REVIEW ARTICLE

Intestinal Permeability In Subjects With Rheumatoid Arthritis: A Critical Therapeutic Priority

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Abstract

Rheumatoid arthritis is increasingly being recognized as the synovial manifestation of a group of systemic autoinflammatory conditions known as immune-mediated inflammatory diseases. While each of these conditions displays unique diagnostic signs and symptoms based on the tissue targeted by inflammation, most immune-mediated inflammatory diseases share common features, including their immune-signaling pathways. Owing to these similarities, great advances have emerged in the past few decades using therapies designed to block downstream inflammatory mediators (eg, cytokine-blocking biologics, Janus Kinase (JAK) inhibitors). Unfortunately, fewer advances have been made in therapies that have the potential to target the upstream antecedents and triggers of these complex inflammatory diseases, such as the immunologic chain of events triggered by intestinal hyperpermeability (ie, leaky gut) or gastrointestinal dysbiosis (ie, alterations in the gut microbiota). In the past few decades, intestinal hyperpermeability has emerged as an important antecedent for a wide range of chronic immunological and metabolic conditions, including celiac disease, obesity, cardiovascular disease, and a number of immune-mediated inflammatory diseases such as inflammatory bowel disease, psoriasis, and rheumatoid arthritis. In this narrative review, we discuss the growing awareness that biomarkers of intestinal permeability are frequently associated with non-gastrointestinal immune-mediated inflammatory diseases, particularly those associated with the gut-joint axis, such as rheumatoid arthritis. We suggest that measures of intestinal permeability, along with lifestyle and nutrient interventions that target gut-barrier function, may be important adjunctive clinical tools to help patients with rheumatoid arthritis achieve and maintain remission.

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Introduction

Immune-mediated inflammatory diseases (IMIDs) describes a wide range of conditions in which dysregulated immune responses mediate chronic inflammation in vulnerable tissues such as the gut (eg, inflammatory bowel disease [IBD]), skin (eg, psoriasis), and joints (eg, rheumatoid arthritis [RA]).[1] While often still categorized as autoimmune disorders, IMIDs are multifactorial autoinflammatory disorders that may be characterized by a lack of specific or causal autoreactive T cells or antibodies.[2,3] Nonetheless, once initiated, IMIDs are mediated by core signaling components of both the innate and adaptive immune systems involving the activities of dendritic cells, mast cells, macrophages, T cells (particularly the helper T cells T_H1 and T_H17), and in some cases, B cells secreting autoreactive immunoglobulins.[4] The cytokine signatures of these diseases are particularly notable, most often involving tumor necrosis factor, interleukin (IL) 6, IL-1β, IL-17, IL-12, and IL-23.[5] Pharmacological therapies for IMIDs and similar autoimmune conditions have centered mostly on agents that block fundamental immune-related functions or, more recently, on blocking downstream mediators of inflammation (eg, cytokine blockade, Janus Kinase (JAK) inhibition).[6] However, upstream antecedents (ie predisposing factors) and triggers associated with IMIDs have similar patterns that represent potential therapeutic targets.

Growing evidence suggests that many IMIDs, especially those with shared immune-signaling mediators, share

common antecedents and triggers often described by a simple triad of genetics, environment, and immune dysregulation.[7] However, it is now recognized that a wide range of exogenous and endogenous signals derived from an individual's environment and lifestyle have the potential to act as antecedents and triggers for the risk, severity, or frequency of relapse of many IMIDs.[8] In recent years, growing attention has focused on signals that directly influence the gut-immune interface, such as those that cause alterations in the gut microbiota (ie, dysbiosis) or that induce intestinal hyperpermeability.[9] Logically, these gastrointestinal alterations would be expected to affect inflammatory signals within the gut and influence IMIDs like IBD.[10,11] However, these same associations are also commonly reported in extra-gastrointestinal IMIDs of the skin and joints; particularly psoriasis, psoriatic arthritis, spondylarthritis (SpA), and RA.[12-16] As we outline below, the lines of evidence connecting gut dysbiosis and intestinal hyperpermeability with chronic inflammation within joints may lead to the development of a new strategy for reducing the burden of these systemic inflammatory conditions.

Intestinal barrier and immune functions

A significant proportion of the human immune system is located at the primary environmental barriers of the body, including the gastrointestinal tract, which hosts greater than 75 percent of immune system cells (collectively known as the gastrointestinal-associated lymphoid tissue [GALT]).[17] The reason for this is 2-fold; the gastrointestinal tract represents the largest surface area exposed to the external environment, which is constantly exposed to antigens and potentially harmful compounds and microbes, and it is also the primary location for training the immune system to appropriately recognize self-antigens, nonself-antigens, and commensal and pathogenic organisms (ie, peripheral immune tolerance). This process involves cells and signals from the innate and adaptive immune systems and is highly dependent upon an intact (controlled) barrier between the gut lumen and the lamina propria. Therefore, the barrier and permeability functions of the gut represent one of the most important interfaces between a person and their external environment.

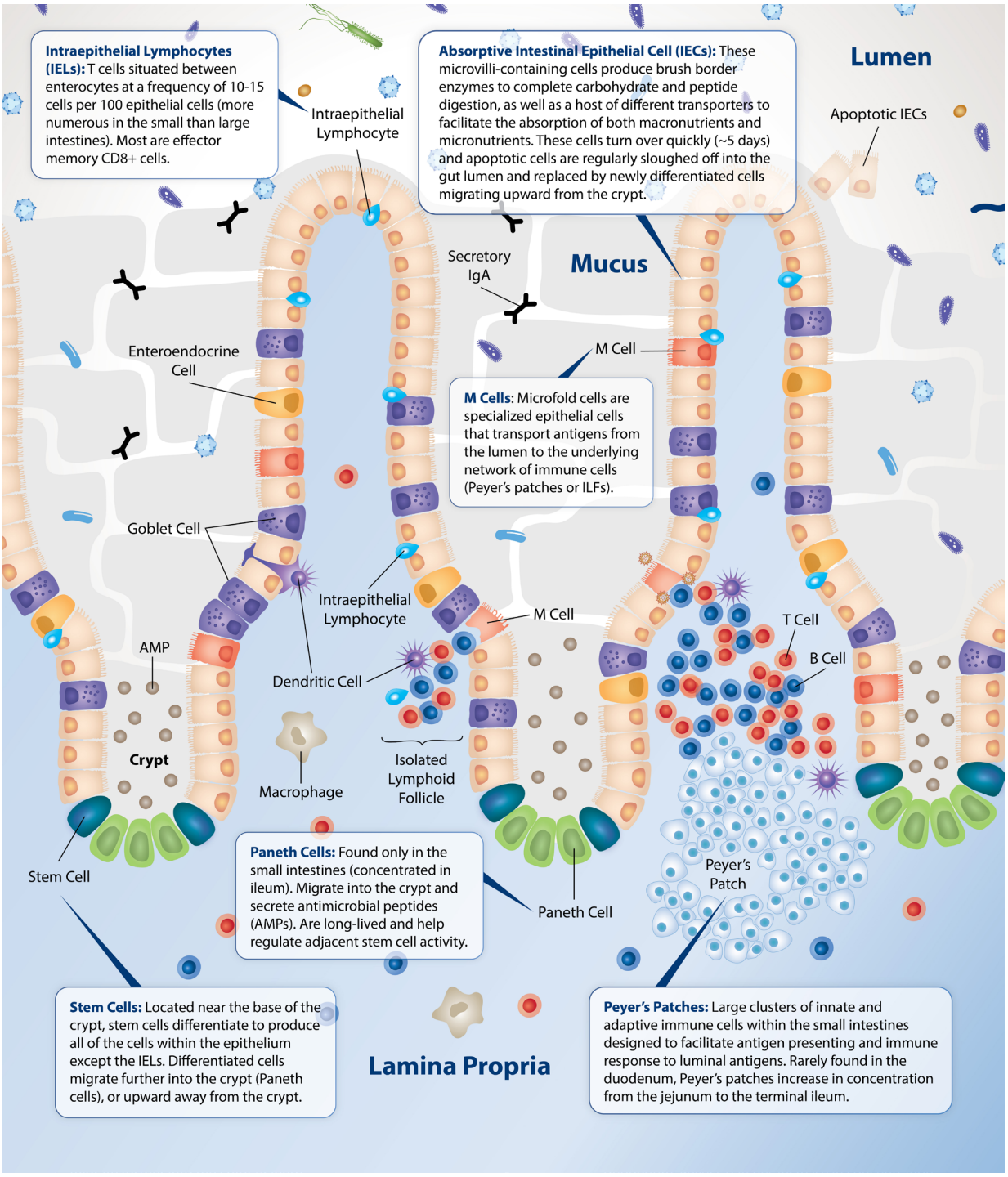
Immunologically speaking, the gut lumen is outside the body, and there is an intricate set of structures designed to ensure it remains so. Similar to other barriers that interface with the external environment, the gastrointestinal mucosal barrier is made of several physical and chemical barriers heavily embedded with immune system surveillance and function (Figure 1). The basic physical feature of this barrier depends on a single layer of columnar cells (eg, enterocytes and colonocytes) that create the foundational interface between the gut lumen and the underlying lamina propria. Both the innate and adaptive immune systems are critical components of the GALT and barrier function of the gut. Approximately 100 to 150 mesenteric lymph nodes are distributed throughout the gut to create numerous "stations" for concentrated interactions between antigens, antigen-presenting cells, regulatory cells, and effector cells. Another prominent feature of the GALT is the 30 or so Peyer patches found primarily along the mucosa of the ileum. These Peyer patches include T cells, B cells, and antigen-presenting cells—mostly dendritic cells—that interface directly with the gut lumen or through the activities of special gut epithelial cells called M cells (microfold cells).[19] These M cells are designed to allow the controlled passage of antigens (eg, commensal bacteria, pathogenic bacteria, viruses, fungi, food particles) from the gut lumen to the lamina propria, where they can be delivered safely to antigen-presenting cells that, in turn, present them to both mature and naive T cells.[20] Depending on the molecular patterns encountered by the innate immune cells (using pattern recognition receptors such as toll-like receptors), signals of activation or tolerance are sent to the adaptive immune cells during antigen presentation. This process of immune surveillance is an important part of the "education" and maturation of the immune system, and also provides an early warning of a potential pathogenic agent in the gut, allowing for a preemptive response.[21] The ultimate goal is to mount appropriate and timely immune responses to harmful and foreign antigens, while creating an active tolerance against harmless antigens or self-antigens.

One of the special features of the adaptive immune response within the GALT, as in most other mucosal tissues, is the abundance of antibody-secreting B cells that produce antibodies of the secretory IgA (sIgA) class.[22] This form of antibody is capable of passing into the lumen of the gut, i passes into breast milk, saliva, and tears, to interact with antigens while they are still "outside" the body. sIgA expression against both pathogenic and commensal organisms is a key regulatory aspect of the intestinal barrier itself.[23,24] Also, there is a well-documented relationship between increased hypothalamic-pituitary-adrenal (HPA) axis stress and reduced sIgA concentration.[25] Laboratory measurements of sIgA concentrations are often used as one of many markers of mucosal immune health and/or HPA axis stress–induced immune suppression; a specific sIgA concentration detected in a stool or saliva sample can indicate a particular antigenic challenge.[26]

Gut barrier disruption and inflammatory signaling

Appropriate immune surveillance within the gastrointestinal tract requires a regulated and intact intestinal barrier, which requires that the paracellular space between each columnar cell limits the uncontrolled passage of harmful substances. This barrier is formed by the connection of these cells to adjacent cells by 3 transmembrane protein complexes: desmosomes, adherent junctions, and tight junctions (TJs). Of the 3 complexes, the TJ regulates the paracellular transport of small ions while acting as a barrier to larger macromolecules. TJs, however, are not just static barriers between epithelial cells but are a dynamic complex of proteins forming a "fence" to keep out large particles and have a network of pores ("gates") for small ions

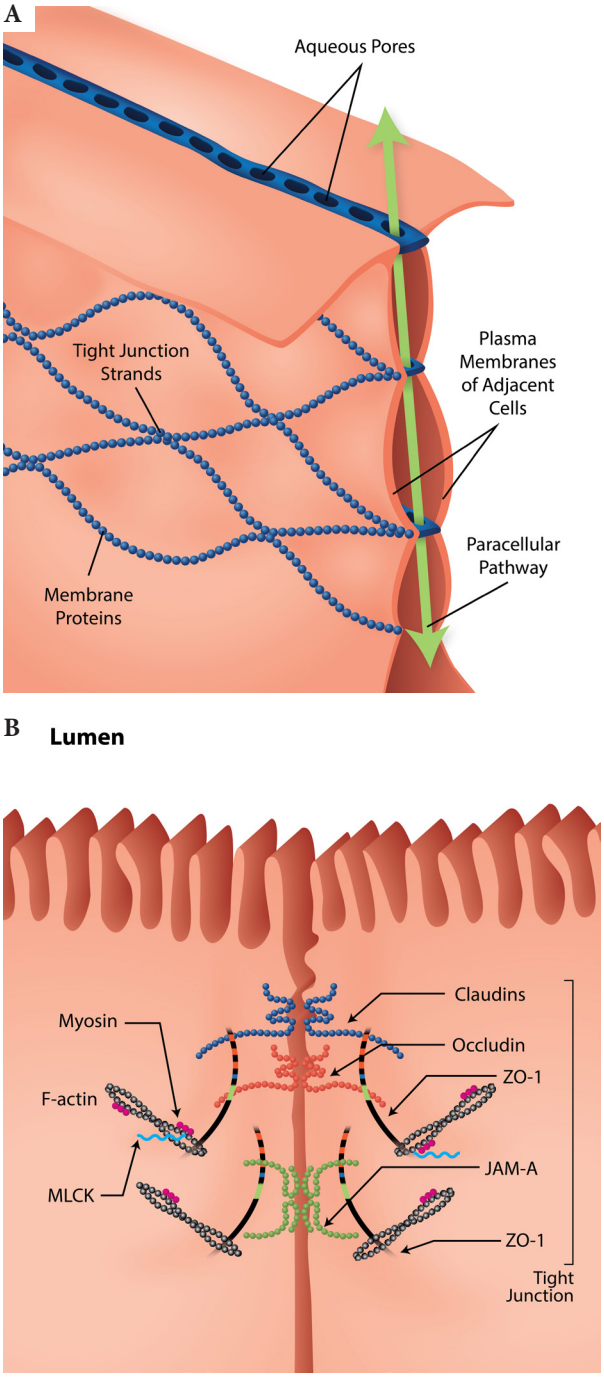
Figure 1. Basic Features of the Gut-Immune Interface.



Note: See text for details. Figure modified with permission.[18]

(~3.5 kDa and smaller) and water (Figure 2). TJs are composed of several different transmembrane proteins, including claudins (at least 24 different kinds), occludin, and junctional adhesion molecule proteins.[27] The extracellular portions of these proteins interact with similar proteins expressed on adjacent cells to form the interlocking TJ. The intracellular portions of these transmembrane proteins are tethered to intracellular actin and myosin filaments by linker or scaffolding proteins, most commonly zonula occludens proteins. The basic structure of the TJ is determined by the expression pattern of the proteins involved (some claudins form pores, while others form impermeable barriers) but can be dynamically altered by phosphorylation of these proteins or of the myosin light chain.[28,29] For instance, myosin light chain phosphorylation triggers the contraction of the myosin light chain, which in

Figure 2. Tight Junctions: Structure and Paracellular Transport. **A,** The gross network of tight junctions creates paracellular pores to control passage of molecules. **B,** A close-up diagram of the proteins that make up each tight junction.



Abbreviations: JAM-A, junctional adhesion molecule A; MLCK, myosin light chain kinase; ZO-1, zonula occludens 1.

turn, opens the paracellular pores in the TJ.[30,31] Signals that trigger these phosphorylation reactions increase markers of gut hyperpermeability and the risk for certain IMIDs.

Many pathogenic organisms trigger phosphorylation events that alter TJ assembly and increase intestinal permeability.[32] These pathogenic or pathobiont organisms disrupt the barrier function of the TJ through signals initiated by directly binding to the gastrointestinal cell or by secreting toxins. Organisms known to trigger TJ disruption include *Vibrio cholerae*, enteropathogenic *Escherichia coli*, enterohemorrhagic *E. coli*, *Clostridium* species, *Helicobacter pylori*, hepatitis C, HIV, and several other viruses (some also disturb TJs in nongastrointestinal barriers).[33-37] In contrast, some commensal organisms (and their related probiotic strains) improve TJ integrity by promoting the formation of TJ-related proteins or inhibiting phosphorylation-induced TJ modulation.[29,38]

While these microbial signals from the gut lumen are one pathophysiological factor that can affect the integrity of the TJ assembly and lead to intestinal hyperpermeability, signals from within enterocytes or from adjacent immune system cells can also lead to similar changes. In particular, inflammatory mediators and other cytokines can trigger the same sorts of phosphorylation patterns of TJ proteins or myosin light chain that lead to increases in TJ pore size or partial disassembly.[39,40] Phosphorylation-mediated TJ disruption have been discovered for quite a range of cytokines, several of which are elevated in the serum of subjects with intestinal permeability–related inflammatory bowel disorders. These cytokines include interferon g, tumor necrosis factor (TNF-α), IL-1β, IL-4, IL-6, and IL-13.

Food antigens may also play a role in altering intestinal permeability. Using gluten exposure and celiac disease as a model, Fasano[41] has postulated a zonulin-mediated loosening of the TJ proteins triggered by gluten exposure in certain individuals (leading to intestinal permeability) as a key trigger in non–celiac disease immune system conditions such as type 1 diabetes, asthma, multiple sclerosis, and IBD. Intestinal permeability, coupled with imbalances within the gut microbiota (ie, dysbiosis), is now considered an important factor in most immune-mediated inflammatory conditions.[9,10,12-14] It is also one of the critical factors mediating dietary influences on immune-mediated inflammation.[15]

Overall, when any of these triggers leads to disruption in the integrity of the intestinal barrier, the mucosal immune system of the gut responds by increasing inflammatory signaling, often characterized by decreased regulatory T cell activity and increased T_H17 activity; these changes are well-known precursors to systemic autoinflammatory conditions such as RA.[42] In fact, the mucosal origin hypothesis of RA suggests that similar immune phenomena from extraintestinal mucosa, such as the gums or lungs, are also likely to play a role as important antecedents.[43]

Zonulin and barrier disruption

The discovery of the protein zonulin and its relationship to the modulation of intestinal permeability has been of great interest over the past several decades. When looking for a human analogue to the zonula occludens toxin produced by *V. cholerae*, Lu and their

team[44], led by Fasano, discovered a ~45 kDa protein produced in the human gut that could mimic the zonula occludens toxin–induced TJ modulations and subsequent increase in intestinal permeability. This protein, which they called zonulin, was later discovered to be the unprocessed precursor of the hemoglobin-binding protein haptoglobin 2. Zonulin is now thought to play an important role in mediating the increased intestinal permeability and immunological reactivity seen in patients with celiac disease and other autoimmune conditions.[45-47]

Zonulin is released from cells of the gastrointestinal epithelium and lamina propria in response to a trigger from the gastrointestinal lumen. The 2 best-described triggers are certain luminal bacteria and gliadin. Once zonulin is secreted into the gut lumen, it binds to receptors on the epithelial cells that trigger a cascade of secondary signals, leading to the phosphorylation of TJ proteins or the myosin light chain and resulting in the destabilization of the TJ and increased intestinal permeability. Gliadin, the protein found in wheat gluten that is related to the prolamins found in barley (hordein) and rye (secalin), is known to trigger the release of zonulin from the gastrointestinal mucosal tissues, a process mediated by its binding to the CXCR3 receptor. Lammers et al[48] have shown that subjects with active celiac disease express higher levels of gut epithelial CXCR3 receptor messenger RNA and zonulin than subjects without celiac disease or subjects with celiac disease on a strict gluten-free diet.

Compared with healthy controls, subjects with RA and pre-RA (ie, elevated autoantibodies with no disease activity) have elevated concentrations of serum zonulin, which correlate with histological changes in the gut barrier and altered expression of TJ proteins.[49] Elevated serum zonulin concentrations in subjects with pre-RA significantly increased their 1-year risk of developing RA, a pattern similar to the presymptom elevations in zonulin seen in the collagen-induced arthritis model in mice. Elevated plasma zonulin concentrations and increased gut permeability also precede disease manifestations in the adjuvant-induced arthritis model in rats.[50] In 1 cohort of 61 subjects with RA in which fecal zonulin was elevated in all subjects, elevated serum zonulin concentrations were associated with disease duration and were more common in subjects positive for rheumatoid factor status.[51] Additionally, elevated zonulin concentration was an independent biomarker that predicted NSAID-treatment failure in subjects with axial spondylarthritis.[52] Measures of intestinal hyperpermeability and inflammation, including elevated zonulin concentration, have been previously reported in subjects with ankylosing spondylitis.[53,54] Though more research is needed across a wider array of subjects with IMIDs, these data suggest that zonulin may be an important biomarker linking gut permeability and immune-mediated joint inflammation.

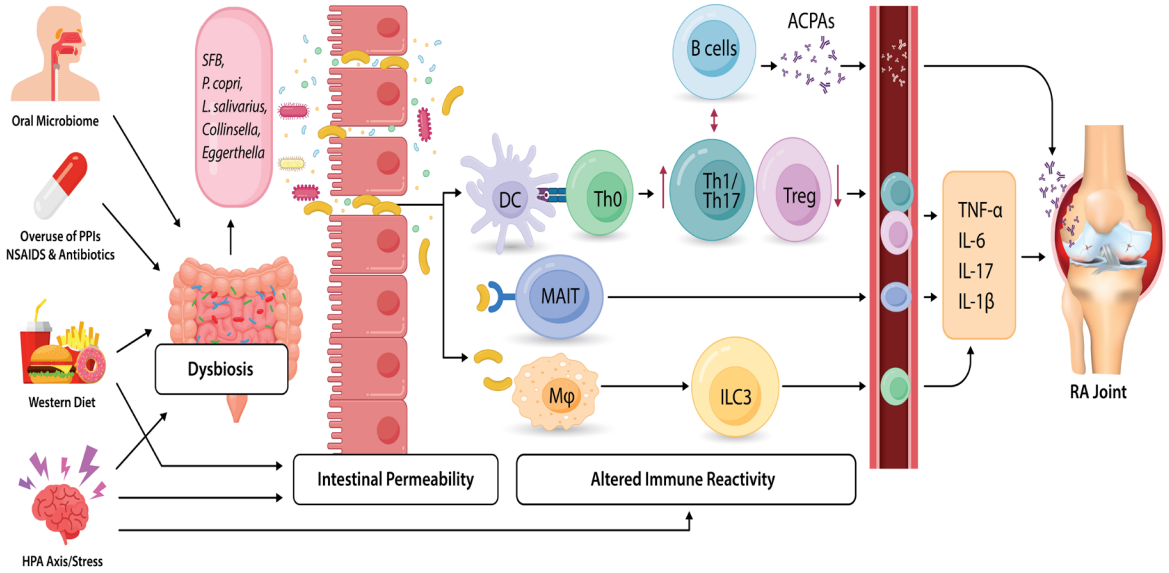
Other measures of intestinal permeability

There are many other experimental and clinical measures of intestinal permeability, several of which have been used to assess patients with RA and related IMIDs. The gold standard experimental method for measuring permeability across a membrane is to calculate the transepithelial electrical resistance (TEER) of cells (biopsied or plated) on porous supports designed to allow the separation of 2 compartments (ie, an Ussing chamber).[55] When these cells are polarized to orient the apical from the basolateral sides, they form a monolayer similar to that formed in the gut. A stable resistance to electrical current shows the proper formation and orientation of the monolayer and a limited flow of ions between the cells. A reduction in the TEER occurs when the paracellular space allows larger ions to flow from 1 chamber to the other; this reduction is considered an objective measure of intestinal permeability. Though more invasive than other methods, measuring TEER in biopsied tissue is still commonly used to assess gut permeability in many clinical and research settings.[56] For example, Hollon et al[57] have demonstrated that tissue biopsied from patients with celiac disease who consumed gluten has a much lower TEER (higher permeability) than tissue from patients with celiac disease on a gluten-free diet.

However, the more common in vivo test for estimating gut permeability is the lactulose-mannitol test. The use of 2 differently sized sugar molecules, neither of which are readily metabolized in the gut or serum, and that are excreted in the urine in a manner that reflects their absorption from the gut, allows for a reliable estimate of gut permeability. The smaller mannitol molecule is thought to freely cross the gut barrier through the epithelial cells, and its urine concentration is considered a general measure of small intestinal surface area; the larger lactulose molecule is thought to cross through the paracellular route only if the pores are enlarged or cells are damaged in some way. Hence, the lactulose:mannitol ratio (L/M) gives a rough estimate of small intestinal hyperpermeability and is commonly elevated in subjects known to have common bowel disorders such as irritable bowel syndrome (IBS), IBD, and celiac disease.[58-62] Similar tests using different molecules (eg, rhamnose, polyethylene glycols [PEGs] of different sizes) or radiolabeled molecules such as chromium have been used in clinical research to measure relative intestinal permeability with similar results as the lactulose-mannitol test.[63-67]

A recent systematic review evaluated 23 studies that reported measures of intestinal permeability in subjects with SpA (12 studies), RA (11 studies), or both (3 studies).[16] Most of these studies were several decades old and used L/M, PEG, or 51Cr-ethylenediaminetetraacetic acid, though the authors included 2 recent studies that measured zonulin in their analysis. Using these methods, there was a stronger association between increased measures of intestinal permeability in SpA compared with RA, though 1 study (using PEG) showed increased permeability in subjects with RA with active disease compared with those in remission.[68]

Figure 3. Dysbiosis, Intestinal Permeability, and Signaling in Relation to the Rheumatoid Arthritis Joint



Immune-mediated inflammation is triggered by dysbiosis and intestinal hyperpermeability, each of which can be influenced by common antecedents. The subsequent immune activation in the gut results in joint inflammation, which is mediated mostly by inflammatory cytokines, often with the production of anti-citrullinated protein antibodies (ACPAs). MAIT- mucosal-associated invariant T cells. SFB- segmented filamentous bacteria. See text for more details. This image has been modified with permission.[84]

Finally, there are a number of other tests and assays used to measure intestinal permeability, though many are indirect measures requiring some interpretation, and only a few have so far been associated with RA or other IMIDs. Increased concentrations of bacteria-related metabolites in the blood or urine (eg, the endotoxin lipopolysaccharide, d-lactate) or increased levels of bacteria within the inner (dense) layer of mucus within biopsied tissue can be an indication of diminished intestinal barrier function.[69] Increased concentrations of lipopolysaccharide and fecal calprotectin (a measure of intestinal inflammation) have been reported in subjects with RA and/or SpA.[50,70] Circulating concentrations of TJ proteins (eg, zonula occludens 1, claudins) are also considered to be associated with increased gut hyperpermeability.[71] While these measures are not commonly used in clinical settings, emerging research suggests an association between TJ protein expression and IMID progression.[72] Finally, intestinal fatty-acid binding protein, expressed in epithelial cells of the mucosal layer of the small intestine tissue and released into circulation when they are damaged, is now emerging as another biomarker linking intestinal permeability and RA disease progression.[73]

Gut permeability testing and treatment can be initiated when the diagnosis of inflammatory arthritis is made, during disease flares, in "difficult to treat" RA, or in a patient with severe progressive RA or another IMID whose treatment with multiple medications failed. Other indications might include patients with low heart rate variability, smokers and those with other risk factors for aggressive disease, high autoantibody titers, and patients with high disease-activity scores despite treatment with combination pharmacologic therapy. Clinically, there are several rationales for the implementation of gut permeability testing in patients with RA and other IMIDs, not the least of which is that addressing gut health and diet gives the patient more agency over the therapeutic process. This sense of agency has been shown to improve clinician-patient relationships and shared decision-making, improve adherence to prescribed therapies, and empower patient self-care.[74] Furthermore, fewer than 25% of patients with RA will achieve clinical remission from their disease process with a pharmacologic, treat-to-target–based algorithm alone.[75] This low clinical remission rate suggests the need to target upstream disease factors with safe therapies alongside guideline-driven approaches to improve rates of clinical remission.

Dysbiosis and intestinal hyperpermeability

While it is well recognized that certain pathogenic organisms trigger (and subsequently exploit) gastrointestinal hyperpermeability, it is less well recognized that normal commensal organisms and pathobionts play a significant role in gut barrier function and subsequent immune activation in subjects with IMIDs.[76-80] Imbalances in the microbial ecosystem (dysbiosis), often only characterized by a decrease in species diversity or an increase of certain genera, have been reported to predictably alter gut barrier function, leading to intestinal hyperpermeability. Also, a disruption in the homeostasis of the communities of microbes in the lumen of the gastrointestinal tract is recognized by the innate immune

system in the gut, even when no barrier disruption is initiated.[81,82] A number of signals can be recognized by the innate immune system, including direct binding of microbe components via innate immune pattern recognition receptors or reduced concentrations of important metabolites like butyrate or secondary bile acids. These signals from a dysbiotic microenvironment can result in a shift in the regulatory T cell–T_H17 balance toward an inflammatory state, resulting in the release of proinflammatory cytokines in the lamina propria. These activated cells, cytokines, and humoral factors (ie, cross-reactive antibodies, if triggered) can migrate to other tissues, such as the synovium, where they damage local tissue and perpetuate a cycle of inflammation. In addition, gut microbes or their metabolites can trigger T-cell responses against self-antigens by molecular mimicry, allowing for the activation of classic autoimmune mechanisms.[83]

Notable differences between the gut microbiomes of subjects with RA or other IMIDs and control subjects have been described.[85] A recent review of the literature examining the relative fecal abundance of gut microbiome bacteria in subjects with RA compared with normal controls summarized some of these differences. Generally, decreases in *Faecalibacterium*, *Fusicatenibacter*, *Enterococcus*, and *Megamonas* and increases in Eggerthellales, *Collinsella*, *Prevotella copri*, *Klebsiella*, *Escherichia*, *Eisenbergiella*, and *Flavobacterium* were noted. There has been a particular interest in the levels of *P. copri* (and related species), as the abundance of these organisms has been associated with early-onset RA and other human diseases. However, there are conflicting interpretations as to the relationship of this organism to these diseases, as some RA cohorts have lower levels of *Prevotella* than control subjects.[86-90] Segmented filamentous bacteria, which have been studied extensively in rodents in connection with upregulating T_H17 inflammatory pathways, have also been discovered in humans and may also play a role in gut-induced systemic inflammation.[91-92] Therefore, while there is no microbiota signature that predicts RA or other IMIDs, or that is always predictive of intestinal hyperpermeability, the evidence suggests that a person's gut microbiome clearly influences immune tolerance and systemic inflammation in subjects vulnerable to IMIDs. Furthermore, recent investigation suggests microbiome-related mechanisms exist for several drugs used to treat RA (some of which are known antimicrobial agents), perhaps allowing for a personalized therapeutic approach to be developed based on a person's microbiota.[93-96]

Future of RA therapeutics—addressing the antecedents and triggers

Most guidelines for treating RA focus primarily on helping clinicians and patients choose appropriate pharmaceutical agents that inhibit mediators of inflammation (ie, disease-modifying antirheumatic drugs [DMARDs]).[97-101] While these drugs can be remarkably effective in blocking inflammation and tissue damage in patients with RA, they remain ineffective for many, are associated with significant side effects and immune vulnerabilities, are expensive, and generally do not address the upstream antecedents and triggers of immune system activation.[102,103] Furthermore, reducing the frequency of relapse in subjects taking DMARDs or successfully de-escalating DMARD therapies in eligible patients requires eliminating as many potential drivers of immune-mediated inflammation as possible.

Emerging evidence from human clinical trials and animal models suggests that gastrointestinal hyperpermeability may be a significant trigger for immune-activated systemic inflammation, which in vulnerable individuals, results in the tissue-specific manifestation of IMIDs such as IBD, psoriasis, psoriatic arthritis, and RA. Moreover, research investigating common antecedents associated with intestinal hyperpermeability and/or therapeutic strategies to improve intestinal barrier function is regularly associated with chronic metabolic and inflammatory conditions.[104-106] Several known antecedents of intestinal hyperpermeability have been previously associated with RA and may be clinically relevant in disease initiation or progression in vulnerable subjects. Among others, these antecedents include gut microbiota dysbiosis, dietary habits, HPA axis stress, and the use of certain pharmaceuticals.

Regular use of proton pump inhibitors is associated with an increased risk of RA in women, a risk that appears to increase with higher doses and longer duration of use.[107,108] This association may be due to changes within the user's gut microbiota and/or subsequent changes to intestinal permeability, both of which are consequences of proton pump inhibitor use.[109,110] Antibiotic use, also known to affect both gut microbiota and intestinal barrier function, is also associated with increased risk for RA (in a dose- and frequency-dependent manner) in some studies, though not during short-term antibiotic use.[111-113] The use of sulphonamide and trimethoprim antibiotics, in particular, are associated with a 70% increase in RA flare in the first 3 months after use.[114]

Modulation of the gut microbiome through dietary interventions or the use of supplemental probiotics or prebiotics is a promising approach for treating RA.[115] A variety of dietary interventions, most of which are designed to avoid inflammatory and immunogenic triggers or are known to promote beneficial gastrointestinal microbiota, benefit subjects with IMIDs, including RA.[116,117] Intermittent fasting and fasting-mimicking diets have also shown promising effects for reducing symptoms in subjects with IMIDs.[118,119] However, clinical success often requires choosing a personalized dietary approach for each subject and maintaining these changes for more than 3 months to see substantial improvements.[120,121] Research on the use of probiotic supplements in subjects with RA is also promising,

The characteristics of Patients with IMIDs that are likely to benefit from this approach

1. Consuming a Western diet (processed food, sugar/artificial sweeteners, saturated and animal fats)
2. Recurrent gastrointestinal symptoms (ie, gas, bloating, diarrhea, constipation)
3. Recurrent antibiotic use (or historically heavy use)
4. Chronic use of proton pump inhibitors
5. Chronic use of NSAIDs
6. Celiac disease
7. Diagnosed irritable bowel syndrome or inflammatory bowel disease
8. Significantly elevated cyclic citrullinated protein antibodies
9. Metabolic disorders associated with intestinal permeability (eg, diabetes, metabolic syndrome, obesity)

Therapeutic Recommendations

- All patients with inflammatory arthritis should be screened for the risk factors listed above and, where necessary, given appropriate therapeutic intervention.
- Consider the following analyses for evaluating and addressing dysbiosis and intestinal hyperpermeability:
  1. Test for gastrointestinal permeability using one of the following tests:
     - Serum zonulin
     - Lactulose-mannitol test
  2. Fecal microbiome testing
     - Measures of diversity, genera, species, abundance
     - Measures of short-chain fatty acids and/or other important metabolites
  3. Measure fecal calprotectin (as a measure of gut inflammation)
  4. Identify and treat pathogens
  5. Assess for HPA axis stressors/perceived stress

Based on the results, the following interventions might be initiated:

1. Dietary intervention (prioritized by a nutritional specialist if possible)
   - Mediterranean Diet or similar, anti-inflammatory, avoidance of known sensitive foods
   - Consider fasting or fasting-mimicking protocols
   - Dietary fiber
2. Oral therapies to improve gut barrier:
   - Gut-supporting nutrients (eg, vitamin A, vitamin D, glutamine, omega-3)
   - Bovine-derived immunoglobulins (serum or colostrum)
   - Anti-inflammatory and gut-soothing botanicals
3. Probiotics, prebiotics, and postbiotics
4. Suggest regular moderate exercise (intense exercise exacerbates intestinal permeability)

→ Retesting may be indicated if gastrointestinal symptoms are not improving, or if more information is required to optimize the dietary and/or supplement protocol.

though more research is needed to make specific recommendations concerning species, strains, and doses.[122-125] Nonetheless, the mechanisms connecting probiotic bioactivities with microbiome alteration, improved intestinal permeability, and immune modulation are likely to explain these potential benefits.[126] Finally, the use of supplemental nutrients to improve intestinal barrier function may be beneficial for many subjects, though many of these supplements have not been tested specifically for improvements in measures of IMID-related outcomes. These supplements include vitamin A, vitamin D, glutamine, iron (when deficient), and omega-3 fatty acids.[127,128]

Perceived stress and HPA axis activation have long been associated with RA incidence, severity, or symptom relapse, though many factors complicate this relationship.[129-131] For instance, in a recent case-control study, female patients with RA were nearly 3 times more likely to attribute the onset of their RA symptoms to a stressful life event (compared with recently hospitalized controls but no such relationship was found in a similar cohort of men.[132] In contrast, patients with RA who have been treated with glucocorticoids for any length of time are at high risk for tertiary adrenal insufficiency and glucocorticoid resistance, both of which compromise the stress response.[133] While many mechanisms are predicted to explain the complex relationship between the HPA axis and RA, emerging research suggests that both intestinal hyperpermeability and dysbiosis are likely to play a role through signals collectively known as the gut-brain axis.[134,135] Corticotropin-releasing factor, one of the key mediators of the stress response, has direct and immune-mediated influences on TJ integrity and intestinal permeability.[136] In fact, reports showing that vagus nerve stimulation improves intestinal barrier function through cholinergic mechanisms lend credence to the potential benefit of stress-related therapies in complex gastrointestinal-associated chronic inflammatory conditions.[137]

Summary

While our understanding of the relationship between gut permeability and IMIDs, such as RA, continues to evolve, clinicians are often left to navigate these clinical scenarios without significant training or guidelines. This is primarily because professional associations for the clinicians involved in taking care of such patients generally do not address gut microbiota or intestinal permeability, often due to the lack of published clinical trials. Nonetheless, our patients look to us for answers; especially relating to safely applying the emerging

evidence that fundamental gastrointestinal issues may meaningfully influence their chronic inflammatory conditions. Therefore, even though we recognize the need for more published research, properly conducted clinical trials, and insurance reimbursement for tests and therapies, the benefits of attending to signs and symptoms of intestinal hyperpermeability and dysbiosis are likely to extend well beyond their association with a patient's diagnosed IMID. Empowering patients to successfully choose healthy dietary changes while helping them to avoid harmful foods, habits, and stressors is critical for improving their goals of reaching and sustaining remission.

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