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Characterization of Gut Microbiome Dysbiosis and Its Association with Systemic Inflammation and Clinical Severity in Sick Cell Disease

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Abstract: Sick cell disease (SCD) is a hereditary hemoglobinopathy characterized by chronic hemolysis, recurrent vaso-occlusive crises, endothelial dysfunction, and persistent systemic inflammation. Although advances in newborn screening, hydroxyurea therapy, chronic transfusion protocols, and more recently gene-based therapies have improved patient survival, chronic inflammatory complications continue to contribute substantially to morbidity and mortality. In recent years, the gut microbiome has emerged as a critical regulator of immune homeostasis, metabolism, vascular integrity, and inflammatory signaling. Alterations in gut microbial composition, collectively referred to as gut microbiome dysbiosis, have been implicated in numerous chronic inflammatory disorders, including inflammatory bowel disease, obesity, diabetes mellitus, cardiovascular disease, and autoimmune conditions. Growing evidence suggests that similar alterations occur in patients with SCD, where repeated ischemia-reperfusion injury, intestinal hypoxia, frequent antibiotic exposure, altered dietary patterns, and compromised epithelial barrier integrity collectively disrupt the normal intestinal microbial ecosystem.

Gut microbiome dysbiosis may contribute directly to chronic inflammation through increased intestinal permeability, translocation of microbial products, activation of innate immune receptors, and excessive production of pro-inflammatory cytokines. These mechanisms promote neutrophil activation, endothelial dysfunction, platelet aggregation, and enhanced adhesion of sickled erythrocytes, thereby exacerbating vaso-occlusive events and multiple organ damage. Several studies have demonstrated significant reductions in beneficial commensal bacteria together with enrichment of pathogenic taxa in individuals with SCD, suggesting that microbial imbalance may represent both a biomarker of disease severity and a potential therapeutic target.

This review critically examines current knowledge regarding the composition of the gut microbiome in SCD, the mechanisms linking intestinal dysbiosis with systemic inflammation, and the relationship between microbial alterations and clinical manifestations of disease severity. Emerging microbiome-directed interventions, including probiotics, prebiotics, dietary modulation,



and fecal microbiota transplantation, are also discussed. Finally, current research limitations and future directions for microbiome-based precision medicine in SCD are highlighted.

Keywords: Sick cell disease; gut microbiome; dysbiosis; systemic inflammation; intestinal permeability; vaso-occlusive crisis; microbiota; cytokines; precision medicine.

1. Introduction

Sickle cell disease (SCD) represents one of the most common inherited monogenic disorders worldwide and remains a major public health concern, particularly in sub-Saharan Africa, India, the Middle East, and parts of the Mediterranean. The disease results from a single nucleotide substitution in the β -globin gene that replaces glutamic acid with valine at the sixth position of the β -globin chain, producing abnormal hemoglobin S (HbS). Under conditions of reduced oxygen tension, HbS undergoes polymerization, leading to erythrocyte deformation, membrane damage, increased cellular rigidity, and premature hemolysis. These pathological events initiate recurrent vaso-occlusion, chronic inflammation, endothelial injury, and progressive multi-organ dysfunction [1–3].

Despite remarkable improvements in clinical management, including hydroxyurea therapy, chronic blood transfusion programs, improved infection prevention, and curative hematopoietic stem cell transplantation for selected patients, individuals living with SCD continue to experience significant morbidity arising from chronic inflammatory complications. Repeated vaso-occlusive episodes contribute to tissue ischemia, reperfusion injury, pulmonary hypertension, nephropathy, stroke, osteonecrosis, and chronic pain syndromes. Increasing evidence indicates that these complications cannot be explained solely by erythrocyte sickling but involve complex interactions among immune cells, endothelial cells, platelets, inflammatory mediators, and microbial-derived products originating from the gastrointestinal tract [4–6].

The human gastrointestinal tract contains one of the most complex microbial ecosystems known, harboring approximately 10^{14} microorganisms comprising bacteria, fungi, viruses, archaea, and protozoa. Collectively referred to as the gut microbiome, these microorganisms perform numerous physiological functions essential for maintaining host health. They participate in nutrient metabolism, vitamin synthesis, immune maturation, maintenance of epithelial barrier integrity, regulation of inflammatory responses, and production of bioactive metabolites such as short-chain fatty acids (SCFAs). These metabolites, particularly butyrate, acetate, and propionate, influence epithelial integrity, T-cell differentiation, macrophage polarization, and systemic immune regulation [7–9].

Under physiological conditions, the gut microbiome exists in a dynamic equilibrium characterized by high microbial diversity and functional stability. However, disruption of this balance, termed dysbiosis, results in reduced microbial diversity, depletion of beneficial commensal organisms, and expansion of potentially pathogenic microorganisms. Dysbiosis has been associated with several chronic inflammatory diseases, including inflammatory bowel disease, rheumatoid arthritis, obesity, diabetes mellitus, cardiovascular disease, chronic kidney disease, neurodegenerative disorders, and malignancies. These observations have transformed the gut



microbiome from a passive microbial community into an active regulator of systemic immunity and human disease [10–12].

In patients with SCD, several disease-related factors predispose to intestinal dysbiosis. Chronic anemia and repeated vaso-occlusive events reduce intestinal oxygenation, leading to ischemic injury of the gut mucosa. The resulting epithelial damage increases intestinal permeability, allowing bacterial components such as lipopolysaccharide (LPS), peptidoglycans, and microbial DNA to enter systemic circulation. Concurrently, frequent hospitalization, recurrent antibiotic use, altered dietary intake, chronic opioid therapy, and immune dysregulation further modify microbial composition, creating a self-perpetuating cycle of intestinal inflammation and systemic immune activation [13–15].

The concept of the gut–immune axis has become increasingly relevant in understanding the pathophysiology of SCD. Studies have demonstrated that intestinal microbial products stimulate Toll-like receptors (TLRs), activate nuclear factor-kappa B (NF- κ B) signaling pathways, promote neutrophil maturation, and increase production of inflammatory cytokines including tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and interferon-gamma (IFN- γ). These inflammatory mediators enhance endothelial activation through increased expression of vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and E-selectin, facilitating adhesion of sickled erythrocytes and leukocytes to the vascular endothelium. Consequently, dysbiosis may contribute directly to vaso-occlusive crises and disease progression [16–18].

Recent advances in high-throughput sequencing technologies have enabled comprehensive characterization of intestinal microbial communities in SCD. Studies employing 16S ribosomal RNA sequencing and whole-metagenome sequencing have identified significant alterations in microbial diversity among patients with SCD. Beneficial butyrate-producing bacteria, including *Faecalibacterium*, *Roseburia*, and members of the family *Lachnospiraceae*, are frequently depleted, whereas opportunistic pathogens belonging to *Enterobacteriaceae*, *Enterococcus*, and other pro-inflammatory taxa appear enriched. Although findings vary between geographic populations and age groups, these observations consistently suggest that gut microbial imbalance contributes to chronic inflammation and disease severity [19–21].

Interest in microbiome research has expanded rapidly because microbial composition is modifiable. Unlike genetic determinants of SCD, intestinal microbial communities may be altered through nutritional interventions, probiotics, prebiotics, synbiotics, antibiotics, fecal microbiota transplantation, and microbiome-targeted therapeutics. Such interventions have shown promise in other inflammatory disorders and may represent novel adjunctive strategies for reducing inflammatory burden in SCD. Nevertheless, understanding the mechanisms by which dysbiosis influences disease progression remains an important prerequisite for successful clinical translation [22,23].

This review synthesizes current evidence regarding gut microbiome dysbiosis in SCD and critically examines its relationship with systemic inflammation and clinical severity. Particular emphasis is placed on microbial alterations associated with vaso-occlusive crises, endothelial dysfunction, immune activation, and emerging microbiome-based therapeutic strategies. By



integrating recent discoveries from microbiology, immunology, hematology, and systems biology, this review aims to provide a comprehensive overview of the expanding role of the gut microbiome in SCD pathogenesis while identifying key knowledge gaps that warrant future investigation.

2. Gut Microbiome in Human Health

The human gastrointestinal tract harbors a highly diverse microbial ecosystem that evolves throughout life and exerts profound effects on host physiology. It is estimated that the adult gut contains more than one thousand bacterial species, with the majority belonging to the phyla **Firmicutes**, **Bacteroidetes**, **Actinobacteria**, **Proteobacteria**, and **Verrucomicrobia**. Although bacterial composition varies considerably among individuals, healthy microbiomes generally maintain high taxonomic diversity and functional redundancy, ensuring resilience against environmental perturbations [24,25].

Colonization of the intestinal tract begins immediately after birth and is influenced by delivery mode, breastfeeding practices, antibiotic exposure, environmental conditions, genetics, and dietary habits. During infancy and early childhood, microbial communities undergo progressive maturation before stabilizing in adulthood. Throughout life, continuous interactions between host immunity and microbial populations maintain intestinal homeostasis, while disturbances to this equilibrium may predispose individuals to chronic inflammatory diseases [26].

One of the primary functions of the gut microbiome is the fermentation of indigestible dietary carbohydrates into SCFAs, principally acetate, propionate, and butyrate. These metabolites serve as major energy sources for colonocytes and regulate multiple immunological processes. Butyrate promotes epithelial cell differentiation, strengthens tight junction proteins, suppresses NF- κ B activation, and enhances differentiation of regulatory T cells (Tregs). Consequently, adequate production of SCFAs contributes significantly to maintenance of intestinal barrier integrity and immune tolerance [27].

The gut microbiome also participates in synthesis of vitamins, including vitamin K and several B-complex vitamins, metabolism of bile acids, detoxification of xenobiotics, and regulation of host lipid and glucose metabolism. Furthermore, intestinal microorganisms compete with pathogenic bacteria for ecological niches and nutrients while producing antimicrobial peptides that inhibit pathogen colonization. These collective activities reinforce the concept of the microbiome as a functional metabolic organ essential for human health [28].

Beyond local gastrointestinal functions, the gut microbiome exerts systemic immunomodulatory effects. Continuous sampling of microbial antigens by intestinal dendritic cells shapes adaptive immune responses and influences the balance between pro-inflammatory T helper (Th1 and Th17) cells and anti-inflammatory regulatory T cells. Dysregulation of these interactions promotes excessive cytokine production, chronic immune activation, and systemic inflammatory diseases. Emerging evidence further indicates bidirectional communication between the gut microbiome and distant organs through immune, endocrine, metabolic, and neural pathways, collectively referred to as the gut-organ axes [29,30].



Given the central role of the gut microbiome in regulating immune homeostasis, maintenance of epithelial integrity, and inflammatory balance, disruption of microbial communities has profound implications for chronic diseases characterized by persistent inflammation. In SCD, where systemic inflammation is a defining pathological feature, understanding the composition and function of the intestinal microbiome provides a crucial foundation for elucidating disease mechanisms and identifying innovative therapeutic approaches. [30].

3. Gut Microbiome Dysbiosis in Sickle Cell Disease

The intestinal microbiome has emerged as an important contributor to the pathophysiology of sickle cell disease (SCD), extending the traditional understanding of the disorder beyond erythrocyte sickling and vascular occlusion. Although the genetic mutation responsible for SCD has been well characterized for decades, the considerable heterogeneity in disease severity among patients with identical genotypes suggests that additional environmental and host-related factors influence disease progression. Among these factors, alterations in the intestinal microbial ecosystem have attracted increasing attention because of their capacity to regulate systemic immune responses, endothelial function, and inflammatory signaling. Recent investigations using culture-independent molecular techniques have consistently demonstrated that patients with SCD possess distinct intestinal microbial profiles compared with healthy individuals, supporting the hypothesis that gut dysbiosis contributes to chronic inflammation and clinical complications of the disease [31–33].

Gut microbiome dysbiosis refers to qualitative and quantitative alterations in microbial composition, diversity, and metabolic activity that disrupt host–microbial homeostasis. In healthy individuals, the intestinal microbiota is characterized by high species richness and predominance of beneficial anaerobic bacteria belonging mainly to the phyla *Firmicutes* and *Bacteroidetes*. These microorganisms participate in nutrient metabolism, production of short-chain fatty acids (SCFAs), maintenance of epithelial integrity, and regulation of mucosal immunity. In contrast, dysbiosis is characterized by reduced microbial diversity, depletion of beneficial commensals, expansion of opportunistic pathogens, and altered microbial metabolic pathways, all of which promote inflammatory responses and compromise intestinal barrier function [34,35].

Several factors inherent to SCD predispose affected individuals to microbial imbalance. Chronic hemolytic anemia reduces oxygen delivery to the intestinal mucosa, while recurrent vaso-occlusive episodes produce repeated ischemia–reperfusion injury within the gastrointestinal tract. These pathological events impair epithelial regeneration, disrupt tight junction proteins, and alter the intestinal microenvironment, thereby favoring colonization by pro-inflammatory microorganisms. Furthermore, frequent hospitalization, repeated exposure to broad-spectrum antibiotics, prolonged opioid use for pain management, nutritional deficiencies, recurrent infections, and altered gastrointestinal motility collectively contribute to long-term perturbations of the intestinal microbiome [36,37].

The introduction of high-throughput sequencing technologies has significantly advanced understanding of microbial alterations in SCD. Studies employing 16S ribosomal RNA sequencing have demonstrated significant reductions in microbial alpha diversity among patients with SCD compared with healthy controls. Reduced diversity is widely regarded as an indicator of impaired



ecosystem resilience and has been associated with numerous chronic inflammatory disorders. In addition to diminished diversity, SCD patients exhibit marked shifts in bacterial abundance, including reductions in beneficial butyrate-producing organisms such as *Faecalibacterium prausnitzii*, *Roseburia* spp., *Blautia*, and members of the family *Lachnospiraceae*. These microorganisms normally contribute to epithelial integrity through production of butyrate, an essential energy source for colonocytes with potent anti-inflammatory properties [38–40].

Conversely, several studies have reported increased abundance of opportunistic pathogens belonging to the phylum *Proteobacteria*, including members of the family *Enterobacteriaceae*, together with enrichment of *Enterococcus*, *Escherichia*, and other facultative anaerobes capable of inducing inflammatory responses. Expansion of these bacterial groups is frequently associated with increased production of endotoxins, particularly lipopolysaccharide (LPS), which activates innate immune receptors and promotes systemic inflammation. Although variations exist between geographical populations, age groups, and analytical methodologies, the overall pattern consistently indicates a transition from an anti-inflammatory to a pro-inflammatory microbial ecosystem in SCD [41–43].

Animal studies have provided compelling mechanistic evidence supporting the contribution of intestinal microbiota to SCD pathogenesis. Experimental murine models have demonstrated that depletion of intestinal bacteria using non-absorbable antibiotics reduces circulating aged neutrophils, decreases endothelial adhesion, and significantly attenuates vaso-occlusive events. These findings suggest that continuous stimulation by intestinal microorganisms contributes to neutrophil activation and vascular inflammation. Restoration of microbial diversity following antibiotic withdrawal or microbiota manipulation further supports the dynamic relationship between intestinal microorganisms and disease activity [44,45].

An additional characteristic feature of dysbiosis in SCD is impairment of microbial metabolic function. Healthy gut bacteria produce numerous metabolites that regulate immune homeostasis, including SCFAs, indole derivatives, secondary bile acids, and polyamines. Reduced abundance of SCFA-producing bacteria decreases butyrate synthesis, thereby weakening epithelial tight junctions, increasing intestinal permeability, and promoting inflammatory cytokine production. Simultaneously, dysbiosis alters bile acid metabolism and amino acid fermentation, generating metabolites capable of activating inflammatory signaling pathways and oxidative stress responses. Consequently, functional alterations may be equally important as taxonomic changes in driving disease progression [46,47].

Geographical variation further influences microbial composition among patients with SCD. Differences in dietary practices, sanitation, environmental exposures, genetic background, healthcare accessibility, and antibiotic prescribing patterns contribute to substantial variability in microbial communities across populations. Studies conducted in sub-Saharan Africa, Europe, and North America have reported distinct bacterial signatures despite consistent evidence of reduced diversity and increased inflammatory taxa. These observations highlight the necessity for region-specific microbiome investigations before translating microbial biomarkers into clinical practice [48].



Age also appears to influence microbiome composition in SCD. Pediatric patients experience continuous maturation of intestinal microbial communities during early life, rendering them particularly susceptible to environmental perturbations. Early antibiotic exposure, recurrent infections, and nutritional deficiencies may alter microbial development during critical periods of immune maturation, potentially influencing disease trajectory throughout adulthood. In contrast, adult patients often exhibit cumulative effects of chronic inflammation, repeated hospitalization, and prolonged medication use, resulting in more pronounced microbial alterations. Longitudinal studies following patients from infancy into adulthood remain limited but are essential for understanding temporal relationships between microbiome development and disease progression [49,50].

Collectively, current evidence indicates that gut dysbiosis represents an important component of SCD pathophysiology rather than a secondary consequence of chronic illness. Alterations in microbial diversity, depletion of beneficial commensals, enrichment of pro-inflammatory organisms, and disruption of microbial metabolic pathways create conditions that favor immune activation and endothelial dysfunction. These observations have stimulated interest in microbiome-targeted therapeutic strategies aimed at restoring microbial homeostasis and reducing inflammatory complications in SCD.

4. Mechanisms Linking Gut Dysbiosis to Systemic Inflammation

Systemic inflammation is a defining characteristic of SCD and contributes directly to vaso-occlusive crises, endothelial dysfunction, chronic pain, pulmonary hypertension, nephropathy, and progressive organ damage. While hemolysis and ischemia–reperfusion injury remain fundamental drivers of inflammation, increasing evidence indicates that the gastrointestinal tract serves as an additional source of inflammatory stimulation through disruption of the gut–immune axis [51].

One of the earliest consequences of gut dysbiosis is impairment of intestinal barrier integrity. Under physiological conditions, epithelial tight junction proteins—including occludin, claudins, and zonula occludens proteins—maintain selective permeability between the intestinal lumen and systemic circulation. Beneficial microorganisms reinforce these structures through production of butyrate and other SCFAs. However, depletion of butyrate-producing bacteria weakens epithelial junctions, resulting in increased intestinal permeability, commonly referred to as a "leaky gut." This structural disruption permits translocation of microbial components, including LPS, bacterial DNA, peptidoglycans, and flagellin, into the bloodstream, where they initiate widespread immune activation [52,53].

Microbial products entering systemic circulation are recognized by pattern-recognition receptors expressed on macrophages, dendritic cells, neutrophils, and endothelial cells. Among these receptors, Toll-like receptor 4 (TLR4) plays a particularly important role by recognizing LPS derived from Gram-negative bacteria. Activation of TLR4 triggers intracellular signaling cascades involving myeloid differentiation factor 88 (MyD88), nuclear factor-kappa B (NF- κ B), and mitogen-activated protein kinase (MAPK) pathways. These signaling networks stimulate transcription of numerous pro-inflammatory mediators, including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and interleukin-8 (IL-8), thereby amplifying systemic inflammation [54,55].



Persistent cytokine production profoundly affects vascular function in SCD. Endothelial cells exposed to inflammatory mediators increase expression of vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), P-selectin, and E-selectin. These adhesion molecules facilitate attachment of sickled erythrocytes, activated neutrophils, monocytes, and platelets to the vascular endothelium, promoting microvascular obstruction and tissue ischemia. Recurrent ischemia is followed by reperfusion injury, generating reactive oxygen species (ROS) that further amplify endothelial activation and inflammatory signaling, establishing a self-perpetuating cycle of vascular injury [56].

Neutrophils occupy a central position within this inflammatory network. Patients with SCD exhibit chronically elevated neutrophil counts, and activated neutrophils contribute significantly to vaso-occlusive crises through formation of heterocellular aggregates with erythrocytes and platelets. Experimental studies have demonstrated that gut-derived microbial signals regulate neutrophil maturation within the bone marrow and influence circulating populations of aged neutrophils characterized by enhanced adhesive properties. Increased abundance of these activated neutrophils has been associated with greater frequency of vaso-occlusive episodes, suggesting that intestinal microbiota indirectly modulate vascular inflammation through regulation of innate immune cell function [57,58].

Oxidative stress provides another important mechanistic link between dysbiosis and inflammation. Chronic hemolysis releases free hemoglobin and heme into circulation, overwhelming endogenous antioxidant defenses. Simultaneously, dysbiosis-induced inflammatory signaling increases production of ROS by activated neutrophils and macrophages. Excessive oxidative stress damages endothelial cells, oxidizes membrane lipids, impairs nitric oxide bioavailability, and enhances erythrocyte sickling, thereby intensifying vascular dysfunction. Reduced production of antioxidant microbial metabolites further aggravates oxidative injury [59,60].

These interconnected mechanisms demonstrate that gut microbiome dysbiosis is not merely associated with systemic inflammation in SCD but actively contributes to immune dysregulation through impaired barrier function, microbial translocation, innate immune activation, endothelial dysfunction, neutrophil activation, and oxidative stress. Understanding these pathways provides a biological rationale for microbiome-directed therapeutic interventions aimed at reducing inflammatory burden and improving long-term clinical outcomes.

6. Emerging Microbiome-Based Therapeutic Strategies

Growing recognition of the gut microbiome as a key regulator of immune homeostasis has stimulated considerable interest in microbiome-directed therapies for sickle cell disease (SCD). Unlike the β -globin mutation responsible for SCD, the intestinal microbiome is dynamic and modifiable throughout life. Consequently, restoration of microbial homeostasis has emerged as a promising adjunctive strategy to reduce chronic inflammation, improve intestinal barrier function, and mitigate vaso-occlusive complications. Although these interventions remain largely investigational, accumulating evidence supports their potential role in future precision medicine approaches [61, 62].



6.1 Dietary Intervention

Diet is one of the strongest environmental determinants of gut microbial composition. Dietary fibre, resistant starches, whole grains, legumes, fruits and vegetables promote the proliferation of beneficial anaerobic bacteria capable of fermenting complex carbohydrates into short-chain fatty acids (SCFAs), principally butyrate, acetate and propionate. These metabolites maintain epithelial barrier integrity, suppress nuclear factor-kappa B (NF- κ B) activation, stimulate regulatory T-cell differentiation and reduce systemic inflammatory responses [63].

In SCD, depletion of butyrate-producing bacteria including *Roseburia* spp. and *Faecalibacterium prausnitzii* has been consistently associated with chronic inflammation and increased intestinal permeability. Restoration of these bacterial populations through dietary modification may therefore improve gut barrier function and reduce microbial translocation into systemic circulation. Although randomized dietary intervention studies in SCD remain scarce, current evidence strongly supports incorporating nutritional counselling into comprehensive disease management [64].

6.2 Probiotics, Prebiotics and Synbiotics

Probiotics are defined as live microorganisms that confer health benefits when administered in adequate quantities. Common probiotic organisms include *Lactobacillus*, *Bifidobacterium*, *Lactocaseibacillus* and *Saccharomyces* species. These microorganisms compete with pathogenic bacteria for ecological niches, reinforce epithelial tight junctions, stimulate mucus production and enhance synthesis of antimicrobial peptides [65].

Recent reviews have identified next-generation probiotics such as *Akkermansia muciniphila* and *Roseburia* species as particularly promising candidates for SCD because of their capacity to preserve intestinal barrier integrity, increase butyrate production and attenuate chronic inflammation. Experimental evidence further suggests that restoration of these bacterial populations may reduce endothelial activation, neutrophil adhesion and vaso-occlusive events, although confirmation through randomized clinical trials is still required [66].

Prebiotics which includes inulin, fructooligosaccharides and galactooligosaccharides—selectively stimulate proliferation of beneficial microorganisms, whereas synbiotics combine probiotics with prebiotic substrates to enhance microbial survival and colonization. Systematic reviews indicate that these interventions improve microbial diversity and reduce inflammatory biomarkers in several chronic inflammatory disorders, suggesting potential applicability to SCD [67].

6.3 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) involves transfer of processed intestinal microbiota from healthy donors to recipients with severe dysbiosis. FMT has become an established treatment for recurrent *Clostridioides difficile* infection and is being investigated for inflammatory bowel disease, metabolic syndrome and immune-mediated disorders.



Although no large clinical trials have evaluated FMT in SCD, restoration of microbial diversity may theoretically reduce intestinal permeability, endotoxemia and systemic inflammation. However, the immunocompromised state associated with functional asplenia, recurrent antibiotic exposure and chronic organ dysfunction necessitates rigorous donor screening and long-term safety evaluation before FMT can be considered for routine clinical application [68].

6.4 Precision Microbiome Medicine

Advances in metagenomics, metabolomics and computational biology are transforming microbiome research from descriptive ecology into precision medicine. High-resolution sequencing now permits characterization of microbial genes, metabolic pathways and host–microbe interactions rather than simple taxonomic composition.

Integration of microbiome profiles with transcriptomics, metabolomics, inflammatory biomarkers and clinical phenotypes may enable prediction of vaso-occlusive crises before symptom onset. Artificial intelligence and machine learning are increasingly being explored to identify microbial signatures associated with disease severity and therapeutic response. Such approaches may facilitate individualized microbiome-based interventions tailored to each patient's microbial ecosystem [69].

7. Current Research Gaps and Future Perspectives

Despite rapid advances in microbiome research, several challenges limit translation of current findings into routine clinical practice. First, most published studies involve relatively small patient cohorts and cross-sectional study designs, preventing definitive conclusions regarding causality between dysbiosis and disease severity. Longitudinal multicentre studies are required to determine whether microbial alterations precede vaso-occlusive crises or merely reflect chronic inflammation [70].

Second, substantial heterogeneity exists among microbiome studies owing to differences in sequencing platforms, DNA extraction protocols, bioinformatic pipelines, dietary habits, antibiotic exposure, geographical location and patient demographics. Standardization of laboratory and analytical methods is therefore essential to improve reproducibility across studies.

Third, future investigations should move beyond taxonomic profiling toward functional characterization of microbial communities. Metagenomic sequencing combined with metabolomics and transcriptomics will provide greater insight into microbial metabolic pathways responsible for immune regulation and vascular inflammation. In particular, characterization of SCFA biosynthesis, bile acid metabolism and microbial amino acid pathways may identify novel therapeutic targets [71].

Future research should also evaluate microbiome-targeted interventions through adequately powered randomized controlled trials. Dietary fibre supplementation, next-generation probiotics, synbiotics and engineered microbial therapeutics represent promising areas of investigation. Their effectiveness should be assessed using standardized clinical outcomes including frequency of



vaso-occlusive crises, inflammatory biomarkers, endothelial activation markers and patient-reported quality-of-life measures.

Finally, precision medicine approaches integrating genomic, metabolomic, microbiome and clinical datasets may substantially improve risk stratification and individualized patient management. Such multidisciplinary strategies are expected to transform future SCD care by enabling early identification of high-risk patients and targeted prevention of inflammatory complications.

8. Conclusion

Recent advances in microbiome science have substantially expanded current understanding of sickle cell disease pathophysiology. Beyond the classical mechanisms of haemoglobin S polymerization and erythrocyte sickling, compelling evidence indicates that intestinal dysbiosis contributes significantly to chronic inflammation, endothelial dysfunction and vascular injury.

Reduced microbial diversity, depletion of beneficial SCFA-producing bacteria and enrichment of pro-inflammatory microorganisms collectively impair epithelial barrier integrity and facilitate microbial translocation into systemic circulation. Subsequent activation of innate immune pathways amplifies cytokine production, endothelial activation and neutrophil adhesion, thereby promoting vaso-occlusive crises and progressive organ damage [71].

Emerging therapeutic strategies including dietary modulation, probiotics, prebiotics, synbiotics and precision microbiome engineering offer promising opportunities to restore intestinal homeostasis and complement existing disease-modifying therapies. Nevertheless, translation into routine clinical practice requires robust longitudinal studies, standardized microbiome analyses and large randomized controlled trials.

Overall, the gut microbiome represents one of the most promising frontiers in SCD research. Continued interdisciplinary collaboration among hematologists, microbiologists, immunologists, nutrition scientists and computational biologists will be essential for translating microbiome discoveries into clinically effective interventions capable of reducing morbidity, improving quality of life and advancing precision medicine for individuals living with sickle cell disease.

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