "rescue" windows during flares.[49,50,80] PAD4 inhibitors or controlled DNase delivery may reduce NET burden and thromboinflammatory risk without fully blocking recruitment.[54]
2. Microenvironment repair. Restoring barrier tone (MLCK inhibitors; junction stabilizers), mucin architecture, and epithelial metabolism (butyrate/AhR ligands) attenuates the cues that lock PMN into damage-amplifying states.[72,73,75,76] Targeting stromal circuits (eg., OSM–fibroblast activation) may break therapy-resistant loops.[59]
3. Pro-resolving immunopharmacology. Leveraging specialized SPMs to bias PMN toward efferocytosis-competent, non–NET-forming phenotypes offers a route to terminate inflammation without immunosuppression.[79] Combining SPMs with microbiome-directed strategies could potentiate durable remission by re-establishing tolerogenic metabolite landscapes.

Biomarker-Guided Precision Medicine

Translation of PMN biology into precision tools will rely on modular, composite biomarkers that predict flare, track healing, and inform drug selection. Near-term candidates include: (i) fecal calprotectin (activity monitor), (ii) stool/serum MPO and chlorotyrosine (oxidative load), (iii) fecal NET complexes (MPO–DNA) as indices of NETosis, and (iv) tissue OSM expression as a predictor of anti-TNF nonresponse.[12,51,52,59] Next-generation panels will likely integrate: (a) blood PMN transcriptional modules (eg., OSM/IL1B/STAT3 targets), (b) stool metabolomics (SCFAs, tryptophan–AhR ligands, chlorinated adducts), and (c) spatial biopsy metrics (PMN proximity to crypt base stem cells, fibroblast niches).[38,80,104] Prospective trials should stratify enrollment by these signatures to test therapy selection (eg., OSM^high^ → non-TNF biologics or OSM/OSMR pathway inhibitors; NET^high^ → PAD4/DNase add-on).

Technology and Systems Biology Roadmap

A practical roadmap combines: (i) standardized tissue and stool sampling during flare/remission; (ii) multi-omics profiling (scRNA-seq/spatial transcriptomics + proteomics + metabolomics + microbiome) to build patient-specific PMN state maps; and (iii) machine-learning models that integrate clinical covariates (disease extent, prior biologics) with PMN modules to forecast outcomes.[38,104] Model interpretability is crucial: Shapley or rule-based methods should highlight actionable drivers (eg., OSM, MPO, PAD4) rather than black-box risk scores. Interventional studies can then test whether modulating the identified driver (eg., MPO inhibition in chlorotyrosine^high^ patients) shifts both molecular signatures and clinical endpoints.

For real-world deployment, assays must be robust and scalable. Stool-based panels (calprotectin + NET markers + chlorinated adducts) and blood transcriptional signatures could serve as routine monitoring tools, while spatial profiling is reserved for diagnostic biopsies or treatment failure workups. Harmonizing protocols and data models across centers will accelerate validation and regulatory acceptance. Together, these advances suggest that PMN represent not only drivers of pathology but also tractable nodes for precision intervention in mucosal inflammatory disease.

Conclusion

PMN are no longer viewed as short-lived, single-purpose effectors but rather as versatile regulators of the mucosal immune ecosystem. Their recruitment, retention, metabolic reprogramming, and effector outputs collectively determine whether inflammation resolves or progresses to chronicity.[38,71] In IBD, PMN exemplify this paradox: while they provide indispensable antimicrobial defense, their persistence drives epithelial barrier disruption, ECM remodeling, dysbiosis, and maladaptive immune activation.[10,59]

Emerging insights from single-cell and spatial profiling reveal distinct PMN states, ranging from pathogenic NET- and OSM–producing subsets to potentially reparative populations enriched for pro-resolving lipid mediator pathways.[60,105] Importantly, these states appear to be shaped by local cues, including microbiota-derived metabolites, hypoxia, and cytokine gradients, underscoring the context-dependent nature of PMN biology.[34,75] Rather than representing a uniform effector population, PMN occupy distinct spatial niches, such as crypt abscesses, ulcer margins, subepithelial vasculature, and fibroblast-rich zones, where local gradients of oxygen, metabolites, cytokines, and microbial products shape discrete transcriptional and functional states.[106] Emerging data suggest that PMN localized to these niches exhibit divergent programs, ranging from highly oxidative, NET- and protease-rich phenotypes associated with tissue injury and therapy resistance to potentially reparative states enriched for pro-resolving and barrier-supportive signals.[106,107]

From a translational standpoint, the therapeutic challenge lies in striking a balance: tempering oxidative, proteolytic, and NET-mediated damage while preserving antimicrobial defense. Strategies under investigation include blocking trafficking (CXCR2 antagonists, integrin inhibitors), dampening effector outputs (MPO and protease inhibitors, PAD4 blockade), restoring barrier tone, and supplementing microbiome-derived metabolites.[50,80] Precision medicine approaches that integrate PMN-derived biomarkers—such as fecal calprotectin, MPO-DNA complexes, OSM expression, and chlorinated tyrosine adducts—with patient stratification hold particular promise for tailoring therapies to PMN-driven disease signatures.[13,59]

Looking forward, PMN should be reframed not only as destructive mediators of tissue injury but also as targetable regulators of mucosal protection and repair. By combining PMN-directed therapies with microbiome and metabolite-based interventions, and by leveraging systems biology approaches, future strategies may transform PMN from drivers of pathology into partners in durable mucosal healing.

Highlights

PMN are central regulators of mucosal inflammation, functioning as rapid responders to barrier disruption across the gastrointestinal tract, lung, and other mucosal tissues. Their capacity to both defend against pathogens and remodel the tissue microenvironment underscores their dual role in host protection and tissue injury, making them pivotal targets for translational strategies in acute and chronic inflammatory diseases.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

Faiz Minhajuddin; Conceptualization, writing – original draft, review and editing, Ian Cartwright; Conceptualization, Writing – original draft, Writing – review and editing, and Sean Colgan; Conceptualization, writing review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

United States Veterans Administration: BX006475, BX002181, BX005710. United States National Institutes of Health: GM149812, DK104713, DK095491, DK050189.

Disclosure

The authors have no interest to declare.

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