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Review Article:

The Microbiome–Sickle Cell Disease Axis: Emerging Mechanisms Linking Dysbiosis, Inflammation, Vaso-Occlusion and End-Organ Injury

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ABSTRACT:
Sickle cell disease (SCD) is a genetic haemoglobin illness characterised by persistent haemolytic anaemia, recurrent vaso-occlusion, inflammation and gradual end-organ damage. While polymerisation of deoxygenated haemoglobin S is the fundamental molecular event in SCD, the clinical expression of the disease is increasingly understood to be the product of interactions among erythrocytes, leukocytes, endothelial cells, platelets, inflammatory mediators, metabolic pathways and environmental factors. Recently, the gut microbiome has been identified as a potentially essential element of this complicated pathophysiologic network. Intestinal hypoxia-reperfusion damage, compromised epithelial integrity, repeated antibiotic exposure, diet, drugs and systemic inflammation could be responsible for dysbiosis in SCD. Conversely, microbial composition and microbial metabolites may alter intestinal permeability, immunological activation, neutrophil ageing, endothelial dysfunction and vaso-occlusion. Human and experimental investigations of patients and animal models with SCD have shown considerable modifications in gut microbiota including bacterial diversity and abundance of possibly pro-inflammatory and short-chain-fatty-acid-producing organisms. The gut microbiome has also been involved with chronic SCD pain through microbial metabolites and gut–brain signalling, based on experimental studies. Our results imply that dysbiosis may be part of a microbiome-SCD axis linking gut injury to systemic inflammation, vaso-occlusive crises and end-organ damage. However, for many postulated pathways, the existing data is insufficient to prove causation. Indeed, much of the mechanistic evidence stems from animal models or rather small human research. However, the knowledge of this axis could help to discover new indicators and treatment targets such as dietary interventions, probiotics, prebiotics, microbial metabolites and other microbiome-targeted strategies. Thus, the microbiome–SCD axis provides a nascent paradigm for understanding disease heterogeneity and devising complimentary approaches to mitigate inflammation, vaso-occlusion and organ damage.

Keyword: Microbiome, Sickle Cell Disease, Pathogenesis, Dysbiosis, Inflammation, Vaso-occlusion, End-organ Injury

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INTRODUCTION

Sickle cell disease is one of the most researched hereditary blood diseases and continues to be a prominent source of morbidity and premature death globally. It is mostly due to a single nucleotide alteration in β-globin gene resulting in haemoglobin S. In the deoxygenated state, polymerisation of haemoglobin S inside erythrocytes occurs, resulting in cellular distortion, decreased deformability and enhanced adherence to the vascular endothelium. These anomalies predispose to microvascular constriction and hypoxia of the tissue while increased erythrocyte destruction leads to chronic haemolysis. The interaction between sickled red blood cells, leukocytes, platelets, endothelial cells and coagulation pathways ultimately results in the characteristic complications of SCD including vaso-occlusive pain, acute chest syndrome, stroke, renal dysfunction, pulmonary vascular disease and progressive multiorgan injury [1]

The classic concept of SCD pathogenesis centred on red blood-cell sickling and vascular occlusion. The current view, however, is that SCD is a chronic inflammatory and vascular disease in which there is ongoing interaction between haemolysis, oxidative stress, endothelial activation, leukocyte adhesion and immunological dysregulation. Thus, vaso-occlusion is not only a mechanical result of stiff erythrocytes. Activated neutrophils, monocytes and platelets are involved in the start and propagation of vascular blockage. Endothelial dysfunction and inflammatory cytokines contribute to cellular adhesion and vascular

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damage. Repeated episodes of ischaemia and reperfusion eventually lead to cumulative damage in organs such as the kidneys, lungs, brain, spleen, liver and bones [2].

In this increasingly complicated model, the gastrointestinal tract and its resident microbial population have received increased attention. The human gut houses a massive and complex microbial ecology, consisting mostly of bacteria but also including archaea, fungi, viruses and other species. These organisms contribute to digestion, food metabolism, short-chain fatty acid (SCFA) synthesis, modulation of the epithelial barrier, and development of immunological homeostasis. Therefore, alterations in the composition or functional activity of the gut microbiome, sometimes referred to as dysbiosis, can have effects well beyond the gastrointestinal tract [3].

The hypothesis of the microbiome-SCD axis suggests a bidirectional link between intestinal microbes and systemic pathophysiology of SCD. On the other hand, sickling, vaso-occlusion and repeated hypoxia-reperfusion damage may impact the gastrointestinal tract and modify the microbial milieu. On the other side, microbial dysbiosis, increased intestinal permeability and microbial metabolites can impact systemic inflammation, activation of immune cells and vascular function. Hence, the gut may be a link between local intestine damage and systemic consequences of SCD [4].

This notion was supported by investigations that characterised the gut flora of SCD patients. Brim and colleagues studied faeces and saliva samples from people with SCD and healthy controls, as well as humanised SCD mice models. The study revealed significant variations in the gut microbiomes of people with SCD, including changes in bacterial families and a reduced ratio of Firmicutes to Bacteroidetes. Importantly, identical dysbiosis was found in the Townes SCD mouse model, offering an experimental setting for exploring microbiome related processes [5].

One proposed pathway starts with intestinal microvascular dysfunction. The gastrointestinal tract is highly vascularised and is susceptible to sickling and vaso-occlusion. Repeated occurrences of intestinal ischaemia and reperfusion can cause oxidative stress and epithelium damage. The intestinal epithelium generally forms a selective barrier that separates luminal bacteria from the systemic circulation. Tight connections between epithelial cells control the transit of materials over this barrier. Compromise of these structures can lead to increased intestinal permeability and the passage of bacterial products and other microbial compounds into the circulation [6].

This may be especially relevant in SCD since the illness already creates a highly inflammatory systemic milieu. Immune and endothelial cells possess pattern-recognition receptors that are activated by microbial components such as lipopolysaccharide. This can trigger inflammatory pathways, and increase the production of cytokines and other mediators. Therefore, intestinal barrier disturbance may be another source of inflammatory activation in a condition where inflammation is key in vaso-occlusion [7].

The connection may so become self-reinforcing. Vascular obstruction associated with SCD causes hypoxia in the intestines and damage to the epithelium. Epithelial damage changes microbial composition and increases permeability. Microbial products stimulate systemic inflammation. Inflammation promotes activation of leukocytes and endothelium, which may contribute to further vaso-occlusion. This concept does not imply that dysbiosis independently causes SCD. Rather, it shows that the microbiome might serve as a modulator that potentiates pre-existing pathogenic processes [8].
Neutrophils are a key mechanistic connection between gut microbes and vaso-occlusion. Neutrophil activation is a known factor to SCD vascular disease. Activated neutrophils stick to endothelial cells and interact with sickled red blood cells and platelets resulting in microvascular blockage. Studies have shown that the gut microbiota can alter the ageing of neutrophils. In SCD, increasing numbers of elderly neutrophils may have greater adhesive and inflammatory features. Previous experimental work has suggested that intestine microbial signals may influence this neutrophil phenotype and hence vulnerability to vaso-occlusive crisis [9].

This is important because it presents a potential biological pathway that links the gut microbiota to a known cellular mechanism of vaso-occlusion. Not only may the microbiome be a marker of ill health, it may also affect the number or activity of immune cells that directly contribute to vascular blockage.

Metabolites of microbes give another method. SCFAs are the most researched metabolites and include acetate, propionate and butyrate These chemicals are formed on

fermentation of dietary fibre by gut bacteria. SCFAs regulate epithelial metabolism, immunological control and inflammatory signalling. Butyrate, for example, is a key energy source for colonic epithelial cells and is involved in the maintenance of the intestinal barrier integrity [10].

Dysbiosis leading to a decrease in the quantity or activity of SCFA-producing bacteria can consequently compromise intestinal barrier function and immunological homeostasis. Conversely, a gut environment richer in organisms able to produce beneficial compounds, may theoretically enhance epithelial integrity and minimise inflammatory signalling. However, the link between bacterial abundance and metabolite synthesis is not straightforward. Bacterial taxonomy alone does not necessarily predict microbial behaviour, as the same bacterial species might behave differently depending on nutrition and environmental conditions [11].

Special attention has been given to Akkermansia muciniphila and Roseburia spp. in connection to SCD. A. muciniphila is related with the intestinal mucus layer and has been examined for its possible part in the preservation of the epithelial barrier function. Roseburia species are key butyrate-producing bacteria. A recent analysis suggested that alterations in these organisms may contribute to intestinal barrier failure, inflammation and chronic discomfort in SCD. But the findings is still preliminary and must be validated in bigger clinical research.

One of the most interesting advances in this research is the link between microbiota and chronic pain. Chronic pain is a characteristic of SCD with repeated episodes of acute pain potentially evolving into chronic pain. Chronic SCD pain is multifaceted in origin including persistent inflammation, neuronal sensitisation, tissue damage and impaired nociceptive processing [12].

Laboratory studies have shown that gut microbes may play a role in this process. Sadler et al. found that modulation of the intestinal microbiome altered pain-related behaviour in transgenic SCD mice. Their investigation involved microbial metabolites and signalling via the vagus nerve, with lower abundance of Akkermansia muciniphila found as one potentially relevant cause. More recent study has further established this experimental association by showing that transplanting of SCD-associated gut microbiota into wild-type mice can produce chronic pain-related behaviour. This mechanism was shown to include a metabolite linked to haemolysis, bilirubin, and vagal signalling [13].

These findings are crucial since they demonstrate how a metabolic consequence of haemolysis may interact with the gut flora and nervous system. In this paradigm, bilirubin is produced by haemolysis; changes in the intestinal environment modify microbial populations; microbial and host metabolites affect sensory pathways; and brain signalling contributes to chronic pain. Much of this information is still experimental, but it broadens the traditional view of SCD pain to include more than just direct tissue ischaemia.

The microbiome may possibly be involved in end-organ damage. CKD is a prominent consequence of SCD and is a result of a combination of medullary hypoxia, haemolysis, endothelial dysfunction, glomerular hyperfiltration and increasing nephron damage. Pulmonary problems are similarly a consequence of interactions between haemolysis, endothelial dysfunction, inflammation and vascular remodelling. Neurological damage, including silent cerebral infarcts and overt stroke, has been related with persistent vascular and inflammatory abnormalities [14].

Systemic inflammation and endothelial dysfunction are prevalent routes in these problems, and hence microbiome-derived inflammatory signals might possibly contribute to their development. Repeated activation of innate immune pathways systemically can occur via increased intestinal permeability and microbial translocation. Activated leukocytes and inflammatory cytokines may in turn exacerbate endothelial dysfunction and tissue injury [15].

But there is a difference between biological plausibility and proved clinical causation. There is more evidence that the gut microbiota is disrupted in SCD than that these modifications directly induce particular kinds of end-organ damage. Most human research include limited numbers of subjects, and the makeup of the microbiome is altered by several confounding variables. Antibiotic usage is particularly significant as many people with SCD are given antibiotics in childhood or after illnesses. Diet, age, geographical location, socioeconomic situations and medication usage can greatly modify microbial composition [16].

The microbiota may thus be both a cause and result of SCD disease. For example, individuals with repeated hospitalisation may take antibiotics and may eat varied diets, whereas serious sickness per se may impair physical activity, nutrition and gastrointestinal function. These variables can also have independent effects on the microbiota. Therefore, future studies need to adopt longitudinal designs to differentiate disease-related microbial alterations from effects of environment and therapy.

The microbiome–SCD association also prompts crucial considerations regarding traditional therapy. Hydroxyurea is a key disease-modifying medication for SCD, mainly by the induction of foetal haemoglobin and decrease of sickling. It also influences leukocyte activation and inflammatory responses. Recent work has started exploring the potential for interaction between hydroxyurea and the gut microbiota and if residual dysbiosis can remain in the setting of standard therapy. However, evidence of direct hydroxyurea impacts on microbiota is yet preliminary [17].

This field of study has the potential to facilitate a combined therapy strategy where standard haematological treatment would be augmented by microbiome-directed therapies. Possible strategies include change of dietary fibre, supplementation with chosen microbial metabolites, probiotics, prebiotics and synbiotics. The goal would not be to eradicate all potentially harmful bacteria, but rather to restore microbial activities related to epithelial integrity and proper immunological control.

Diet is perhaps the most feasible intervention that targets the microbiome since it may affect microbial metabolism without sophisticated technologies. Increasing fibre intake can boost SCFA synthesis, however dietary treatments need to be evaluated especially in SCD patients. Probiotics may add chosen helpful organisms and prebiotics may stimulate the growth of beneficial micro-organisms already present in the gut.

Dysbiosis alters microbial products and metabolites Microbial products regulate immune and endothelial cells Immune activation leads to vaso-occlusion Repeated vascular injury causes pain and Fa intestinal hypoxia Intestinal injury modifies the epithelial barrier and microbial ecosystem Edecal microbiota transplantation is a more aggressive strategy but is still experimental in SCD. FMT has been shown to be effective for several gastrointestinal illnesses, but it has not been shown safe and effective for SCD. Possible issues are transfer of infectious agents and uncertain impact on the recipient's microbiota. Another exciting field is the creation of microbiome-based biomarkers. Stool microbial profiles, microbial metabolites, indicators of intestinal permeability, and circulating inflammatory mediators may be used to identify patients with elevated inflammatory or vaso-occlusive activity. Such indicators may supplement traditional measurements such as haemoglobin concentration, reticulocyte count, bilirubin, lactate dehydrogenase and inflammatory markers. This hypothesis is particularly pertinent for populations with high burden of SCD, including sub-Saharan Africa. Microbiome research in African people are important, as microbial communities are shaped by nutrition, location, sanitation, disease exposures and cultural practices. Findings in North American or European populations may not be immediately relevant to African individuals.

Emerging data thus supports a hypothesis in which the gut microbiota acts as a biological link between the gastrointestinal tract and systemic SCD disease. The axis can be represented as a series of interlinked events: sickling and vaso-occlusion → intestinal hypoxia → intestinal injury → epithelial barrier and microbial environment change → dysbiosis → microbial products and metabolites → effects on immune and endothelial cells → immune activation → vaso-occlusion → recurrent vascular injury → pain and end-organ damage.

At the same time, the model should be careful enough. Dysbiosis does not confirm that dysbiosis is the initiator of problems of SCD. Some microbial changes may be a result, rather than a cause, of illness. Larger longitudinal human investigations, mechanistic experiments and controlled intervention trials are necessary to determine which microbial alterations are pathogenic, which are protective and which are just a reflection of disease severity or therapy exposure [18].

CONCLUSION

The microbiome–sickle cell disease axis is an emerging paradigm that has the potential to greatly expand the understanding of SCD pathogenesis. The classic view is that SCD is caused by polymerisation of haemoglobin S, sickling of red-cells and vaso-occlusion. Current information indicates that disease manifestation is also significantly dependent on inflammation, leukocyte activation, endothelial dysfunction, haemolysis and

metabolic abnormalities. Each of these processes could be affected by the gut microbiota.

The association seems to be bidirectional. Sickle cell-induced intestinal hypoxia and recurrent episodes of ischaemia-reperfusion damage may impact on epithelial integrity and the intestinal microbial environment. Dysbiosis may then induce increased intestinal permeability, changes in microbial metabolites, and systemic inflammatory signalling. These alterations may possibly lead to vaso-occlusion and chronic pain via impacts on neutrophil ageing, immunological activation, endothelial dysfunction, and neurological pathways. Experimental data showing a role for gut microbes in neutrophil activation and SCD pain give key mechanistic bases for this growing topic. Special emphasis is placed on the probable association to end-organ damage. In SCD, repeated inflammatory and vaso-occlusive episodes are key to the progressive damage affecting the kidney, brain, lungs, bones and other organs. If microbiome-related inflammatory signals worsen vascular dysfunction, then the microbiome may be a hitherto overlooked modulator of long-term disease development. But direct causal evidence linking particular microbial modifications to certain types of end-organ damage is scarce.

The microbiome should not be viewed as an established major driver of SCD yet, although evidence is mounting suggesting it could be a significant disease modulator. The microbiome–SCD axis offers a novel conceptual framework to comprehend disease complexity by integrating intestinal integrity, microbial metabolism and immune activation, vaso-occlusion and brain signalling. Ongoing research of this link may identify new biomarkers and therapy options that might reduce inflammation, vaso-occlusion, chronic pain, and eventually the burden of end-organ damage in persons with sickle cell disease.

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