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PERSPECTIVES

Biomarker Quantification of Gut Dysbiosis-Derived Inflammation: A Review

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Abstract: Gut dysbiosis, an alteration or imbalance in the composition and function of the gut microbiome can lead to a range of health issues. Inflammation in this setting leads to increased permeability of the intestinal barrier and the activation of immune responses which contributes to a range of inflammatory, autoimmune and metabolic diseases. Therefore, precise quantification of gut-derived inflammation is important to gain insights into the development and progression these diseases and to develop treatments. This review highlights the underlying mechanisms leading to gut inflammation and the markers of gut dysbiosis mediated inflammation. We then discuss strategies including disposable and wearable biosensing devices, biomedical imaging, sequencing and AI-based methods for the quantification of dysbiosis-derived inflammation. Challenges and future perspectives for quantification of gut dysbiosis mediated inflammation are proposed.

Keywords: gut dysbiosis, inflammation, lipopolysaccharide, cytokines, disposable device, ingestible devices

Introduction

Inflammation is the immune system's natural response to injury, infection, or harmful substances through the protection of immune cells and molecular signals.[1] Persistent inflammation can harm and will cause chronic diseases.[2] This involves chemical releases, vessel dilation, and classic signs,[3] with chronic inflammation linked to multiple diseases.[4]

Quantifying inflammation is important as it provides insights into disease states and their potential for progression, thereby potentially guiding treatment. By measuring specific biomarkers such as C-reactive protein (CRP), an acute-phase reaction protein used for monitoring inflammation and non-specific infections[5] and calprotectin, whose fecal concentration will elevate during gut inflammation, as well as other biomarkers including lipopolysaccharide (LPS), LPS-binding protein (LBP), cytokines, secretory Immunoglobulin A (sIgA), zonulin, short-chain fatty acids (SCFAs), toll-like receptors (TLRs), indicative metabolites of inflammation and microRNAs, the intensity and activity of inflammation within the body can be quantified.[6] Quantification methods such as imaging and biopsies complement these measurements and are vital for the accurate assessment of inflammatory diseases.[7] Regular monitoring of biomarker levels that quantify inflammation also helps provide tailored treatments to individual patient needs, thus optimizing management.

A recently recognized and central mediator of these systemic inflammatory processes is the gut microbiota (GM), a complex assembly of microorganisms intrinsic to gastrointestinal health and the regulation of various physiological functions. The GM comprises up to 1000 bacterial species and over 10^{14} organisms pivotal for synthesizing vitamins, processing lipids, producing short-chain fatty acids for epithelial cells, and for modulating gene expression.[8] The GM is shaped early in life by factors such as birth delivery methods, illness, and antibiotic usage, and later by diet, environmental factors, and host genetics.[9] It also plays a vital role in nutrient metabolism,[10] immune regulation,[11] and maintaining gut integrity against pathogens.[12]

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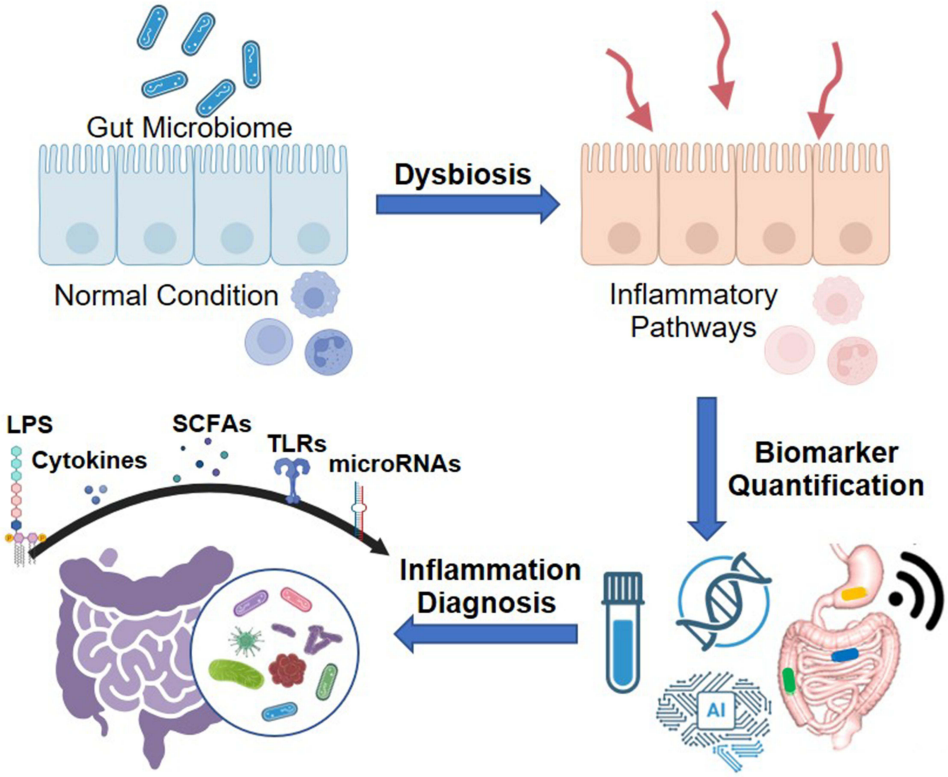
Graphical Abstract



A healthy and stable gut microbiota is able to recover and restore equilibrium after disturbances caused by factors such as an unhealthy diet, antimicrobials, medications, pathogens, and other stressors. However, when resilience is damaged, the GM succumbs to dysbiosis, a state characterised by an imbalance favoring pro-inflammatory microbes, leading to systemic inflammatory responses and chronic disease.[13] Despite extensive research into GM composition, variations in these diseases and the identification of biomarkers and metabolites,[14] the clinical challenge that remains is to accurately monitor and quantify the biomarkers. This review highlights the mechanisms of gut dysbiosis-induced inflammation and dissects the markers and factors contributing to gut-derived inflammation. We discuss current strategies and challenges for quantifying inflammation in the context of gut dysbiosis and propose perspectives for advancing the science of precision inflammation quantification (Figure 1).

Survey Methodology

The literature review of quantification of biomarkers of gut dysbiosis-derived inflammation was conducted by systematically searching database Web of Science and PubMed for articles and reviews published between January 2020 and August 2025. The search terms included ("gut dysbiosis" OR "intestinal microbiota imbalance") AND ("inflammation" OR "inflammatory response") AND ("biomarker" OR "marker"), and terms for quantification part covers: ("quantification" OR "disposable" OR "wearable" OR "ingestible" OR "imaging" OR "sequencing" OR "AI"). Studies were included if they: (1) focused on human or animal models of gut dysbiosis; (2) identified or validated inflammatory biomarkers; (3) were published in English. The literature selected for final inclusion underwent a comprehensive analysis, and eventually 81 articles and 28 reviews were obtained.

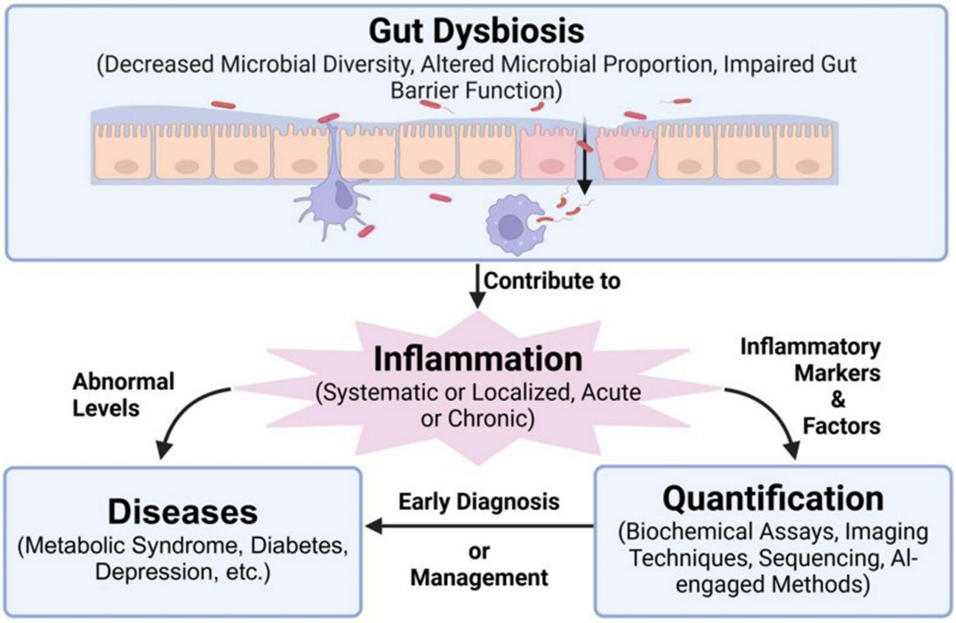


Figure 1 Schematic diagram of aspects discussed in this review.

Mechanisms of Gut Derived Inflammation

Gut dysbiosis can instigate or contribute to a multitude of inflammatory responses, we first discuss the major mechanisms involved such as alterations in metabolites, immune dysregulation, and impaired gut barrier function.[13] All these mechanisms are intimately cross-related as shown in Figure 2, but they are discussed as separate entities for simplicity.

Alterations in Metabolites

Gut microbes produce a wide range of metabolites. Among typical metabolites, bile acids (BAs) play a crucial role in the body as regulators of macronutrient (carbohydrates, fats, and proteins) metabolism.[15] During normal conditions, primary bile acids (PBAs), mainly cholic acids (CAs) and chenodeoxycholic acid (CDCAs) are the very first products synthesized from oxidized cholesterol within the liver.[16] The bile acid-CoA: amino acid N-acyltransferase (BAAT) catalyzes the binding of PBAs with taurine or glycine in different proportions in the liver to form conjugated BAs and are stored in gallbladder.[16] In response to food stimulation, these conjugated BAs are secreted into the duodenum and around 5% to 10% of the BAs escape the reabsorption in terminal ileum to enter the colon to undergo a series of biotransformations.[17] This GM-manipulated biotransformation mainly includes bile salt hydrolase (BSH), an enzyme primarily found in Gram-positive bacteria such as *Bifidobacterium, Clostridium, Enterococcus, Lactobacillus* and the only Gram-negative genus *Bacteroides*, breaks down conjugated BAs into their free form by separating glycine or taurine; and 7α-dehydroxylation, which can be performed by bacteria, including *Clostridium* and *Eubacterium* that encode bai genes,[18,19] converts CA and CDCA into deoxycholic acid (DCA) and lithocholic acid (LCA), the two secondary BAs, respectively.[20] However, when gut dysbiosis and the abundance of BSH and bai genes containing bacteria decreases, less primary BAs can be transformed to secondary BAs.[19] This also results in a decrease in the reabsorption of BAs in terminal ileum through the bile acid transporter apical sodium dependent bile acid transporter (ASBT) with less ASBT expression in TNBS colitis rodent models.[21] This decrease can subsequently affect bile acid–activated receptors (BARs), such as Takeda G-protein-coupled receptor 5 (TGR5), farnesoid X receptor (FXR), and pregnane X receptor (PXR).[19] Inactivation or absence of FXR and TGR5 in dendritic cells (DC) can result in an increase in the production of pro-inflammatory cytokines TNF-α and IL-12,[22] and can induce pro-inflammatory response by promoting M1 macrophage differentiation.[20] The reduced activation through TGR5 and VDR also inhibits the differentiation of T cells towards regulatory T cells (Tregs).[19]

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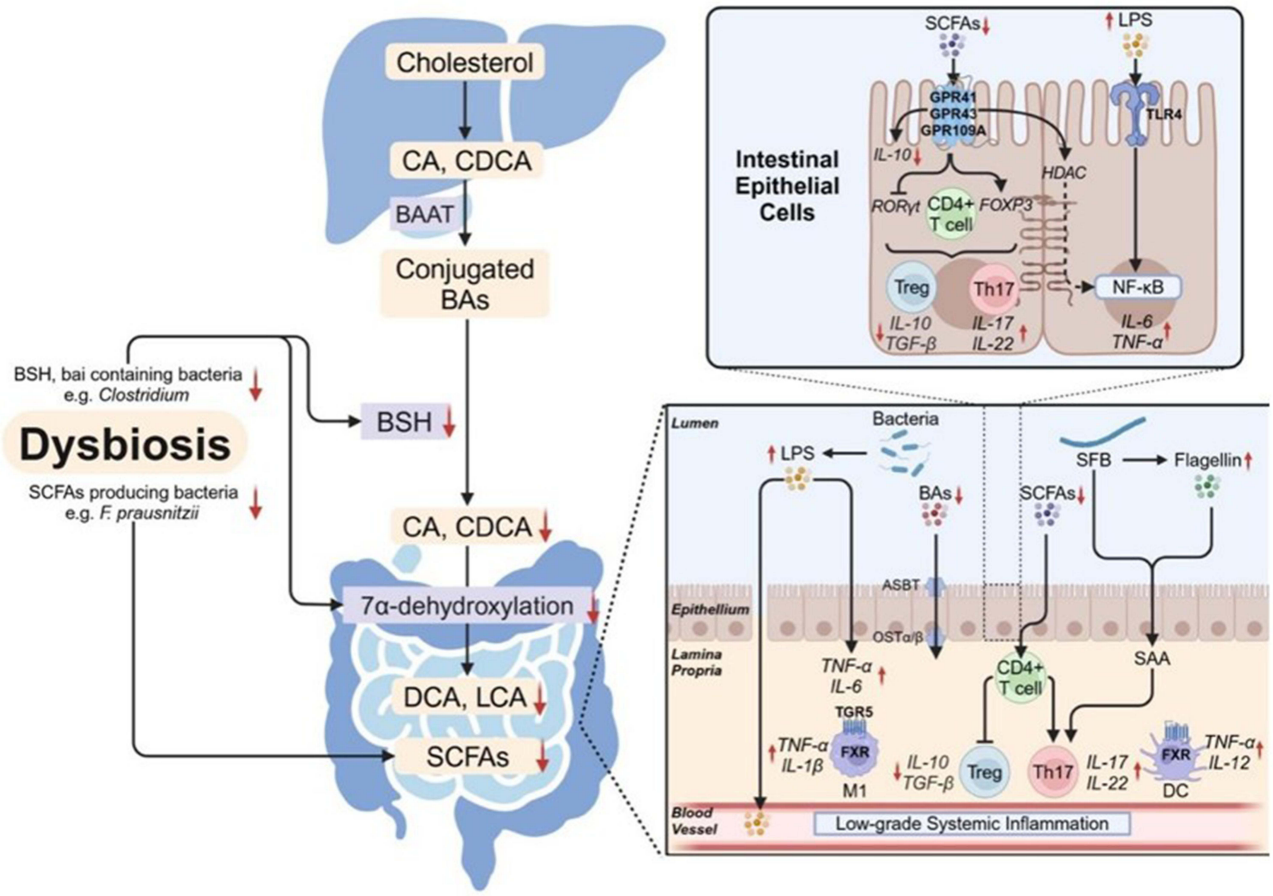

Figure 2 Mechanisms of inflammation caused by gut dysbiosis. The red colored upward and downward arrows indicate significant increase and decrease of concentration respectively.

Abbreviations: BA, bile acids; CA, cholic acids; CDCA, chenodeoxycholic acid; BAAT, bile acid-CoA: amino acid N-Acyltransferase; BSH, bile salt hydrolase; DCA, deoxycholic acid; LCA, lithocholic acid; SCFA, Short-chain fatty acid; GPR41, G-protein-coupled receptor 41; GPR43, G-protein-coupled receptor 43; GPR109A, G protein-coupled receptor 109 A; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; FXR, farnesoid X receptor; TGR5, Takeda G-protein-coupled receptor 5; SFB, segmented filamentous bacteria; HDAC, histone deacetylase; SAA, serum amyloid A.

Short-chain fatty acids (SCFAs), specifically acetate, propionate, and butyrate, are produced through bacterial fermentation (eg, *F. prausnitzii*) in the gut.[23] SCFAs exert anti-inflammatory effects in diabetes, by activating G-protein-coupled receptors (GPCRs) like GPR41, GPR43, GPR109A, and histone deacetylase (HDAC) inhibition.[24] When SCFAs bind to GPR41 and GPR43 receptors under normal conditions, it stimulates the expression of FOXP3 while suppressing RORγt, thus regulating the differentiation of CD4+ T cells into decreased Th17 and increased Treg cells,[25] while GPR109A regulates the expression IL-10, and inhibits colonic inflammation.[26] On the other hand, butyrate reduces the expression of inflammatory cytokines, for example, by blocking the HDAC8/NF-κB pathway and enhances the expression of solute carrier family member 3 (Slc26A3), a transmembrane glycoprotein involved in the transport of Cl^- and $HCO3^-$ and can absorb SCFAs, which aids the integrity of tight junctions.[27] Finally, during gut dysbiosis, changes in the proportion of SCFAs-producing bacteria impairs the host's intestinal digestive function by inhibiting these anti-inflammatory properties, resulting in challenges to metabolizing and utilizing nutrients from food. This leads to impaired digestion, malnutrition, and a heightened risk of inflammation-related diseases.[13]

Immune Dysregulation

Innate immunity plays a critical role in gut's first identifying and reacting to substances produced by GM, and the process starts with the layer of intestinal epithelial cells (IECs). Meanwhile, pattern-recognition receptors (PRRs) including

TLRs, CLRs, and NLRs can protect the balance between the host and microbes by detecting microbe-associated molecular patterns (MAMPs) and then set off defensive immune responses by means of chemokines and cytokines.[28]

However, GM dysbiosis can lead to increased exposure of the intestinal epithelium to pathogen-associated molecular patterns (PAMPs), including bacterial peptidoglycan, lipoteichoic acid (LTA), and flagellin.[29] This heightened exposure activates toll-like receptors (TLRs) present on the surface of epithelial and immune cells and initiates a signaling cascade that primarily involves the NF-κB pathway.[30] Lipopolysaccharide (LPS), which is a typical PAMP has received the most research attention. The activation of TLR4 signaling by proteins such as LPS-binding protein (LBP) and CD14[31] engages both MyD88 and TRIF pathways,[32] contributing to the activation of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways to produce inflammatory cytokines (eg, TNF-α and IL-6).[24] Moreover, the heightened translocation of LPS into the bloodstream can result in low-grade systemic inflammation through interactions with TLRs.[33] Flagellin produced by segmented filamentous bacteria (SFB) as well as SFB itself also manipulate the development of specific CD4+ Th17 cells in the mucosa and promotes the production of cytokines, such as IL-17 and IL-22, and activates IECs to secrete the serum amyloid A (SAA).[34] SAA acts as both a mediator and amplifier of gut inflammation by disrupting the epithelial barrier, recruiting immune cells, and perpetuating cytokine production, contributing to diseases like IBD.

The balance between pro-inflammatory Th17 cells and anti-inflammatory Tregs is another critical determinant of immune homeostasis and plays a pivotal role in regulating inflammatory responses. The initiation of Th17 cells differentiation requires IL-1β and TGF-β, with subsequent enhancement by TNF, IL-6, and IL-21. Their expansion and survival are dependent on IL-23, while the transcription factors STAT3 and RORγt manage this entire differentiation process.[35] IL-17, as the key pro-inflammatory cytokine produced by Th17 cells, plays multifaceted roles in these processes.[35] Tregs also play a crucial role in maintaining immune balance, primarily through the action of Foxp3,[36] which influences Treg activity by altering key signaling pathways and transcription factors like NFAT and AP-1, and suppresses inflammatory responses and enhances their immune-regulatory capacity.[36]

An imbalance in the GM may lead to a metabolic imbalance and altered cytokine production that affects the Th17/Treg balance.[37] For example, gut dysbiosis in Graves' disease (GD) significantly reduces SCFA-producing bacteria such as *Bacteroides fragilis* and leads to a decrease in propionic acid levels, which disrupts the balance between Tregs and Th17 cells.[38] The reduction of specific bacterial populations, including those within the genus *Clostridium* can also lead to a decreased promotion of the differentiation of naïve CD4+ T cells into Tregs while concurrently weakening the inhibition of differentiation of pro-inflammatory Th17 cells in myasthenia gravis patients.[39]

In ulcerative colitis (UC) and Crohn's disease (CD), a large number of $CD68^{+}$ macrophages infiltrate the intestinal mucosa and are widely distributed throughout the thickened mucosa and submucosa.[40] These macrophages derived from monocytic cell polarization in an inflamed state secrete multiple pro-inflammatory cytokines, such as TNF, IL-6, IL-8, IL-23, IL-1β, and IFN-γ, as well as the chemokine CCL2, which attracts more monocytes to the site of inflammation.[40]

Impaired Gut Barrier

The gut barrier defends the interface between the gut and host body, comprising a mucus layer, epithelial cells, and the lamina propria with immune cells.[41] This multi-layered system not only fosters nutrient absorption and water homeostasis but also provides a robust barrier against pathogens and toxins, maintaining gut integrity and immune balance.[41] Elevated gut permeability and decreased gut barrier function are common threats in various disease, notably inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and liver-related disorders such as alcohol related liver disease, metabolic dysfunction associate fatty liver disease, and cirrhosis.[42]

Gut dysbiosis disrupts the intestinal environment, leading to a weakened mucus layer, and is often caused by a low-fiber diet which results in the GM degrading the protective mucus layer by utilizing mucosal glycoproteins for nutrition. In contrast, a high-fiber diet enhances the proliferation of IECs and repairs the mucosal barrier by boosting the population of fiber-degrading bacteria that produce SCFAs.[43] Gut dysbiosis also compromises the tight junctions between epithelial cells and reduces the production of critical antimicrobial peptides and secretory immunoglobulin A (SIgA), key components for maintaining mucosal immunity and barrier integrity.[44] Thus, when more pathogens pass through tight junctions, it activates immune cells and contribute to chronic inflammation in the lungs, skin, and intestines.

Biomarkers Related to Gut Dysbiosis Derived Inflammation

Given the complex pathophysiology of inflammatory diseases, a diverse array of biomarkers, including acute-phase proteins/reactants, pathogen-associated molecular pattern (PAMP) and their associated pattern recognition receptors (PRR), tight junction proteins, dietary metabolites, immunoglobulins, specific cytokines and miRNA are implicated (Table 1). Herein, we only discuss the common gut dysbiosis associated inflammatory biomarkers. More biomarkers related to gut inflammation especially in IBD are referred to in reviews.[45]

C-Reactive Protein (CRP)

CRP is an acute-phase protein which can elevate rapidly up to 1000 times the normal level in response to acute infection or inflammation. Pro-inflammatory cytokines, especially IL-6 induces the transcription of the CRP gene in hepatocytes.[5] Elevations in CRP are associated with various conditions linked to gut dysbiosis. For instance a reduced *Firmicutes*-to-*Bacteroidota* ratio is correlated with elevated CRP levels in metabolic disorders and inflammation.[58] The concentration of TNF-α, which is mainly derived through LPS, and CRP secretion by hepatocytes is also positively correlated.[5] As a generic biomarker, CRP is frequently observed in inflammation related biological process in almost all body fluids.

Calprotectin

Calprotectin is a calcium- and zinc-binding protein found in neutrophils and a subset of mononuclear phagocytic cells that are frequently recruited to sites of inflammation.[59] During inflammation, calprotectin synthesis is increased, and the excretion of calprotectin in fecal samples is highly correlated with the severity of intestinal inflammation.[60] In patients with IBD, the increase is associated with neutrophil infiltration of the intestinal mucosa.[60] In comparison to CRP, faecal calprotectin is able to distinguish between non-inflammatory and inflammatory intestinal conditions, especially in IBD.[61] Moreover, it is reported that individuals with a higher level of fecal calprotectin have an increased abundance of gram-negative bacteria and a decreased abundance of SCFA-producing genera.[62]

Lipopolysaccharide (LPS) and LPS-Binding Protein (LBP)

LPS is one of the best known PAMPs that engage TLR4 and results in the secretion of various cytokines and chemokines.[63] This interaction also plays a pivotal role in neuroinflammatory pathways and is thought to contribute to the degeneration of dopaminergic neurons, for instance in Parkinson's disease (PD).[64] It should be noted that LPS-binding protein (LBP) is involved in TLR4 and LPS binding and allows LPS to translocate into the bloodstream to trigger inflammatory responses.[65]

Cytokines (IL-6, TNF-α, IL-10)

Cytokines are signaling proteins that mediate and regulate immunity, inflammation, and hematopoiesis.[66] Interleukin-6 (IL-6) initiates the immune response by promoting the survival and differentiation of T cells, particularly Th17 cells, which exacerbates mucosal inflammation. IL-6, through its interaction with the IL-6 receptor (IL-6R) and subsequent activation of signal transducer and activator of transcription 3 (STAT3), confers an antiapoptotic milieu that sustains Th1 cell populations within inflamed tissues.[4] TNF-α plays a multifaceted role in impairing gut barrier functions including mucus composition and secretion, permeability via tight junctions, and epithelial cell fate decisions such as survival, apoptosis, and proliferation.[67] In contrast, IL-10 acts as a key anti-inflammatory cytokine that dampens the immune response. Enhanced IL-10 production suppresses the pro-inflammatory activities of other immune cells, and reduces their ability to present bacterial antigens via the major histocompatibility complex class II (MHCII) to colonic T cells.[68] Indeed, cytokines and chemokines are reported to be biomarkers contributing to gut dysbiosis derived inflammation.[13,69]

Secretory Immunoglobulin A (sIgA)

As an important mucosal immunoglobulin, secretory immunoglobulin A (sIgA) contributes to maintaining the intestinal and respiratory mucosal immune barrier, regulates intestinal flora, and prevents bacterial infection.[70] In terms of GM, IgA and IgM produced by plasma cells in the lamina propria of the intestinal mucosa are transported into the intestinal

Table 1 Inflammatory Markers and Factors for Gut Dysbiosis Derived Inflammation.

Biomarkers	Class of Biomarkers	Detection Method/Analyzer	Sample Type	Concentration	Inflammation States	Related Diseases	References
C-reactive protein (CRP)	Acute phase proteins/reactants	Blood Biochemistry Test (chemistry analyzer)	Serum	>0.60 mg/L	Chronic/Systemic	Post-COVID-19 syndrome	[46]
		N/A	Blood	≥96.8 mg/L	Chronic/Systemic	Severe COVID-19	[47]
		Automatic biochemical analyzer	Serum	≥4.90 mg/L	Chronic/Systemic	Metabolic syndrome	[48]
		Enzyme-linked immunosorbent assay (ELISA)	Plasma	N/A	N/A	Colorectal cancer (CRC)	[49]
		Turbidometric method	Serum	>4.30 mg/L	Chronic	Major depressive disorder(MDD) and Obesity	[50]
LPS-Binding Protein (LBP)		Enzyme-linked immunosorbent assay (ELISA)	Serum	>16.82 ng/mL	Chronic	Gestational diabetes mellitus	[51]
Calprotectin		Enzyme-linked immunosorbent assay (ELISA)	Serum	>9.74 mcg/mL	Systemic	Sporadic Parkinson's disease (PD)	[52]
		Enzyme-linked immunosorbent assay (ELISA)	Fecal	>92.06 mcg/g	Systemic	Sporadic Parkinson's disease (PD)	[52]
		Enzyme-linked immunosorbent assay (ELISA)	Fecal	>70.14 pg/mL	Chronic	Gestational diabetes mellitus	[51]
		Enzyme-linked immunosorbent assay (ELISA)	Fecal	>200.00 mg/kg	Chronic	Ankylosing spondylitis and Ulcerative colitis	[53]
Lipopolysaccharide (LPS)	Pathogen-Associated Molecular Pattern (PAMP)	Enzyme-linked immunosorbent assay (ELISA)	Serum	>203.30 EU/L	Chronic	Major depressive disorder(MDD) and Obesity	[50]
		Enzyme-linked immunosorbent assay (ELISA)	Fecal	>117.31 ng/L	Chronic	Gestational diabetes mellitus	[51]
		Enzyme-linked immunosorbent assay (ELISA)	Serum	>272.50 ng/L	Chronic	Gestational diabetes mellitus	[51]
Toll-like Receptor 4 (TLR4)	Pattern recognition receptor (PRR)	Enzyme -linked immunosorbent assay (ELISA)	Serum	>529.63 pg/L	Chronic	Major depressive disorder(MDD) and Obesity	[50]
Zonulin	Tight junction protein	Enzyme-linked immunosorbent assay (ELISA)	Serum	>3.80 ng/L	Chronic	Major depressive disorder(MDD) and Obesity	[50]
		Enzyme-linked immunosorbent assay (ELISA)	Serum	>21.99 ng/mL	Systemic	Sporadic Parkinson's disease(PD)	[52]
		Enzyme-linked immunosorbent assay (ELISA)	Fecal	>50.56 ng/mL	Systemic	Sporadic Parkinson's disease(PD)	[52]
		Enzyme-linked immunosorbent assay (ELISA)	Serum	>1623.24 pg/mL	Chronic	Gestational diabetes mellitus	[51]
Imidazole propionate (ImP)	Dietary metabolites	Liquid chromatography–tandem mass spectrometry (LC–MS/MS)	Serum	>20.0 nmol/L *	Chronic/Systemic	T2D	[54]
Trimethylamine N-oxide (TMAO)		Nuclear Magnetic Resonance (NMR)	Serum	>12.72ng/mL	Chronic/Systemic	Colorectal cancer (CRC)	[55]
SCFA (AA/PA/BA/VA)		Gas chromatography-mass spectroscopy (GC-MS) analysis	Serum	N/A	Systemic	Polycystic ovary syndrome (PCOS)	[56]
Secretory Immunoglobulin A (sIgA)	Immunoglobulin	16S rRNA gene sequencing (Coated with microbiota)	Fecal	N/A	Chronic	Gestational diabetes mellitus	[51]
Cytokines (IL-6)	Pro-/ anti-inflammatory cytokines	Enzyme-linked immunosorbent assay (ELISA)	Plasma	N/A	N/A	Colorectal cancer (CRC)	[49]
Cytokines (TNF-α)		Enzyme-linked immunosorbent assay (ELISA)	Serum	>46.10 ng/L	Chronic	Major depressive disorder(MDD) andObesity	[50]
Cytokines (IL-10)		Enzyme-linked immunosorbent assay (ELISA)	Serum	<133.70 ng/L	Chronic	Major depressive disorder(MDD) and Obesity	[50]
miRNA	miRNA	Human-specific TaqMan gene expression assays	Plasma	N/A	N/A	Autism Spectrum Disorder	[57]

lumen.[71] These immunoglobulins can shape the gut microbiome by inhibiting certain bacterial groups and promoting the growth of others. Conversely, bacterial metabolites regulate the production and secretion of immunoglobulins. In the case of patients with IBD, the proportion of bacteria targeted by IgA changes when the gut microbiota is dysregulated, reflecting the gut immune system's response to dysbiosis, rather than simply due to the dysbiosis itself.[72]

Zonulin

Zonulin is an essential protein that regulates the permeability of tight junctions between epithelial cells in the gut.[73] This protein is a precursor of pre-haptoglobin 2 and functions by activating protease-activated receptor 2 (PAR2).[73] Gut dysbiosis leads to excess production of zonulin, which causes the loss of intestinal barrier function.[74] In autoimmune diseases such as celiac disease and type 1 diabetes, zonulin expression is increased.[73] This allows antigens and endotoxins from the intestinal lumen to enter the lamina propria, triggering innate and immune regulatory responses[74] to producing cytokines such as IFN-γ and TNF-α that further increase intestinal permeability resulting in a vicious inflammatory cycle.[74]

Short-Chain Fatty Acids (SCFAs)

As previously mentioned, SCFAs are metabolites produced by gut bacteria that reduce inflammation by activating specific receptors and pathways (GPGR & HDAC). Their production and health impact varies through life due to changes in gut microbiota composition. SCFAs promote T effector and Treg cells differentiation through inhibition of HDAC or the activation of the mTOR-S6K kinase pathway.[75] Moreover, by modulating the frequency of Treg cells in the gut and distant tissues they alleviate the progression of autoimmune diseases such as uveitis, and by regulating the activity of macrophages in adipose tissue impacts obesity-related chronic inflammation. SCFAs can regulate the function of M1 and M2 type macrophages through the activation of the GPR43 receptor.[75] Meanwhile in the gut-kidney axis, SCFAs maintain intestinal barrier integrity to regulate immune responses and inflammation.[76]

Toll-Like Receptors (TLRs)

TLRs are part of the pattern recognition receptors (PRRs) family and identify molecules commonly found in pathogens, known as pathogen-associated molecular patterns (PAMPs) and microbe-associated molecular patterns (MAMPs).[77] Besides TLR4, the remaining TLRs fall into two categories, the bacterial products-sensing and nucleic acid-sensing TLRs, which are expressed on immune and gut epithelium cells membranes, and the membrane of intracellular compartments, respectively.[77] TLRs play essential roles in the interactions between the host and microbiota and are crucial for maintaining a healthy epithelial barrier.[78] Their functions span the formation and differentiation of epithelial lineages, regulation of permeability, production of antimicrobial peptides, and secretion of mucus into the lumen.[78]

Metabolites Indicative of Inflammation (Eg, ImP, TMAO)

Imidazole propionate (ImP) is produced by an altered microbiome in conditions such as T2D through the alternative metabolism of histidine. ImP can impair glucose metabolism by activating p38γ-mTOR1-S6K1 signaling.[79] ImP can also affect insulin signaling and metformin response by inhibiting AMPK activity.[80] Trimethylamine N-oxide (TMAO) is a small organic compound which belongs to the amine oxide family and is produced by gut bacteria that metabolize choline, betaine, and carnitine.[81] TMAO activates various signaling pathways such as Smad3, leading to myocardial hypertrophy and fibrosis, and triggers inflammatory responses by activating the NLRP3 inflammasome, promoting the release of inflammatory IL-1β and IL-18, while inhibiting nitric oxide synthase activity.[82]

MicroRNAs

MicroRNAs are capable of regulating the expression of genes associated with inflammation. For instance, miR-21 can target the TNF-α pathway, enhancing inflammatory responses; miR-320 can suppress inflammation by targeting the NOD2 gene.[83] Certain specific miRNAs, like miR-155, are upregulated during the inflammatory process and participate in regulating inflammation-related signaling pathways.[83] Furthermore, miR-155 can promote the expression of IL-8 by inhibiting the FOXO3a gene, thereby intensifying intestinal inflammation.[83] The expression of miRNAs I turn is

regulated by inflammatory factors such as LPS, IFN-β, and TNF-α, and conversely, miRNAs can regulate the release of these inflammatory factors, resulting in a feedback regulatory mechanism.[83]

Quantitative Analysis of Gut Dysbiosis Derived Inflammation

Inflammation can be quantified using various clinical, laboratory, and imaging tools, depending on the type and location of the inflammation. These tools can be used individually or in combination for a comprehensive profile of the inflammatory activity (Figure 3). In this section, we discuss common methods for quantitative analysis of gut dysbiosis derived inflammation, including disposable and wearable biosensing devices, ingestible devices, biomedical imaging, sequencing, and AI-engaged methods. All the following devices and methods are in the trial stage, and not commercially available yet.

Disposable and Wearable Devices

Development of biochemical assays for quantitative detection of inflammation is in high demand. An engineered prebiotics system is promising for being disposable and being able to be recycled for detecting inflammation in diseases such as IBD.[84] These engineered bacteria can generate sfGFP fluorescence for the real-time detection of inflammatory biomarkers thiosulfate. They are also helpful for the immediate and historical information about disease in bacteria genomes from a CRISPR/Cas9 editing system, where a gain-of-function mutation (ACG to ATG) occurs in the promoter codon of lysoprotein E, thus activating the expression of lysoprotein E. When these two signals are detected, bacterial lysis is induced and controlled by a double switch of thiosulfate and xylose (Figure 4A). Owing to its disposal and recyclable properties, this system can avoid long-term bacterial retention in the body and prevent problems such as horizontal gene transfer.[84]

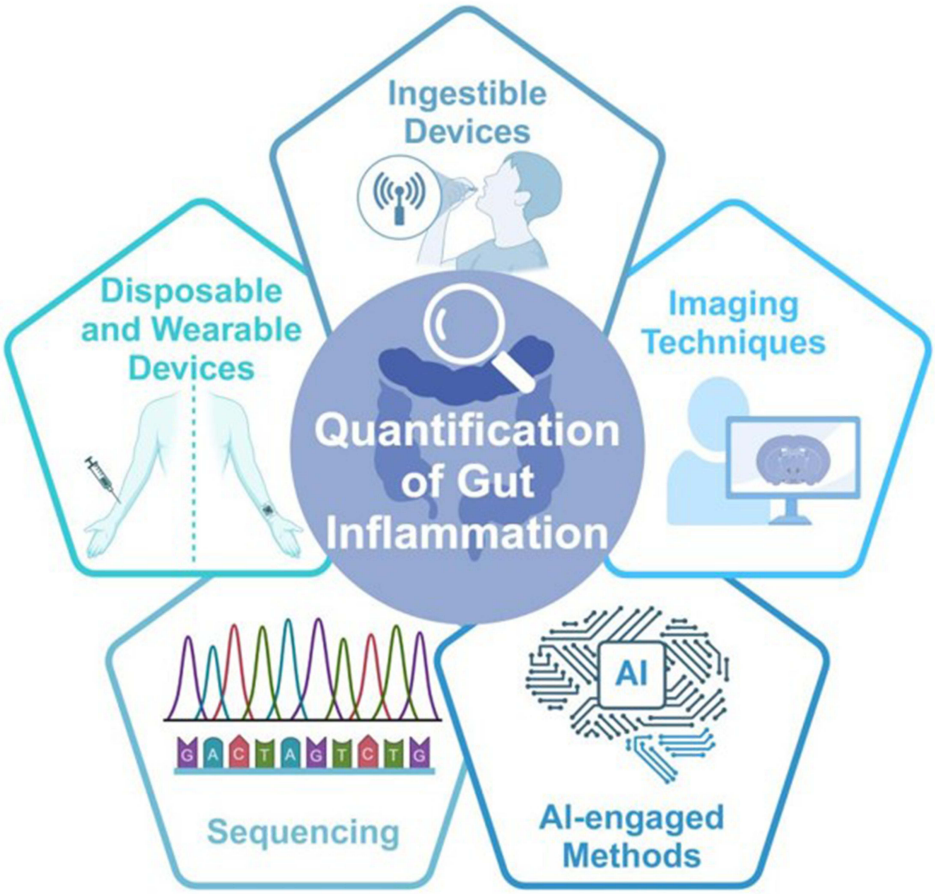

Figure 3 Schematic illustration of methods for the quantification of gut derived inflammation.

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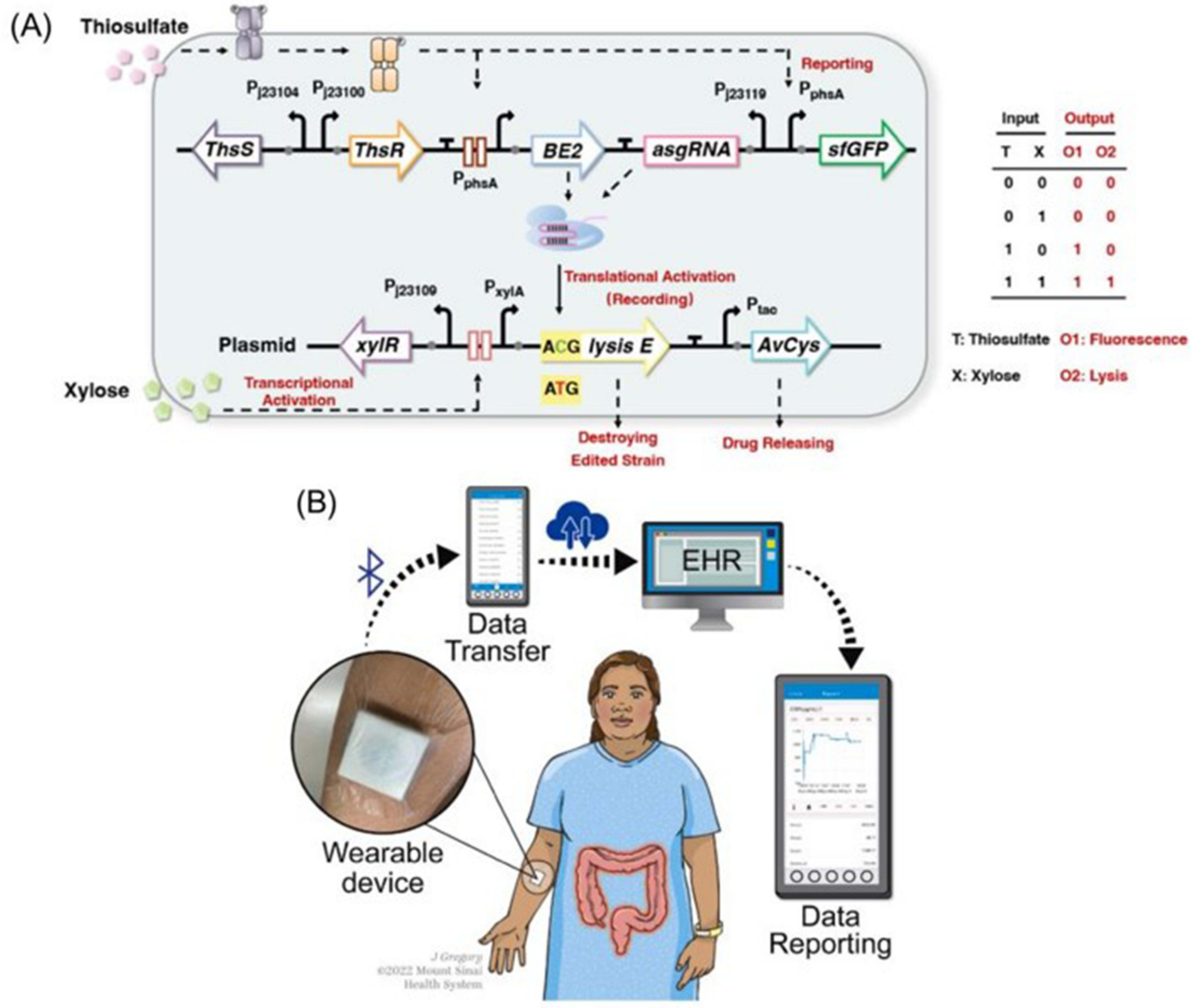

Figure 4 Schematic illustration of disposable and wearable devices for quantitative analysis of gut dysbiosis derived inflammation. (**A**) Design of the prebiotics-controlled disposable engineered bacteria for intestinal diseases. Reprinted with permission from Fang -T-T, Zou Z-P, Zhou Y, Ye B-C. Prebiotics-controlled disposable engineered bacteria for intestinal diseases. ACS Synthetic Biol. 2022;11(9):3004–3014. Copyright 2022 American Chemical Society.[84] (**B**) The workflow of IBD AWARE device. Reprinted with permission from Hirten RP, Lin K-C, Whang J, et al. Longitudinal monitoring of IL-6 and CRP in inflammatory bowel disease using IBD-AWARE. Biosensors Bioelectronics. 2024;16:100435. https://creativecommons.org/licenses/by/4.0/.[86]

In terms of wearable sensors, the IBD AWARE device can detect TNF-α[85] as well as CRP and IL-6 levels in sweat[86] in patients with IBD. The device comprises a replaceable sweat-sensing strip with zinc oxide (ZnO) coated electrodes and a plastic reader to detect and quantify TNF-α, CRP, and IL-6 levels in sweat (Figure 4B). The sensor employs a screen-printing technique, monoclonal antibodies, and non-faradaic electrochemical impedance spectroscopy (nf-EIS). IBD AWARE can provide near-continuous readings of protein analytes in sweat, which can be transferred via Bluetooth to a cloud server for real-time disease state assessment by healthcare providers or patients.[85,86] For example, it can differentiate between subjects with active IBD and healthy individuals with an area under curve (AUC) of 0.962 for TNF-α and an AUC of 0.85 for CRP.

Ingestible Devices

A miniature smart capsule to monitor reactive oxygen species (ROS) levels as a biomarker of GI inflammation.[87] The capsule is fitted with sensors for pH and oxidation-reduction potential (ORP) and features an enhanced electronic

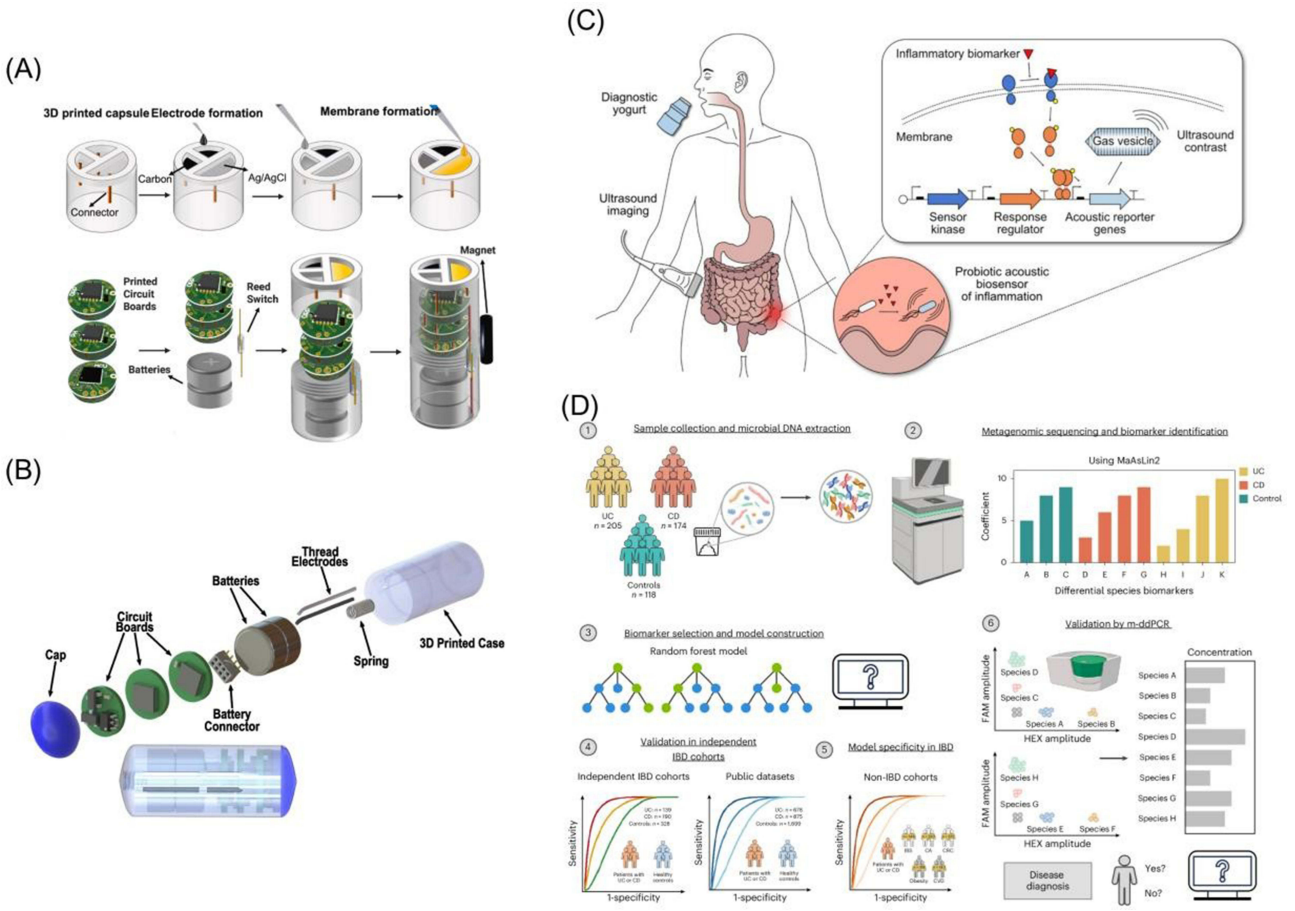

Figure 5 Schematic illustrations of ingestible devices, imaging techniques and sequencing for quantitative analysis of gut dysbiosis derived inflammation. (**A**) 3D printing of smart capsule housing with sensor connectors. Reprinted from Biosensors and bioelectronics: X, 14, Gopalakrishnan S, Thomas R, Sedaghat S, et al. Smart capsule for monitoring inflammation profile throughout the gastrointestinal tract. Biosensors Bioelectronics. 100380, Copyright 2023 with permission from Elsevier.[87] (**B**) The complete assembly and the internal components of the smart sensing pill. Reprinted from Asci C, Sharma A, Del-Rio-Ruiz R, Sonkusale S. Ingestible pH sensing device for gastrointestinal health monitoring based on thread-based electrochemical sensors. Mikrochim Acta. 190(10):385. 2023, Springer Nature.[88] Copyright 2023, Springer Nature. (**C**) Concept of probiotic biosensors for ultrasound imaging of gastrointestinal (GI) inflammation. Reprinted from Buss MT, Zhu L, Kwon JH, Tabor JJ, Shapiro MG. Probiotic acoustic biosensors for noninvasive imaging of gut inflammation. bioRxiv. 2024;2024:614598. http://creativecommons.org/licenses/by/4.0/.[89] Copyright 2025, Springer Nature. (**D**) Workflow of utilizing metagenomic sequencing data to identify and validate gut microbial biomarkers for the diagnosis of IBD. Reprinted from Zheng J, Sun Q, Zhang M, et al. Noninvasive, microbiome-based diagnosis of inflammatory bowel disease. Nature Med. 30:1–13. 2024, Springer Nature.[90]

interface for wireless data transmission (Figure 5A). It is engineered to provide reliable performance within the typical pH (1–8) and ORP (−500–+500 mV) ranges of the GI tract and maintains efficiency of measurements across this range. Thus, the smart capsule marks a major step forward for regular and precise monitoring of digestive disorders, especially IBD, which typically follows a relapsing course.[87]

Another capsule combines a thread-based electrochemical sensor for monitoring pH levels within the GI tract.[88] The system uses two electrodes, a carbon electrode with a polyaniline coating as the working electrode, and an Ag/AgCl-coated electrode as the reference electrode (Figure 5B). Both sensors are housed in a small, 3D-printed capsule that includes the necessary circuitry. The design allows for easy addition of more biosensors to monitor different GI biomarkers. To save energy, the capsule stores data locally instead of sending it wirelessly, which enables energy harvesting in future models.[88]

Biomedical Imaging Techniques

The in vivo visualization of gut inflammation has evolved over recent decades. A non-invasive imaging technology utilizing probiotic-based acoustic biosensors is now accessible for gut inflammation visualization.[89] This biosensor utilizes a probiotic strain of Escherichia coli Nissle that is genetically modified to sense specific inflammatory markers

(thiosulfate and tetrathionate). When these markers are detected, the bacteria produce gas vesicles, which in turn scatter ultrasound waves (Figure 5C). For the test, yogurt containing specially engineered probiotics which can temporarily multiply in the GI tract are ingested by the patient. Then by applying the two component systems (TCSs; thiosulfate and tetrathionate), these bacteria express acoustic reporter genes (ARGs) that code for gas vesicles (GVs) upon detection of inflammatory biomarkers. The binding of biomarkers to membrane sensor kinases initiates a phosphorylation cascade, leading to the transcription of ARGs from specific promoters. The technique provides a promising alternative for the diagnosis and monitoring of IBD.[89]

Sequencing

Novel diagnostics for IBD have been devised based on microbiome analysis.[90] Using metagenomic sequencing, the diversity and richness of the microbiome in IBD is reduced while there are significant differences in gut microbiome composition between ulcerative colitis (UC) and Crohn's disease (CD) (Figure 5D). Specific bacterial species can be identified that are enriched or reduced in UC and CD when analyzed by multivariable associations in linear models (MaAsLin2). These species are then used to construct a random forest plot to distinguish IBD from control patients. Furthermore, a multiplex droplet digital PCR (m-ddPCR) assay has been developed for selected IBD-associated bacterial species, to aid in the diagnosis of IBD. A general IBD model is constructed with good diagnostic performance (AUC of 0.78), showing its potential for clinical application.[90]

AI-Engaged Methods

A supervised machine learning (ML) model trained on gut microbiome data is accessible and useful for the prediction of IBD, including Crohn's disease (CD) and ulcerative colitis (UC).[91] In this study, 16S subgenomic data from IBD and non-IBD subjects were analyzed and 50 bacterial taxa differences between the two groups were found via linear discriminant analysis effect size (LEfSe) with the linear discriminant analysis (LDA) score larger than 3. Additionally, the AUC for random forests (RF) that distinguishes IBD and non-IBD achieved a value of 0.80. Using the first 500 high-variance operational taxonomic units (OTUs) as features, the AUC of the ML model improves to 0.82. The researchers also successfully distinguished between CD and UC samples in an independent cohort using differential classification features or high-variance OTU features with an AUC of more than 0.90.[91]

In type 1 diabetes (T1D), LEfSe and RF were applied and 21 genera-based features demonstrated the highest capability to distinguish between cases and controls, achieving an AUC of 0.962 for the discovery set and 0.745 for the validation set.[92] Phylogenetic Investigation of Communities by Reconstruction of Unobserved States (PICRUST2), a software to predict functional abundance based on marked gene sequences was also utilized to investigate the interactions between GM and metabolic pathways, aiming to gain a more profound insight into how the gut microbiome influences the development of T1D.[92] Currently there are only a few AI-engaged methods for quantitative analysis of gut dysbiosis derived inflammation and none are in routine clinical practice. With the development of more technologies to quantify biomarkers of gut dysbiosis derived inflammation, it is hoped that they can be integrated into clinical care pathways.

Challenges and Perspectives for Inflammation Quantification in Gut

Gut dysbiosis is an important cause of inflammation across the body. In previous sections, we reviewed the mechanisms of gut dysbiosis derived inflammation, its associated biomarkers and current technologies to measure the inflammation. Quantifying inflammation, especially for clinical practice, however, poses several challenges due to its complexity and variability (Figure 6). Inflammation varies across tissues and evolves dynamically (acute, chronic, resolving, relapsing). For the heterogeneity of targets, for instance, single-cell analyses reveal functional heterogeneity in immune cells (eg, only subsets of macrophages produce both IL-10 and TNF-α).[93] Current biopsies can capture limited snapshots, which miss the focus on systemic dynamics. Thus, no single biomarker captures full scope of inflammation. Reliance on non-specific markers (eg, CRP, ESR) complicates source identification.[94] Additionally, clinical models of animals may not accurately reflect human immune responses. Finally, inter-laboratory variability in quantifying inflammation is a hurdle that requires the development of quality assurance standards.

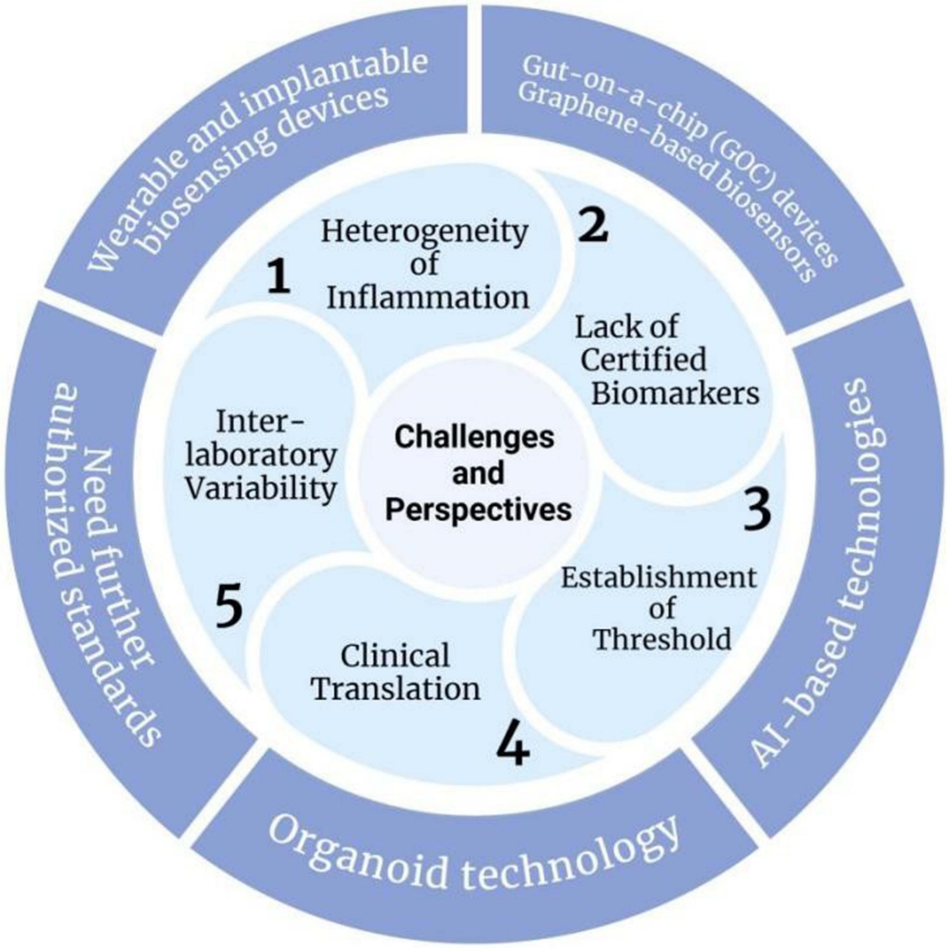

Figure 6 Schematic illustration of challenges (interior circle) and perspectives (exterior circle) of inflammation quantification in gut.

Current quantification practices are applied in multiple clinical scenarios but still in laboratory-based research and preliminary validation. For instance, the quantification via the IBD-AWARE device measuring sweat CRP and IL-6 with 16 IBD patients from the Mount Sinai Hospital and 10 healthy controls from The University of Texas at Dallas. Linear correlations between sweat and serum CRP/IL-6 were observed, especially at lower concentrations, and sweat CRP could distinguish active IBD from healthy controls (AUC=0.85), while IL-6 had weaker correlation (R^2=0.601) and failed to be distinguished from groups.[86] For the integrated pH and ORP sensors, high linearity and stability within physiologically relevant ranges of the gastrointestinal tract was achieved, with calibration coefficients R2=0.9925 (pH) and R2=0.974 (ORP) but lacked performance in real gastrointestinal environments.[87] These methods can potentially reduce costs by replacing invasive procedures, but high development and manufacturing costs. By implementing early detection of sub-clinical inflammation, these measurements could help prevent diseases in the at-risk population, though such preventive benefits remain to be validated in clinical studies.

Conclusion

Gut dysbiosis derived inflammation is related with complex mechanisms defined by its inflammation states. This review hihglights various biomarkers (eg, microbial metabolites, immune mediators, and gut barrier markers) can reflect these mechanisms and dynamics, collectively forming objective indicators of gut inflammatory activity and helping to differentiate between pathological and physiological conditions. Although different quantification methods have been developed, there is a need for further research to validate the threshold and normal ranges of muti-biomarkers in gut-

derived inflammation that are reproducible and backed by robust quality assurance for clinical practice. Despite the multiple challenges, integrating advanced technologies such as biotechnology, nanotechnology, advanced material science and AI, the future for gut-derived inflammation quantification is promising.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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