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The microbiome's relationship with congenital heart disease: more than a gut feeling

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Abstract

Patients with congenital heart disease (CHD) are at risk for developing intestinal dysbiosis and intestinal epithelial barrier dysfunction due to abnormal gut perfusion or hypoxemia in the context of low cardiac output or cyanosis. Intestinal dysbiosis may contribute to systemic inflammation thereby worsening clinical outcomes in this patient population. Despite significant advances in the management and survival of patients with CHD, morbidity remains significant and questions have arisen as to the role of the microbiome in the inflammatory process. Intestinal dysbiosis and barrier dysfunction experienced in this patient population are increasingly implicated in critical illness. This review highlights possible CHD-microbiome interactions, illustrates underlying signaling mechanisms, and discusses future directions and therapeutic translation of the basic research.

Keywords: Congenital Heart Disease, Microbiome, Intestinal barrier dysfunction, Systemic inflammation, Cardiopulmonary bypass

Introduction

Congenital heart disease (CHD) remains an important risk for morbidity and mortality in the pediatric population, accounting for up to 50 % of mortality due to birth defects[1]. Surgical techniques and post-operative management have improved survival to adulthood from 30 to 85 % over the past 30 years, but CHD remains a significant cause of death in patients less than one year of age [2–4]. Contributors to poor outcomes include delayed repair, multiple organ dysfunction from heart failure, infection, prematurity, and arrhythmia [4–7]. Although survival to adulthood continues to improve [8–12], the inflammatory response and low cardiac output syndrome often seen in these patients remain important mediators of disease [13, 14]. Pre- and post-operative inflammatory responses can lead to abnormalities in the intestinal microbiome and contribute to worse outcomes following cardiac surgery.

The intestinal microbiome is important in regulating health and homeostasis [15–18], and its dysregulation (termed intestinal dysbiosis) has been well studied in critical illness [19–21] and the cardiac surgical population [22–24]. With dysbiosis, an imbalance in the normal microflora of the gut occurs. This imbalance has been implicated in autoimmune disorders, inflammatory bowel disease, and obesity [18, 19, 25–27]. Recently, hypertension, stroke, myocardial infarction, diabetes-induced cardiac dysfunction, and heart failure have also been linked to intestinal dysbiosis [28–30].

While interactions between the microbiome and cardiovascular disease continue to grow, CHD has received little attention in this regard. CHD patients remain at risk for developing intestinal dysbiosis and intestinal

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epithelial barrier dysfunction (EBD) due to numerous stressors including abnormal gut perfusion, hypoxemia, impaired nutrition, and poor cardiac output secondary to abnormal cardiac function, valvar regurgitation, and/or residual cardiac shunts [31]. Dysbiosis has been shown to be present in patients with CHD [32–34]. It is unclear if dysbiosis or its resolution induces or improves EBD because the effects of probiotics and synbiotics in CHD patients have not been well studied [35, 36]. The interaction between CHD and the microbiome will be discussed throughout this review and is illustrated in Fig. 1.

In this review we examine the composition of the intestinal microbiome, discuss the evidence of the microbiota's relationship with CHD, and discuss future directions for research and therapeutic interventions to improve outcomes.

The Microbiome

The microbiome is a complex system interacting with every organ system in the human body [15]. The intestinal microbiome is populated by ~ 100 trillion bacteria from greater than 2000 species. These bacteria co-exist and form an integral aspect of homeostasis [37]. There are six main bacterial phyla which exist in the intestinal tract: *Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia.* In a healthy individual, *Bacteroidetes* and *Firmicutes* make up roughly 90 % of the bacterial composition [38]. *Proteobacteria*, a group of pro-inflammatory opportunistic and

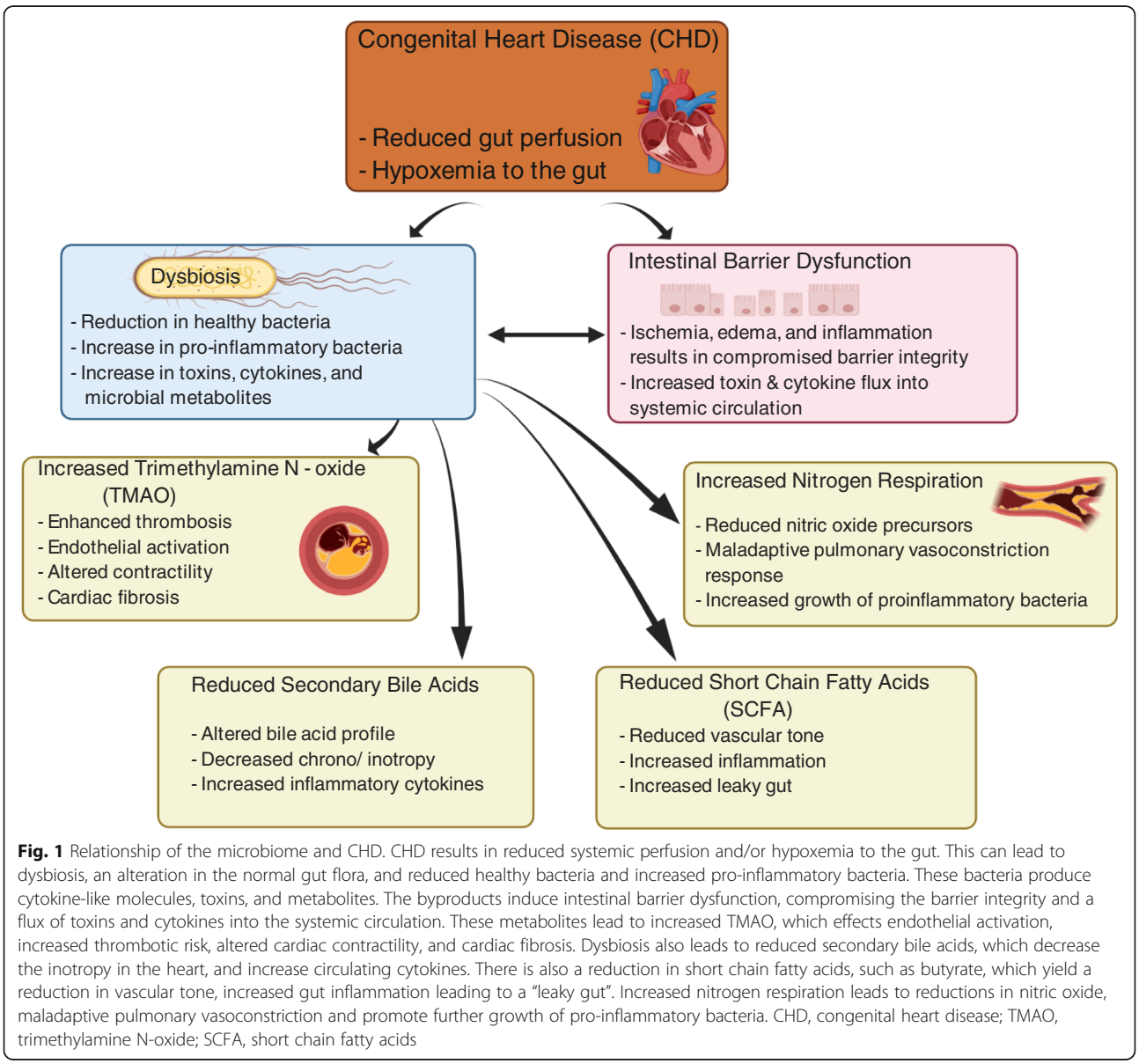

Fig. 1 Relationship of the microbiome and CHD. CHD results in reduced systemic perfusion and/or hypoxemia to the gut. This can lead to dysbiosis, an alteration in the normal gut flora, and reduced healthy bacteria and increased pro-inflammatory bacteria. These bacteria produce cytokine-like molecules, toxins, and metabolites. The byproducts induce intestinal barrier dysfunction, compromising the barrier integrity and a flux of toxins and cytokines into the systemic circulation. These metabolites lead to increased TMAO, which effects endothelial activation, increased thrombotic risk, altered cardiac contractility, and cardiac fibrosis. Dysbiosis also leads to reduced secondary bile acids, which decrease the inotropy in the heart, and increase circulating cytokines. There is also a reduction in short chain fatty acids, such as butyrate, which yield a reduction in vascular tone, increased gut inflammation leading to a "leaky gut". Increased nitrogen respiration leads to reductions in nitric oxide, maladaptive pulmonary vasoconstriction and promote further growth of pro-inflammatory bacteria. CHD, congenital heart disease; TMAO, trimethylamine N-oxide; SCFA, short chain fatty acids

pathogenic bacteria, makes up less than 5 % of the bacterial population. *Proteobacteria* include organisms associated with disease such as *E. coli*, *Shigella, Salmonella, Klebsiella*, and *Pseudomonas* [39].

Bacteroidetes and *Firmicutes*, the predominant constituents, are integral to maintaining gut health. A crude measure of microbiome well-being is the *Firmicutes* to *Bacteroidetes* (F/B) ratio. In infants, the F/B ratio is ~ 0.4, while in adults, it is ~ 10 indicating that *Firmicutes* contribution increases with maturity [40]. Higher F/B ratios have been associated with obesity, coronary artery disease, stroke, heart failure, and autoimmune disease [26, 41].

Organisms within different bacterial phyla regulate gut health through a variety of mechanisms. Increases in pro-inflammatory bacteria are associated with a decrease in bile acid synthesis and correlate with EBD [42, 43]. Beneficial bacteria, such as *Lactobacillus reuteri* and *Lactobacillus rhamnosus*, assist in developing the intestinal mucus barrier, an important defense system for the gut [43]. Similarly, small molecule signaling between bacterial organisms and host cells via butyrate, trimethylamine N-oxide (TMAO), nitric oxide, cytokines, and endotoxins have been reported. The magnitudes of these signals are dynamic in cardiovascular diseases.

The Microbiome and Cardiovascular Disease

The gut microbiome is implicated in a variety of cardiovascular disease states, from hypertension and stroke to heart failure [44]. Elevations of pro-inflammatory bacteria, *Proteobacteria*, in the blood have been associated with an increased risk of developing cardiovascular diseases [45]. Dysbiosis is a noted factor in the development of atherosclerosis through increases in endotoxins and cytokines. Lipopolysaccharides (LPS) and peptidoglycans activate reactive oxygen species and inflammatory pathways when they are released into the bloodstream [46]. These reactive oxygen species can induce arrhythmias, cardiac remodeling through apoptosis and necrosis, endothelial smooth muscle hypertrophy, and oxidative damage to endothelial cells [47, 48]. Increased amounts of *Enterobacteriaceae*, a large family of pathogenic and LPS-producing organisms within the phylum *Proteobacteria*, concurrently with reduced amounts of *Bacteroidetes* have been noted in patients with identified atherosclerotic cardiovascular disease [49, 50]. Patients with heart failure typically have intestinal wall edema and reduced gut perfusion. This can lead to bacterial translocation through deregulated gut barrier, cytokine production, and endotoxin absorption, which have also been linked to progressive heart failure [51]. This positive feedback loop of heart failure inducing dysbiosis and dysbiosis exacerbating heart failure is an important mechanism of disease severity. All of these changes to the intestinal microbiome can influence the development and exacerbation of multiple cardiovascular disease states.

Other signaling molecules produced by gut microbiota (e.g. TMAO, butyrate, NO) also have cardiovascular effects. Trimethylamine (TMA) is produced by intestinal microbiota in the *Firmicutes* and *Proteobacteria* phyla through conversion of L-carnitine or choline, found in red meats [52]. This is then converted to TMAO in the liver. High intake of red meat results in a higher amount of TMAO, which has been associated with the development of coronary artery disease, atherosclerosis, and stroke [44]. Similarly, inflammatory gut bacteria have also been correlated with elevated TMAO and coronary plaques [53, 54]. The hypothesis of the heart-gut axis is growing in acceptance and relates to the production of increased TMAO and endotoxins, and gut bacterial translocation in the progression of worsening heart failure and advancement of atherosclerotic disease [28, 55].

Butyrate is a short-chain fatty acid essential to the host immune homeostasis and a major energy source for intestinal epithelial cells [56]. The most abundant butyrate-producing organisms are *Clostridium*, *Eubacterium*, *Fusobacterium*, and *Bifidobacterium* [57–59]. The depletion of butyrate-producing organisms contributes to intestinal EBD and upregulated inflammatory responses in the body. Higher F/B ratio and elevations in *Enterobacteriaceae* have been associated with depleted quantities of butyrate-producing organisms, increased systemic inflammation, and stroke [60]. A diet high in fiber promotes butyrate-producing organism growth and has been shown to stabilize plaque size in atherosclerosis [59]. Heart failure and coronary artery disease have also been associated with a reduction in butyrate-producing organisms [59, 61].

Organisms of the oral and intestinal microbiome that are engaged in nitrogen respiration are an important source of nitric oxide (NO). Reactive oxygen and nitrogen species reduce nitrates and nitrites to deplete NO precursors and lead to impairment of NO-dependent vascular function [62, 63]. If there is depletion of nitric oxide, due to either reduced production or increased consumption, this could contribute to pulmonary hypertension (PHTN); recent evidence is beginning to show a link between the microbiota and PHTN [64].

The Microbiome and congenital Heart Disease

Congenital heart disease, while separate from the above cardiovascular diseases, shares the risk for heart failure, hyper-thrombotic states, reduced splanchnic perfusion, and PHTN [65, 66]. Unique to CHD are complex lesions, namely single ventricle physiology, which will require a patient to undergo multiple surgeries using cardiopulmonary bypass (CPB) and live with hypoxemia for extended periods. Intestinal hypoxemia promotes

inflammation, thereby inducing changes to the intestinal microbiome. Similar changes are observed during reduced blood flow [67, 68]. Building from what is known in the adult population, similar processes and cardiovascular abnormalities can give insight into the microbiome's role in CHD and point to future study.

Intestinal epithelial barrier dysfunction has been associated with CPB [69]. This involves hypoxic, ischemic, or inflammatory injury to intestinal cells [70–73]. An intact intestinal barrier is a potent defense against enteric pathogens as well as inflammatory cytokines and toxins secreted from bacteria in the gut. Many patients with CHD experience impaired gut perfusion, either from poor cardiac output, hypoxemia-related vasoconstriction, or both. Intestinal dysbiosis may play a role in worsening EBD by enabling growth of LPS-producing bacteria, such as *Escherichia coli* and *Enterobacteriaceae*, leading to systemic inflammation [72]. Reduced gut perfusion and increased growth of *Enterobacteriaceae* are risk factors in the development of necrotizing enterocolitis [7, 74]. While necrotizing enterocolitis is a relatively uncommon pathology, it poses a risk to these patients and requires exposure to antibiotics, which can further disrupt the normal gut flora[74]. One mechanism for development of intestinal EBD includes inflammation following CPB leading to worsened dysbiosis and activation of cytokines and toxins from pro-inflammatory bacteria [69, 75, 76]. Roughly 25 % of patients with CHD will require cardiac surgery with CPB [77]. We know existing dysbiosis is exacerbated following CPB [34]. Ischemia-induced EBD and dysbiosis, secondary to low cardiac output syndrome in the post-operative period, can also occur [78]. This may result in reduced populations of butyrate-producing organisms [79]. Butyrate is responsible for maintaining the intestinal barrier through modulation of G-coupled proteins and transcription factors, namely the nuclear transcription factor-κB (NF-κB) pathway, to upregulate regulatory T-cells. Loss of butyrate producing organisms can lead to EBD resulting in passive leak of lipopolysaccharides and other microbial toxins, which then bind to toll-like receptors on T cells activating the innate immune response [59, 61, 80, 81]. A third mechanism involves elevated TMAO production leading to EBD and activated inflammatory processes causing further cardiac injury [81–83]. TMAO is known to be associated with barrier dysfunction and activation of inflammatory cytokines [39, 84].

Hypoxemia and inflammatory insults are also known activators of hypoxia-inducible factor 1 (HIF-1) and NF-κB [72]. HIF-1 is a transcription factor known as the master regulator of cellular and developmental responses to hypoxia [85]. NF-κB is a family of transcription factors involved in activation of cytokines and other inflammatory processes [86]. Organisms within *Proteobacteria* and *Firmicutes* can upregulate the NF-κB pathway through binding of damage-associated and pathogen-associated molecular patterns found on epithelial cells, leading to vascular inflammation and cytokine activation [87–91]. During hypoxemic conditions, *Enterobacteriaceae* have been shown to increase both NF-κB and HIF-1α signaling through interferon gamma activation, leading to de-regulation of intestinal epithelial tight junction proteins and activation of inflammatory cytokines [92–96]. Suppression of HIF-1α improves intestinal EBD [72, 95]. HIF-1α has been shown to be upregulated in both cyanotic and acyanotic cardiac lesions [97]. HIF-1α and NF-κB regulate each other through both inflammatory and hypoxic activation [98–100]. In patients with CHD, there can be inflammation from reduced splanchnic blood flow, hypoxemia, or a combination of both. Figure 2 illustrates how these mechanisms are involved in the development of systemic inflammation through intestinal dysbiosis and EBD under hypoxemic and ischemic conditions.

Bacteria and diet may also be involved in promoting PHTN. CHD is a high risk population for PHTN, occurring at rates of 10–30 % [101]. Pro-inflammatory bacteria reduce circulating NO and NO precursors [102]. Disproportionate vasoconstriction and endothelial remodeling drives development of PHTN, and a reduction in bioavailability of NO signaling is a hallmark of PHTN [103]. Risks for developing this in CHD include excessive blood flow to the pulmonary system and a persistent hypoxemic state [104, 105]. Adult studies have shown the oral and intestinal flora correlate with increased risk of PHTN [64]. Certain organisms, such as *Firmicutes* and *Actinobacteria*, result in increased plasma arginase and ornithine transcarbamylase, thereby reducing the amount of circulating L-arginine, the major precursor of NO [103]. These same organisms are also involved in production of TMAO [64]. *Proteobacteria* induce further denitrification resulting in reduction beyond NO to N_2O and NH_3 [106]. Metabolism of nitrate is an important pathway for production of NO, and dysbiosis with elevated *Enterobacteriaceae* can consume NO reducing the availability of this potent vasodilator [106, 107].

Non-traditional signaling pathways involving microRNA (miRNA) also influence CHD and the microbiome [108, 109]. There are miRNA's associated with intestinal dysbiosis, barrier dysfunction, and CHD. These small, evolutionally conserved, non-coding RNA regulate gene expression [110]. Specific miRNA have been identified to be involved in cardiac embryologic development, and their dysregulation can lead to structural abnormalities [111–117]. Upregulated miR-146 may reduce hypoxia-induced cardiomyocyte apoptosis through inhibition of the NF-κB pathway [118]. Studies have also found miRNA produced by intestinal epithelial cells regulate

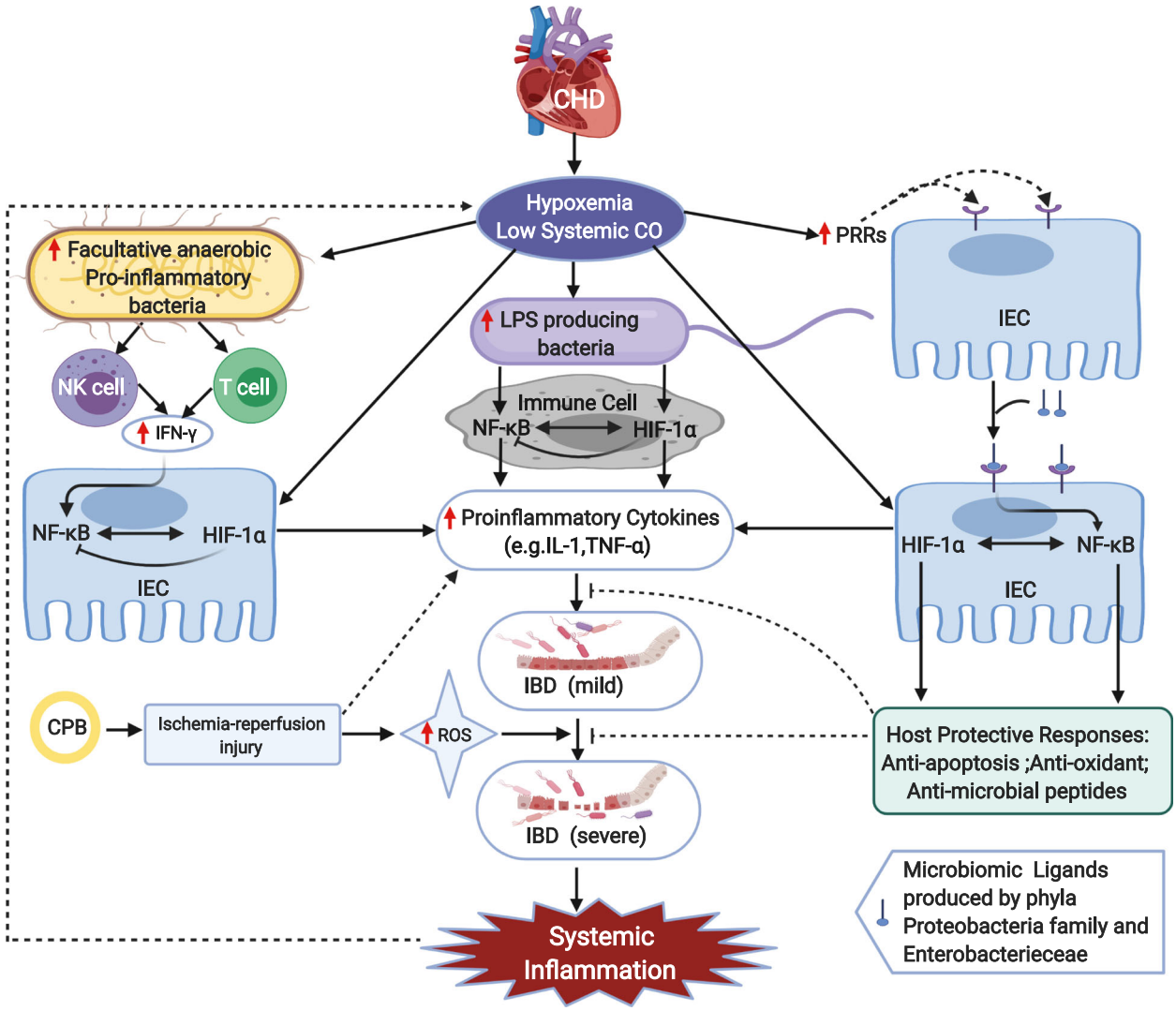

Fig. 2 CHD-induced activation of HIF-1α and NF-κB. Hypoxia and inflammation induced activation of HIF-1α and NF-κB pathways leads to intestinal barrier dysfunction and systemic inflammation. Hypoxia with reduced cardiac output induces selection of pro-inflammatory bacteria activating NK and T cells yielding increased production of IFN-γ. IFN-γ signals activation of NF-κB transcription factors and subsequent activation of the HIF-1α pathway intestinal epithelial cells. HIF-1α activates pro-inflammatory cytokines leading to intestinal barrier dysfunction and permeability of bacteria, toxins, and cytokines into systemic circulation. Hypoxia also induces LPS producing bacterial leading to immune cell activation and subsequent inflammatory cytokine cascade. This induces intestinal barrier dysfunction leading to systemic inflammation. Hypoxia also leads to increase pattern recognition receptors on intestinal epithelial cells which bind to pro-inflammatory microbe ligands activating the HIF-1α pathway and NF-κB transcription factors. This induces a pro-inflammatory cell response as well as host protective measures including anti-apoptosis, anti-oxidant, and anti-microbial peptides. This feeds back to inhibit the barrier disruption and cytokine activation. When patients undergo CPB, this increased systemic inflammation induces significant reactive oxygen species and cytokine activation leading to severe barrier dysfunction and exacerbating the systemic inflammatory process following surgery with CPB. CPB, cardiopulmonary bypass; CO, cardiac output; EBD, epithelial barrier dysfunction; HIF, hypoxia-inducible factor; IEC, intestinal epithelial cell; IFN-γ, interferon gamma; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B cells; NK, natural killer; ROS, reactive oxygen species

the expression of gut microbes [119–121]. MiR-515-5p and miR1226-5p promote growth of *Fusobacterium nucleatum* and *Escherichia coli*, respectively [119]. Both miR-191 and miR-212 are involved in intestinal EBD through disruption of zonula occludens-1, a protein involved in cell tight junctions [122, 123]. While miRNA have been identified in both the microbiome and CHD, no study has demonstrated miRNA with coordinated roles in both CHD and the microbiome. The overlap of miRNA in the microbiome, CHD, and EBD, as well as the complex role of miRNA in regulation of cardiac disease, is illustrated in Fig. 3.

Current gaps in knowledge

Microbiome colonization and diversity is well documented in adult populations of cardiovascular disease, and we continue to learn more about its importance. Very little data exists evaluating the microbiome in CHD. Details related to microbial disparity in varying cardiac lesions, such as cyanotic and acyanotic lesions, and how these change following surgical repair and palliation will be important area of investigation. Dysbiosis has been identified in patients with CHD [32–34], but the effects of probiotics or synbiotics has only been briefly evaluated [35, 36]. This area of research holds potential to identify therapeutic interventions aimed to improve morbidity and mortality in this patient population. Dilli and colleagues [35] demonstrated reduced sepsis, hospital length of stay, and mortality following the use of probiotics in patients with CHD. Probiotics have also been shown to reduce the degree of mucosal

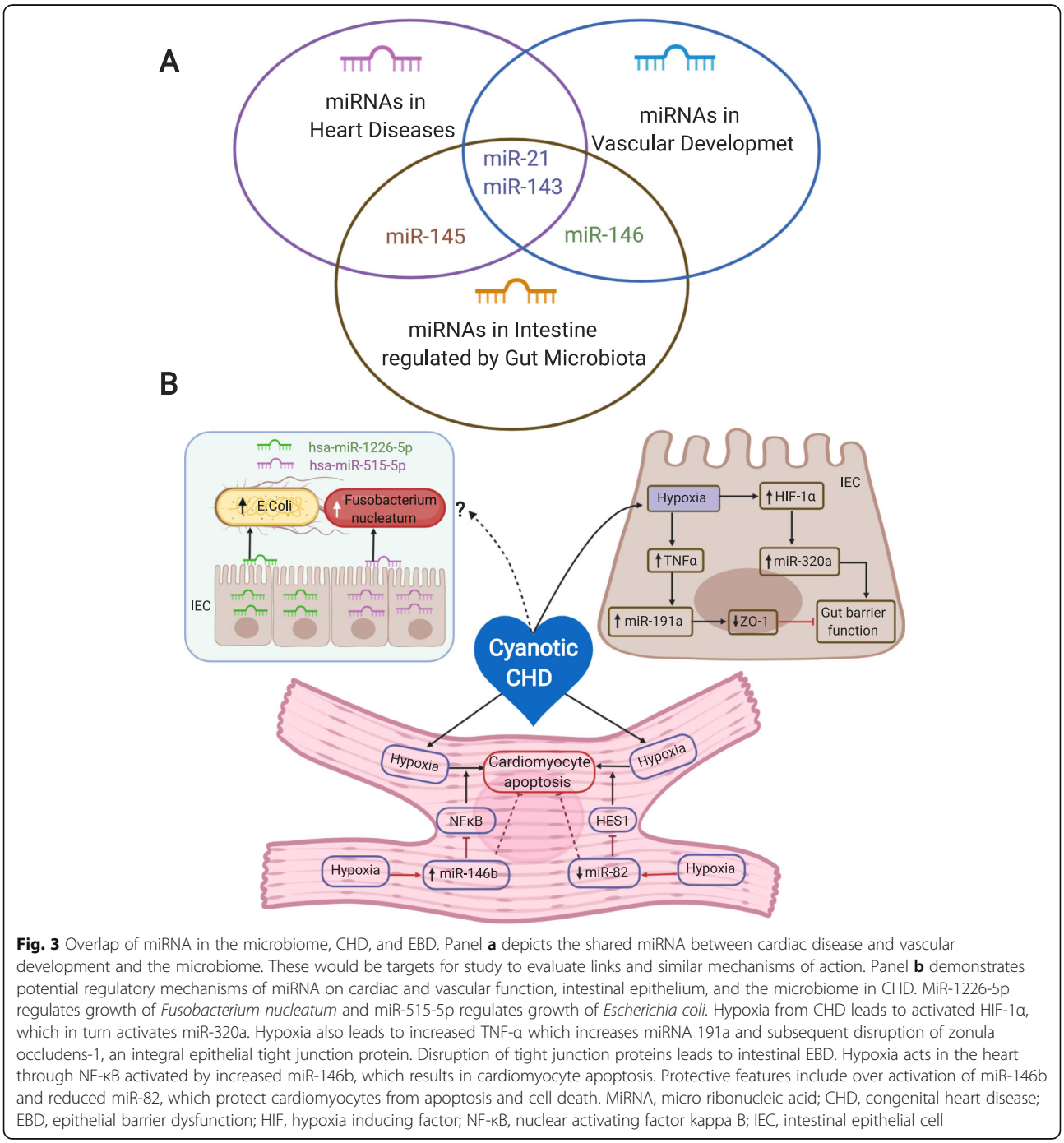

Fig. 3 Overlap of miRNA in the microbiome, CHD, and EBD. Panel **a** depicts the shared miRNA between cardiac disease and vascular development and the microbiome. These would be targets for study to evaluate links and similar mechanisms of action. Panel **b** demonstrates potential regulatory mechanisms of miRNA on cardiac and vascular function, intestinal epithelium, and the microbiome in CHD. MiR-1226-5p regulates growth of *Fusobacterium nucleatum* and miR-515-5p regulates growth of *Escherichia coli*. Hypoxia from CHD leads to activated HIF-1α, which in turn activates miR-320a. Hypoxia also leads to increased TNF-α which increases miRNA 191a and subsequent disruption of zonula occludens-1, an integral epithelial tight junction protein. Disruption of tight junction proteins leads to intestinal EBD. Hypoxia acts in the heart through NF-κB activated by increased miR-146b, which results in cardiomyocyte apoptosis. Protective features include over activation of miR-146b and reduced miR-82, which protect cardiomyocytes from apoptosis and cell death. MiRNA, micro ribonucleic acid; CHD, congenital heart disease; EBD, epithelial barrier dysfunction; HIF, hypoxia inducing factor; NF-κB, nuclear activating factor kappa B; IEC, intestinal epithelial cell

inflammation following CPB in an animal study [124]. Rectified dysbiosis may also facilitate better regulation of maladaptive vasoconstriction to reduce the PHTN seen in these patients.

Further investigation is needed to evaluate signaling mechanisms for EBD, and to evaluate the relationship to stress, altered blood flow, and hypoxia leading to increased systemic inflammation. It is also unknown how small molecules, such as butyrate, TMAO, and nitrates influence inflammatory pathways, such as HIF-1α and NF-κB. Additionally, how these signaling pathways are upregulated in settings of cyanotic heart lesions is an important area which will improve our understanding of how systemic inflammation is generated. As EBD offers a mechanism for toxins and inflammatory metabolites to enter systemic circulation [125–127], methods to prevent or resolve the barrier dysfunction both pre- and post-operatively may also hold promise as therapeutic interventions.

Metagenomic and metabolomic are other tools available to help elucidate mechanisms of dysbiosis and enzyme activation in patients with CHD, which will potentially discern linkages between altered gut flora and systemic inflammation. Biomarkers and pro-inflammatory mediators associated with pronounced systemic inflammation may yield targets by which to identify patients with higher risks of low cardiac output syndrome following CPB. This inflammatory cascade may be suppressed with improvements in the microbiota. There may also be a role to activate specific miRNA to promote bacterial growth and regulate inflammatory pathways. Studies to identify miRNA that

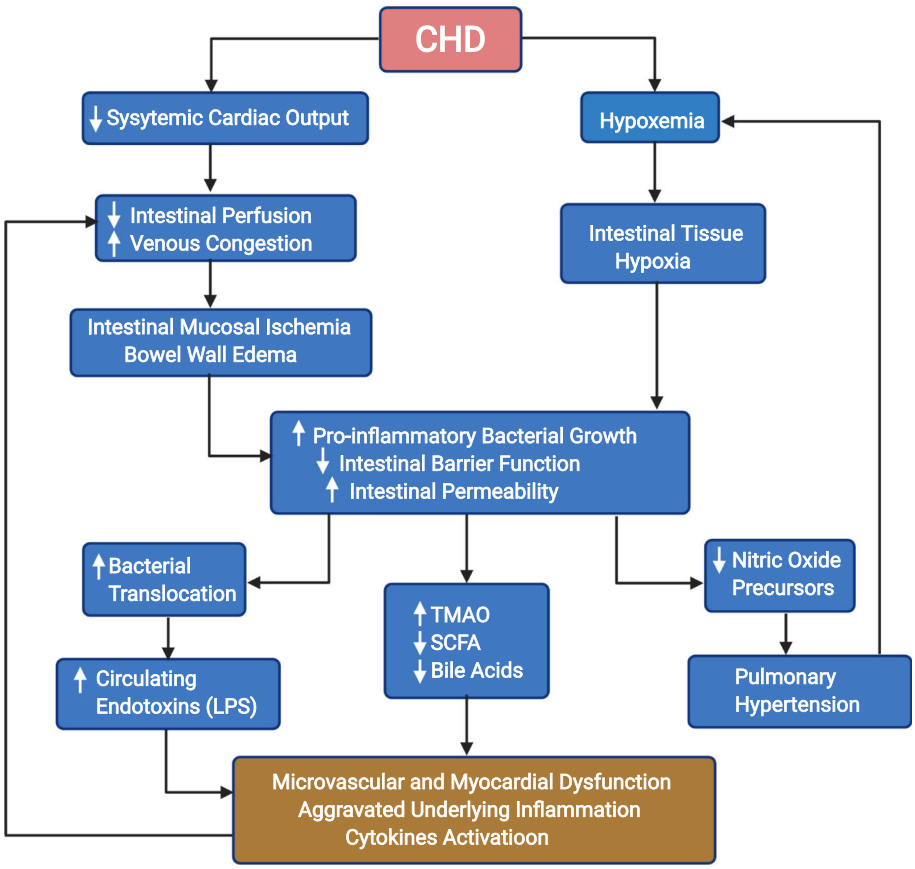

Fig. 4 Hypothesis of the heart-gut axis in congenital heart disease. Flow chart describing the pathogenesis of dysbiosis and the resulting systemic inflammation and end organ changes exacerbating the disease state in CHD. CHD causes reduced cardiac output. This reduced cardiac output leads to less intestinal perfusion and an increase in venous congestion as blood is not being pumped through the system as well. The resulting mucosal inflammation and edema yields an increase in pro-inflammatory growth, a reduction in intestinal barrier function, and increase intestinal permeability often described as a "leaky gut". This increased permeability leads to an increase in bacterial translocation and further leads to an increase in circulating toxins, such as LPS. The increased pro-inflammatory bacterial growth results in an increase in TMAO production through the liver, and a reduction in SCFA and secondary bile acids which are important for barrier regulation and cardiac health. The pro-inflammatory bacterial also engage in nitrogen respiratory which results in fewer nitric oxide precursors and can exacerbate the maladaptive response of pulmonary hypertension from an increase in pulmonary blood flow. The feedback loops exacerbate the pathology. CHD, congenital heart disease; LPS, lipopolysaccharide; SCFA, short chain fatty acid; TMAO, trimethylamine *N*-oxide

are involved in both CHD, the microbiome, and EBD would also improve our understanding of these processes as well as offer potential therapeutic targets to reduce inflammation in these patients. While studies regarding the influence of the microbiome and outcomes in CHD are lacking, there is importance evaluating interventions and expanding our understanding of these relationships. A flow chart indicating mechanisms and feedback promoting ongoing inflammation is provided in Fig. 4.

Conclusions

Intestinal dysbiosis is an important area of focus in patients with congenital heart disease and involves links with intestinal barrier dysfunction and systemic inflammation. Larger studies evaluating the microbiome in this patient population are needed to heighten the understanding of how changes in the microbiota affect CHD outcomes. This understanding will assist in development of animal models evaluating interventions on the microbiome and the degree of systemic inflammation following CPB. Potential interventions include probiotics and synbiotics as well as the possibility of pre-operative fecal microbiome transplant to improve the gut proportion of healthy, gut-protective bacteria. Intestinal dysbiosis present in patients with CHD may be a contributing factor to the intestinal EBD following cardiac repair and CPB. Improving the intestinal microbiome to reduce pro-inflammatory bacteria and increase butyrate producing organisms, reduce nitrate respiration, and modulate pathways such as HIF, NF-κB, and miRNA are important aims for future investigation. These may play a key role in increasing our understanding of signaling mechanisms and identify therapeutic targets. There remains much to be understood about the microbiome's influence on homeostasis in CHD so that additional improvements in health, surgical outcomes, and the quality of life may be accomplished.

Abbreviations

CHD: Congenital heart disease ; CPB: Cardiopulmonary bypass; EBD: Epithelial barrier dysfunction; F/B: Firmicutes/Bacteriodetes ratio; TMA: Trimethylamine; TMAO: Trimethylamine N-oxide; NO: Nitric oxide; LPS: Lipopolysaccharide; HIF: Hypoxia-inducible factor; NF-κB: Nuclear factor kappa B; mRNA: Micro-RNA

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Authors' contributions

Dan Feng – Design, drafting and critical review/revision of the manuscript. Jason T. Christensen – Design, drafting and critical review/revision of the manuscript. Anji T. Yetman – Drafting, and critical review/revision of the manuscript. Merry L. Lindsey – Drafting and critical review/revision of the manuscript. Amar B. Singh –Drafting and critical review/revision of the manuscript. Jeffrey D. Salomon – Design, drafting and critical revision/review of the manuscript. The author(s) read and approved the final manuscript.

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Consent for publication

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Competing interests

The authors declare they have no competing interests.

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