



Gut-Heart Axis in Myocardial Repair: Mechanisms, Cross-Organ Networks, and Therapeutic Opportunities

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ABSTRACT: Cardiovascular diseases remain the leading global cause of morbidity and mortality, placing an escalating burden on health care systems and economies. While the gut microbiota is well recognized in atherosclerosis and cardiometabolic disorders, its influence on myocardial injury, repair, and regeneration is only beginning to emerge. Growing evidence reveals that gut microbes and their metabolites regulate myocardial health through intricate cross-organ networks, including the gut-brain-heart, gut-liver-heart, and gut-lung-heart axes. These findings suggest that the heart plays a key role in systemic host-microbe communication. Advances in metagenomics, metabolomics, and single-cell transcriptomics are now defining the molecular and cellular pathways by which microbial metabolites modulate immune tone, endothelial integrity, metabolic resilience, and cardiomyocyte survival. Studies in gnotobiotic models have established causal links between specific microbial taxa and myocardial outcomes while illuminating their roles in fibrosis resolution, angiogenesis, and regeneration. In this review, we synthesize current knowledge on the bidirectional gut-heart dialogue, emphasizing immunometabolic signaling, cross-organ integration, and regenerative mechanisms. We propose that coupling high-resolution multiomics with mechanistic modeling in controlled microbial systems will be pivotal for next-generation, microbiota-informed diagnostics, and therapeutics. We explore the emerging role of the gut-myocardium axis as both a driver of disease and as a promising modifiable therapeutic target and highlight a new frontier in precision cardiovascular medicine, with the potential to transform strategies for prevention, repair, and tissue regeneration.

Key Words: cardiovascular diseases ■ diet ■ gastrointestinal microbiome ■ heart failure ■ stroke volume

The gut microbiota, a highly complex and dynamic ecosystem comprising bacteria, fungi, viruses, and other organisms, plays a central role in maintaining physiological homeostasis and modulating systemic health.^{1,2} This ecosystem is continuously shaped by intrinsic and extrinsic factors, including sex, aging, disease states, dietary patterns, medications, and environmental exposures. Perturbations in these determinants can impair mucosal barrier integrity, dysregulate immune responses, disrupt metabolic balance, and compromise tissue regeneration.^{3–6} These perturbations contribute to a range of local and systemic pathologies, notably inflammatory and cardiometabolic diseases.

Diet is one of the most powerful modulators of gut microbial composition and function. In turn, gut microbes break down dietary substrates and produce myriad metabolites, some of which influence host cardiometabolic processes, including glucose and lipid metabolism, vascular tone, and immune signaling.^{7,8} These reciprocal interactions underscore the relevance of microbiota-host crosstalk in cardiovascular diseases, including coronary artery disease, myocardial infarction (MI), and heart failure with preserved ejection fraction (HFpEF). One of the most well-known examples is the microbial production of trimethylamine N-oxide from dietary choline and carnitine, which promotes platelet hyperactivity and

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Nonstandard Abbreviations and Acronyms

ACE2	angiotensin-converting enzyme 2
ACSS2	acetyl-CoA synthetase 2
CoA	coenzyme A
ECM	extracellular matrix
ESBL	extended-spectrum β -lactamase
FFAR3	free fatty acid receptor 3
FMT	fecal microbiota transplantation
HAT	histone acetyltransferase
HDAC	histone deacetylase
HFpEF	heart failure with preserved ejection fraction
HIF-1α	hypoxia-inducible factor 1 alpha
IL	interleukin
IPA	indole-3-propionic acid
MEF2	myocyte enhancer factor 2
MI	myocardial infarction
NFAT	nuclear factor of activated T cells
NF-κB	nuclear factor- κ B
NLRP3	NLR family pyrin domain-containing 3
NNMT	nicotinamide N-methyltransferase
PHD2	pyruvate dehydrogenase E1 component subunit beta
SCFA	short-chain fatty acid
SIRT3	sirtuin 3
TGF-β	transforming growth factor- β
TLR4	toll-like receptor 4
TNF-α	tumor necrosis factor- α
VEGF-A	vascular endothelial growth factor A

adverse cardiovascular outcomes, a pathway extensively reviewed by Allayee and Hazen.⁸

In recent years, additional microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), bile acid derivatives, branched-chain amino acids, and tryptophan catabolites, have emerged as key regulators of vascular homeostasis, myocardial remodeling, and immune function.^{9–11} Dysbiosis-induced barrier dysfunction further exacerbates disease risks by allowing microbial components and metabolites to enter the systemic circulation, fueling inflammation and metabolism dysregulation.¹² Conversely, myocardial injury and stress can perturb gut microbial composition and immune homeostasis, reinforcing a bidirectional and dynamic relationship.¹³

While Allayee and Hazen provided a broad review emphasizing systemic inflammation, metabolic signaling, and clinical perspectives of the microbiota-cardiac interaction,¹⁴ a comprehensive synthesis of its impact on myocardial injury, repair, and regeneration remains underexplored. In this state-of-the-art review, we move beyond the traditional focus on atherosclerosis and

coronary artery disease to examine the multifaceted interactions between gut microbiota and the myocardium in the context of postinjury repair and remodeling. We further integrate emerging evidence of multiorgan circuitries, such as gut-brain-heart, gut-liver-heart, and gut-lung-heart axes, which are particularly relevant for translational cardiology. Finally, we outline future research priorities encompassing mechanistic insights, gnotobiotic approaches, and decision-grade clinical trial design to accelerate translation from bench to bedside.

MICROBIOTA-HEART CROSSTALK

The Gut-Heart Axis in Myocardial Injury and Remodeling

Accumulating evidence reveals physiological links between the heart and gut, particularly involving alterations in intestinal barrier integrity triggered by infection, dysbiosis, dietary factors, and chronic diseases. Beyond its contribution to atherosclerosis, the gut microbiota exerts critical and multifaceted effects on MI outcomes. Cardiac remodeling following MI involves a tightly orchestrated sequence of biological events: an acute inflammatory response, followed by a reparative proliferative phase, and culminating in scar maturation and ventricular remodeling.¹⁵ Emergency hematopoiesis-derived leukocytes support post-MI repair by clearing debris, depositing collagen, and promoting neovascularization.¹⁶ Perturbations in this process can lead to maladaptive remodeling, characterized by excessive fibrosis, ventricular dilation, and eventual heart failure.

Gut microbiota influences these processes by shaping the balance between adaptive tissue repair and maladaptive structural remodeling. Antibiotic-induced dysbiosis worsens postinfarction cardiac remodeling and functional decline by reducing infiltration of CX3CR1 (CX3C motif chemokine receptor 1)⁺ monocytes and regulatory T cells, thereby amplifying inflammation, fibrosis, and ventricular dysfunction, effects that are reversible through microbiota reconstruction.¹³ Gut dysbiosis-driven systemic inflammation also disrupts endothelial barrier integrity, permits translocation of microbial endotoxins (eg, lipopolysaccharide), impairs immune cell trafficking and polarization, and facilitates neutrophil and monocyte infiltration into the ischemic myocardium via upregulation of vascular adhesion molecules.^{13,17} These changes prolong the proinflammatory milieu and delay the reparative phase. In addition, cardiac pressure overload induces gut dysbiosis and CD4⁺ T-cell infiltration into the myocardium and mediastinal lymph nodes, further contributing to adverse cardiac remodeling.^{18,19} Together, these findings underscore the central role of gut-derived microbial signals in orchestrating myocardial repair.

Microbial-derived metabolites, particularly SCFAs, protect the myocardium after injury by attenuating oxidative

stress, enhancing endothelial function, and reducing cardiomyocyte apoptosis.^{20,21} In a recent multispecies translational study, Chen et al²² reported that MI is associated with depletion of butyrate-producing taxa (eg, *Bifidobacterium adolescentis*, *Faecalibacterium prausnitzii*, and *Eubacterium rectale*) and reduced circulating β -hydroxybutyrate levels. Restoring these taxa improved cardiac function and reduced fibrosis, partly by reprogramming cardiac macrophages toward an anti-inflammatory phenotype.²²

Mechanistically, SCFAs act via G-protein coupled receptors 41 and 43 (GPR41 and GPR43) and HDAC (histone deacetylase) inhibition to regulate gene expression and immune cell differentiation (Figure 1).^{23–25} Butyrate also promotes cardiomyocyte survival and enhances endothelial function via NF- κ B (nuclear factor- κ B) signaling pathway (Figure 1).²⁶ SCFAs additionally modulate cardiac fibroblast activity and ECM (extracellular matrix) turnover; for instance, butyrate suppress TGF- β (transforming growth factor- β)/Smad (intracellular mediators of TGF- β signaling), thereby inhibiting myofibroblast activation and collagen deposition (Figure 1).^{21,27,28} Acetate and propionate, 2 other SCFAs, suppress profibrotic signaling, inhibit myofibroblast activation, and preserve ventricular compliance in pressure-overload models.²¹ These mechanisms are critical for scar maturation and maintenance of ventricular integrity after myocardial injury. Moreover, SCFAs can serve as an alternative energy substrate for the failing heart under pressure-overload conditions (Figure 1).²⁹ Collectively, these actions preserve ventricular geometry, promote adaptive remodeling, and support functional recovery postinjury.

In contrast, other microbial metabolites exert detrimental effects. Phenylacetylglutamine has been implicated in cardiomyocyte stress signaling and platelet hyperreactivity, potentially worsening ischemic injury.³⁰ Phenylacetylglutamine functions as a negative allosteric modulator of β 2-adrenergic receptors, linking microbial metabolism to altered adrenergic signaling and heightened susceptibility to adverse cardiac events.³¹ Likewise, elevated plasma levels of microbial-derived imidazole propionate have been inversely associated with cardiac function and heart failure severity.^{32,33}

Beyond direct metabolic effects, SCFAs and microbial indole derivatives modulate immune responses by promoting monocyte differentiation and macrophage polarization toward anti-inflammatory and tissue-reparative phenotypes. Butyrate promotes expansion of regulatory T cells and anti-inflammatory Ly6C^{low} macrophages, both essential for collagen deposition and scar stabilization.²⁴ Loss of these protective microbial signals due to dysbiosis results in persistent inflammation and aggravated fibrotic remodeling.

Collectively, these findings position the gut-heart axis as an active regulator of myocardial healing, integrating microbial metabolic cues and immune regulation to influence cardiac repair and long-term function.

Gut Microbiota in Metabolic Myocardial Diseases

HFpEF is a multifactorial syndrome characterized by diastolic dysfunction, systemic inflammation, and endothelial impairment, often coexisting with obesity, insulin resistance, and hypertension.³⁴ Patients with HFpEF typically exhibit reduced abundance of beneficial taxa such as *Faecalibacterium prausnitzii*, *Roseburia spp.*, and *Akkermansia muciniphila*, alongside enrichment of pro-inflammatory genera.^{10,35} These alterations correlate with distinct metabolite changes, particularly diminished plasma levels of tryptophan-derived microbial metabolite indole-3-propionic acid (IPA), accompanied by impaired mitochondrial nicotinamide adenine dinucleotide salvage.¹⁰ In murine HFpEF models, IPA supplementation restored coronary microvascular function and diastolic performance via enhanced nicotinamide adenine dinucleotide metabolism through SIRT3 (sirtuin 3) activation and NNMT (nicotinamide N-methyltransferase) inhibition.¹⁰

The impact of microbiota extends beyond isolated myocardial pathology to its interplay with HFpEF comorbidities. In obesity, dysbiosis enhances energy harvest and promotes systemic inflammation.³⁶ In hypertension, gut microbial shifts influence vascular tone via SCFA-sensing receptors (GPR41 and GPR43) and the renin-angiotensin axis.³⁷ Consistent with this, commensal-derived acetate and propionate have been shown to enhance myocardial adaptation in pressure-overloaded models, suggesting therapeutic potential for SCFA supplementation or targeted microbial modulation in HFpEF.³⁷ Moreover, distinct microbial signatures have been associated with atrial fibrillation and chronic kidney disease, further reinforcing the microbiota's contribution to HFpEF pathophysiology.³⁸ Collectively, these findings position the gut microbiota as a central modulator of metabolic myocardial diseases, with the capacity to influence myocardial remodeling, vascular function, and systemic metabolism. Interventions aimed at modulating gut microbial composition or metabolite signaling, through dietary modification, probiotics, or microbiota-derived bioactive molecules, represent promising therapeutic avenues for HFpEF and related cardiomyopathies. Snellson et al³⁹ have provided a broad overview of gut microbiota and their derived metabolites in heart failure pathology and therapeutic implications. In contrast, our discussion centers on postinjury cardiac repair and remodeling, integrating regeneration biology and cross-organ interactions rather than focusing on heart failure in general.

Host-Microbiota Regulation of Immune-Metabolic Pathways

The gut microbiota plays a pivotal role in shaping the immune landscape following MI. Supplementation of SCFAs has been shown to enhance postinjury recovery

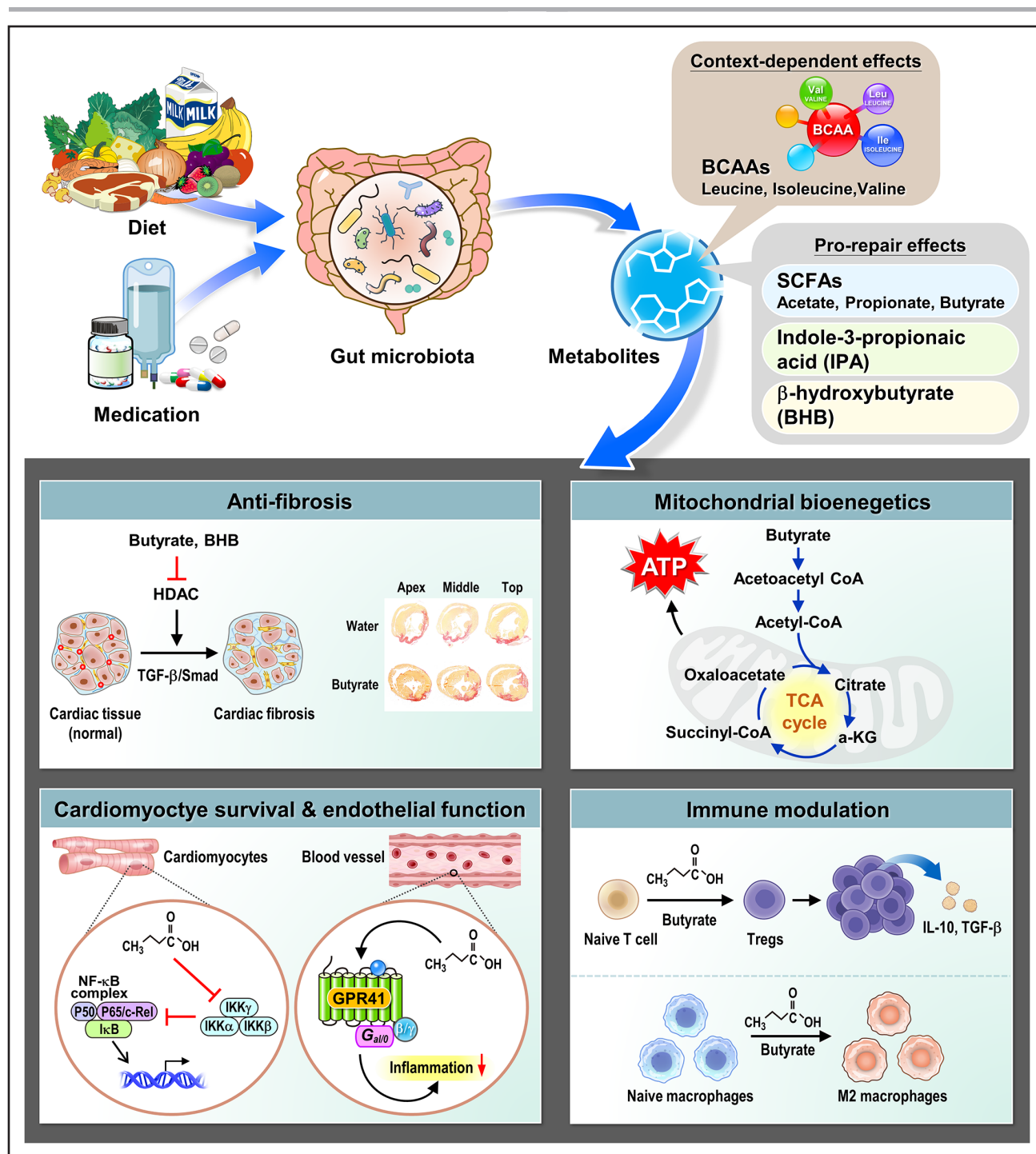


Figure 1. Gut microbial metabolites promote postinjury cardiac repair.

Gut microbiota-derived metabolites, including short-chain fatty acids (SCFAs), β -hydroxybutyrate (BHB), branched-chain amino acids (BCAAs), and indole-3-propionic acid (IPA), contribute to postinjury myocardial repair through multiple mechanisms. SCFAs, derived from dietary fiber fermentation, modulate immune responses by promoting regulatory T-cell (Treg) expansion and M2 macrophage polarization, facilitating inflammation resolution, tissue repair, and scar stabilization. Butyrate and BHB also inhibit HDAC (histone deacetylase) activity, suppressing TGF- β (transforming growth factor- β)/Smad signaling pathway and reducing cardiac fibrosis. These metabolites further enhance cardiomyocyte survival, improve endothelial function, and support mitochondrial bioenergetics, underscoring the multifaceted role of the gut microbiota in myocardial recovery. α -KG, indicates α -ketoglutarate; CoA, coenzyme A; IL, interleukin; Smad, intracellular mediators of TGF- β signaling; and TCA, tricarboxylic acid.

in aged animals through anti-inflammatory mechanisms, notably by expanding regulatory T cells and promoting immune resolution.⁴⁰ Although these effects are well

established in neuroinflammatory contexts, they are increasingly recognized in cardiac injury, particularly in aging, where impaired immune resolution heightens

the risk of fibrosis. Restoring SCFA levels in elderly or metabolically compromised individuals may, therefore, facilitate cardiac repair through immune-metabolic reprogramming.

Gut-derived lipopolysaccharide, a potent endotoxin produced by Gram-negative bacteria, is another critical modulator of post-MI immune responses. Loss of gut barrier integrity enables systemic translocation of lipopolysaccharide, which activates TLR4 (toll-like receptor 4) and NLRP3 (NLR family pyrin domain-containing 3) inflammasome, triggering NF- κ B signaling and upregulating proinflammatory cytokines such as IL (interleukin)-1 β , TNF- α (tumor necrosis factor- α), and IL-6.¹³ These pathways amplify both systemic and cardiac inflammation, aggravating myocardial injury and delaying recovery.

Emerging evidence also indicates that microbial signals influence hematopoiesis and immune programming within the bone marrow niche, modulating neutrophil and monocyte responsiveness to inflammatory cues.⁴¹ Such priming can skew immune cell phenotypes toward proinflammatory states, further exacerbating myocardial injury and impeding tissue repair.

Collectively, these findings highlight the gut microbiota as a central regulator of postinjury immune-metabolic pathways, integrating cytokine cascades, immune cell differentiation, barrier integrity, and fibrotic remodeling to shape cardiac recovery and long-term outcomes.

Bacteria Translocation in MI Progression

Myocardial injury can compromise gut barrier function, enabling the translocation of bacterial components (or in rare cases, whole microbes) to distant organs (Figure 2).⁴² For instance, increased intestinal permeability following stroke facilitates the passage of pathogens or bacterial toxins across the gut epithelium, increasing susceptibility to systemic infections, and worsening cardiovascular outcomes.⁴³ Stroke and MI are associated with elevated proinflammatory cytokines, which promote the dissemination of oral bacteria and lymphocyte apoptosis.^{43,44} Persistent intestinal inflammation weakens epithelial integrity and permits microbial products, such as lipoteichoic acid from Gram-positive bacteria and lipopolysaccharide from Gram-negative bacteria, to enter circulation.⁴⁵ This interplay may exacerbate cardiac dysfunction both via systemic inflammation and through hemodynamic changes that promote microbial translocation.

Emerging evidence highlights the role of gut microbiota in cardiometabolic health. Patients with MI and heart failure exhibit increased gut permeability and elevated plasma endotoxin levels.⁴² This systemic endotoxemia activates the TLR4-inflammasome pathway, exacerbating post-MI cardiac fibrosis and impairing recovery.^{15,42} Mechanistically, lipopolysaccharide-induced endotoxemia triggers the caspase 4 and caspase 11-gasdermin D axis,

leading to pyroptosis and the release of mitochondrial reactive oxygen species.⁴⁶ These reactive oxygen species amplify apoptosis and inflammation, further worsening cardiac function. These findings underscore the influence of gut microbial metabolites and components on myocardial disease progression and emphasize the need for continued investigation into the heart-gut axis. Nonetheless, direct evidence for bacterial translocation into the myocardium during cardiac events remains limited.

Microbial Presence in the Myocardium

Whether gut microbes can translocate to, reside within, and directly affect the myocardium remains an open question. In oncology, distinct tumor-associated microbial communities have been identified, correlating with tumor biology and therapeutic responsiveness.^{47,48} In contrast, the heart, by virtue of its constant blood flow and high-pressure environment, is generally considered inhospitable for microbial colonization. However, transient translocation of gut-derived microbes such as *Bacteroides*, *Lactobacillus*, and *Streptococcus* has been detected in the bloodstream of patients with ST-segment-elevation MI.⁴² Direct localization of these bacteria within myocardial tissues, however, is largely unproven.

An exception is infective endocarditis, in which microbial localization occurs on cardiac valves, typically involving oral, gut, or skin-derived microbes.⁴⁹ These bacteria can enter the bloodstream through dental procedures, gastrointestinal breaches, or systemic infections and subsequently adhere to damaged endocardium.⁴⁹ Infective endocarditis represents an overt infection distinct from the low-level translocation events postulated in metabolic heart diseases. In the absence of definitive evidence of myocardial localization, gut microbes may still modulate myocardial functions via systemic release of microbial products, alterations in host metabolism, and immune system priming.

Although active microbial residence in the heart appears rare outside of overt infection, gut microbes can profoundly influence cardiac structure and function through systemic immune-metabolic pathways and circulating microbial signaling. Future research should explore whether microbes can transiently or conditionally localize to the myocardium (especially during injury) and how such events might influence myocardial repair, remodeling, or dysfunction.

MULTIORGAN-MEDIATED GUT-HEART CROSSTALK

Emerging insights reveal that the influence of gut microbiota on cardiovascular homeostasis extends beyond the traditional gut-heart axis, orchestrating a multiorgan signaling network that includes the brain, liver, and lungs. These interconnected pathways underscore the systemic

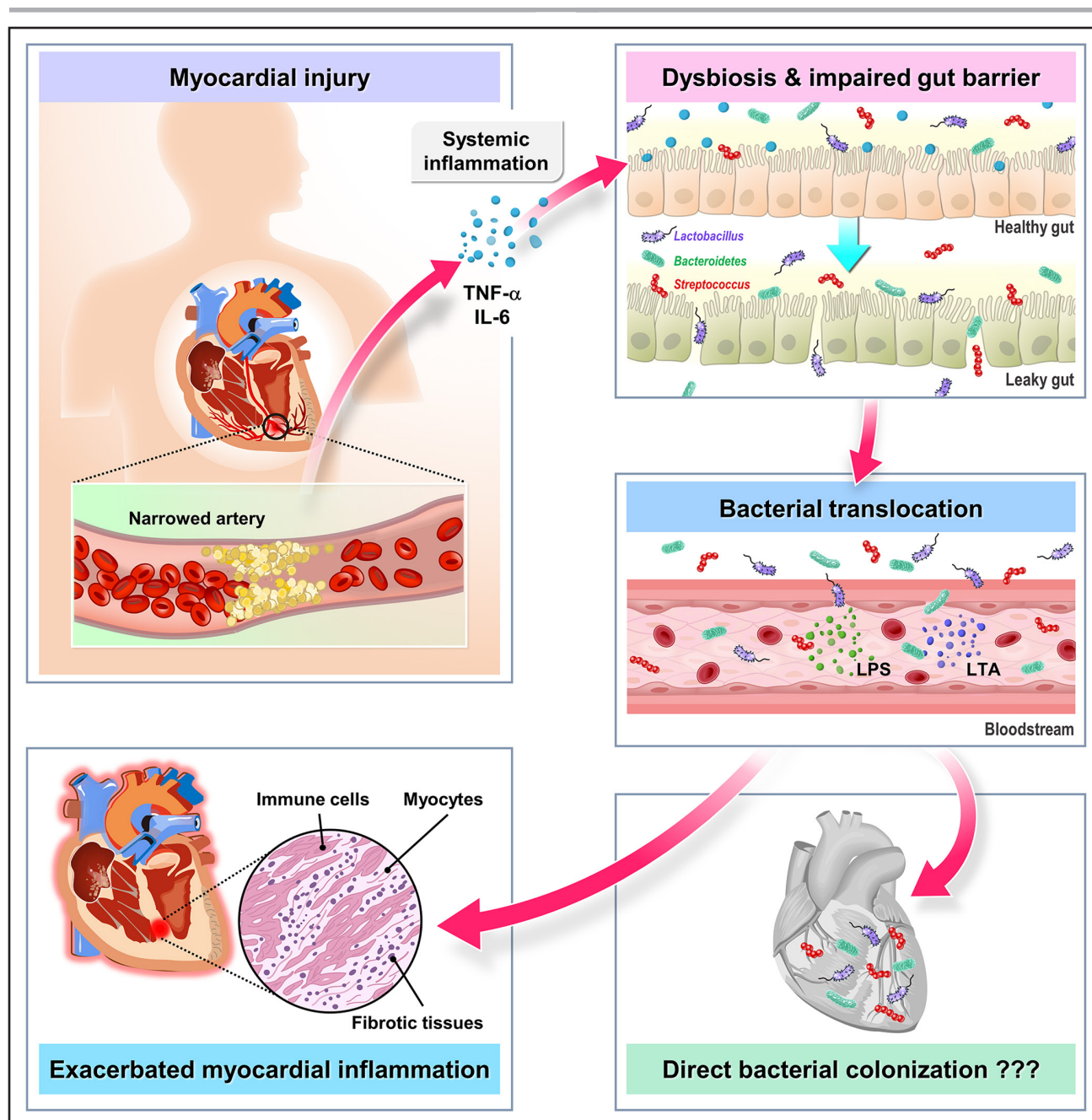


Figure 2. Myocardial injury promotes gut barrier dysfunction and bacterial translocation.

Myocardial injury triggers systemic inflammation, characterized by elevated cytokines such as TNF- α (tumor necrosis factor- α) and IL (interleukin)-6, which compromises gut barrier integrity and alters microbial composition. This disruption permits translocation of bacterial components, including lipopolysaccharide (LPS) and lipoteichoic acid (LTA), into circulation. While direct bacterial colonization of the myocardium remains unproven, transient microbial translocation may exacerbate myocardial inflammation and contribute to functional decline.

reach of microbial metabolites and components, influencing cardiac physiology through neural, immunologic, and metabolic circuits.

Gut-Heart-Brain Axis

The gut-brain axis, traditionally studied in neuropsychiatric and metabolic disorders, is increasingly recognized as a pivotal regulator of cardiovascular function. This

bidirectional communication operates through vagal, endocrine, and immune pathways, with the vagus nerve serving as a primary conduit for sensing microbial metabolites and transmitting signals to the central autonomic center, which regulates heart rate and vascular tone (Figure 3).⁵⁰

Microbiota-autonomic nervous system interactions are particularly relevant following MI and heart failure, conditions characterized by autonomic imbalance (marked by increased sympathetic activity and reduced

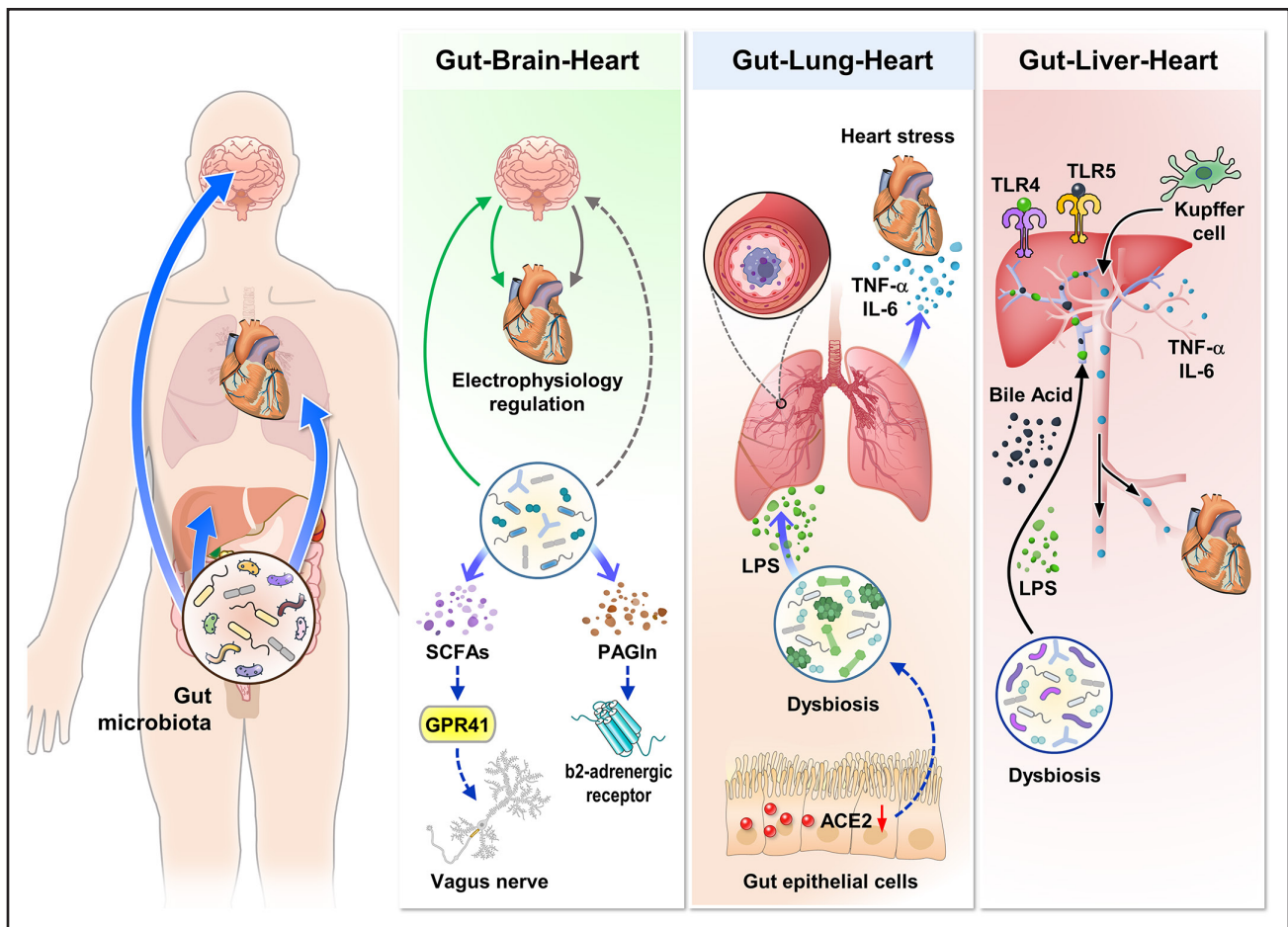


Figure 3. Microbiota-mediated cross-organ axes linking the gut to cardiovascular regulation.

Gut microbiota influences cardiovascular health through multiorgan systems via distinct but interconnected axes. Gut-brain-heart axis: short-chain fatty acids (SCFAs) activate vagal afferents through GPR41 (G-protein-coupled receptor 41), also called FFAR3 (free fatty acid receptor 3), modulating autonomic tone and cardiac electrophysiology. The microbial metabolite phenylacetylglutamine (PAGln) may influence myocardial β_2 -adrenergic receptor signaling, primarily through peripheral mechanisms that increase sympathetic output. Gut-lung-heart axis: ACE2 (angiotensin-converting enzyme 2), present in lung and gut epithelium, maintains vascular tone and barrier integrity; its deficiency alters microbiota composition. Gut dysbiosis impairs pulmonary immune responses by activating alveolar macrophages and elevating cytokines (eg, IL [interleukin]-6 and TNF- α [tumor necrosis factor- α]), which promote pulmonary vascular remodeling and heart strain. Gut-liver-heart axis: bacterial components (eg, lipopolysaccharide [LPS]) enter the portal circulation and activate hepatic TLR4 (toll-like receptor 4) signaling on Kupffer cells, inducing proinflammatory cytokines (TNF- α and IL-6), which contribute to cardiac inflammation and remodeling.

vagal tone), which contribute to arrhythmogenesis and cardiac dysfunction.⁵¹ SCFAs, particularly butyrate and acetate, modulate parasympathetic output and attenuate sympathetic overdrive via GPR41-mediated vagal activation.⁵⁰ In animal models, SCFA supplementation improves baroreflex sensitivity and heart rate variability, suggesting the potential of microbiota-based interventions to modulate autonomic tone in cardiovascular diseases.^{20,37,50} In addition, SCFAs activate FFAR3 (free fatty acid receptor 3), which is highly expressed on vagal afferent neurons.⁵² FFAR3 activation influences brainstem autonomic output, suppresses systemic sympathetic tone, and improves blood pressure control and cardiac electrical stability.⁵⁰ These findings provide a mechanistic rationale for targeting microbiota-derived metabolites to restore autonomic balance, particularly in post-MI autonomic dysfunction and heart failure syndromes.

Moreover, the microbial metabolite phenylacetylglutamine may allosterically modulate β_2 -adrenergic receptors in the myocardium, enhancing peripheral adrenergic responsiveness and contributing to sympathetic excitation.³¹ Elevated circulating phenylacetylglutamine levels are associated with increased cardiovascular event risk in prospective cohort studies,³¹ positioning phenylacetylglutamine as a key node in the gut-brain-heart axis and a promising therapeutic target.

Overall, the gut-heart-brain axis integrates microbial metabolite signaling with autonomic regulation, influencing cardiovascular tone, electrophysiology, and event risk. Building on this mechanistical link, multiorgan pathways, such as SCFA supplementation or phenylacetylglutamine modulation, present potential therapeutic strategies to improve myocardial health.

Gut-Liver-Heart Axis

The liver, as the first recipient of gut-derived metabolites and microbial components via the portal circulation, serves as a central hub in modulating systemic inflammation and cardiometabolic regulation. Loss of intestinal barrier integrity facilitates lipopolysaccharide and other bacterial products into the portal system, where they activate hepatic Kupffer cells through TLR4 signaling. This activation triggers the release of proinflammatory cytokines, including TNF- α and IL-6 (Figure 3), which subsequently enter systemic circulation to promote endothelial dysfunction, cardiac inflammation, and maladaptive remodeling.^{13,15,53}

Beyond immune activation, gut microbiota profoundly influences hepatic metabolism, which, in turn, shapes cardiac energy balance and inflammatory status. In murine HFpEF models, hepatic insulin resistance and steatosis exacerbate systemic metabolic stress, impairing myocardial function.¹⁰ Strategies aimed at modulating the gut microbiota, such as reducing lipopolysaccharide burden, enhancing SCFA production, and restoring hepatic metabolism, have demonstrated benefits, including attenuation of hepatic cytokine release, improved insulin signaling, and reduced fibrogenic activity, collectively contributing to improved cardiac outcomes.²²

The gut-liver-heart axis holds particular relevance for metabolic cardiomyopathies such as HFpEF, where hepatic metabolic dysfunction and inflammation are key drivers of disease progression. Targeting gut-liver metabolic crosstalk, therefore, represents a promising therapeutic avenue for mitigating cardiac remodeling and dysfunction in these patients.

Gut-Lung-Heart Axis

Emerging evidence highlights a dynamic tripartite communication between the gut, lungs, and heart, in which microbial signaling modulates cardiopulmonary inflammation and immune tone. Disruption of intestinal barrier integrity in heart failure facilitates the systemic translocation of lipopolysaccharide and peptidoglycans, which prime lung-resident immune cells such as alveolar macrophages to release proinflammatory cytokines, including IL-6 and TNF- α .^{54,55} These mediators promote pulmonary vascular remodeling, increase right ventricular afterload, and contribute to right heart strain.

Microbial metabolites, particularly SCFAs, also influence lung immunity via indirect immune-migratory mechanisms (Figure 3). SCFA-conditioned intestinal dendritic cells traffic from the gut to the lungs, modulating T helper 2 responses and altering susceptibility to allergic inflammation.⁵⁶ This mechanism underscores the capacity of gut-derived immune signals to affect distal organs, even in the absence of direct bacterial dissemination.

Longitudinal human studies support the relevance of this axis, showing that early life dysbiosis is associated

with an increased risk of chronic lung disease such as asthma and chronic obstructive pulmonary disease.⁵⁷ Parallel findings in murine models demonstrate that dysbiosis exacerbates systemic inflammation, triggers pulmonary vascular remodeling, and impairs cardiac function.^{54,55}

ACE2 (angiotensin-converting enzyme 2), a negative regulator of the renin-angiotensin system, serves as a molecular nexus within this axis. Expressed in both pulmonary and intestinal epithelial cells, ACE2 maintains vascular tone and mucosal barrier integrity.⁵⁸ Loss of intestinal ACE2 disrupts microbiota composition, reduces SCFA availability, promotes systemic inflammation, and increases pulmonary vascular resistance.⁵⁸

Collectively, the gut-lung-heart axis exemplifies the systemic reach of microbial signaling in shaping pulmonary vascular biology, right ventricular loading, and chronic inflammatory states. This emerging field opens a new avenue for microbiota-targeted interventions in cardiopulmonary disease.

FUTURE PERSPECTIVES

Mechanistic and Functional Investigations

To date, most studies on gut microbiota and myocardial health have relied on association or correlation analysis. A critical next step is to define causal mechanisms by which specific gut microbes influence cardiac function. Gnotobiotic studies using germ-free mice colonized with defined microbial communities or single bacterial strains have been instrumental in elucidating the bidirectional communications between gut microbes and the cardiovascular system. A clinically relevant strategy involves identifying altered gut microbial taxa from patient samples and validating their functional effects in appropriate germ-free and specific-pathogen-free (SPF) mouse models (Figure 4). When combined with genetically engineered bacterial strains or host models, these approaches can provide mechanistic insights into microbe-heart interactions.

This strategy has revealed the cardioprotective roles for butyrate-producing bacteria such as *Roseburia intestinalis*, *Butyricimonas virosa*, *Streptococcus parasanguinis*, and *Bifidobacterium adolescentis*.^{17,22} In ketogenesis-deficient mice, inoculation with these butyrate producers enhances postinjury cardiac repair by modulating host immune responses and reducing fibrosis, mediated through the production of butyrate and β -hydroxybutyrate.²² In another example, combining bacterial metabolite administration with antisense oligonucleotide therapy revealed that gut bacteria-derived IPA promotes host SIRT3 expression while suppressing NNMT, thereby enhancing the nicotinamide adenine dinucleotide salvage pathway.¹⁰ This demonstrates how IPA, a bacterial tryptophan derivative, improves diastolic function in HFpEF.¹⁰

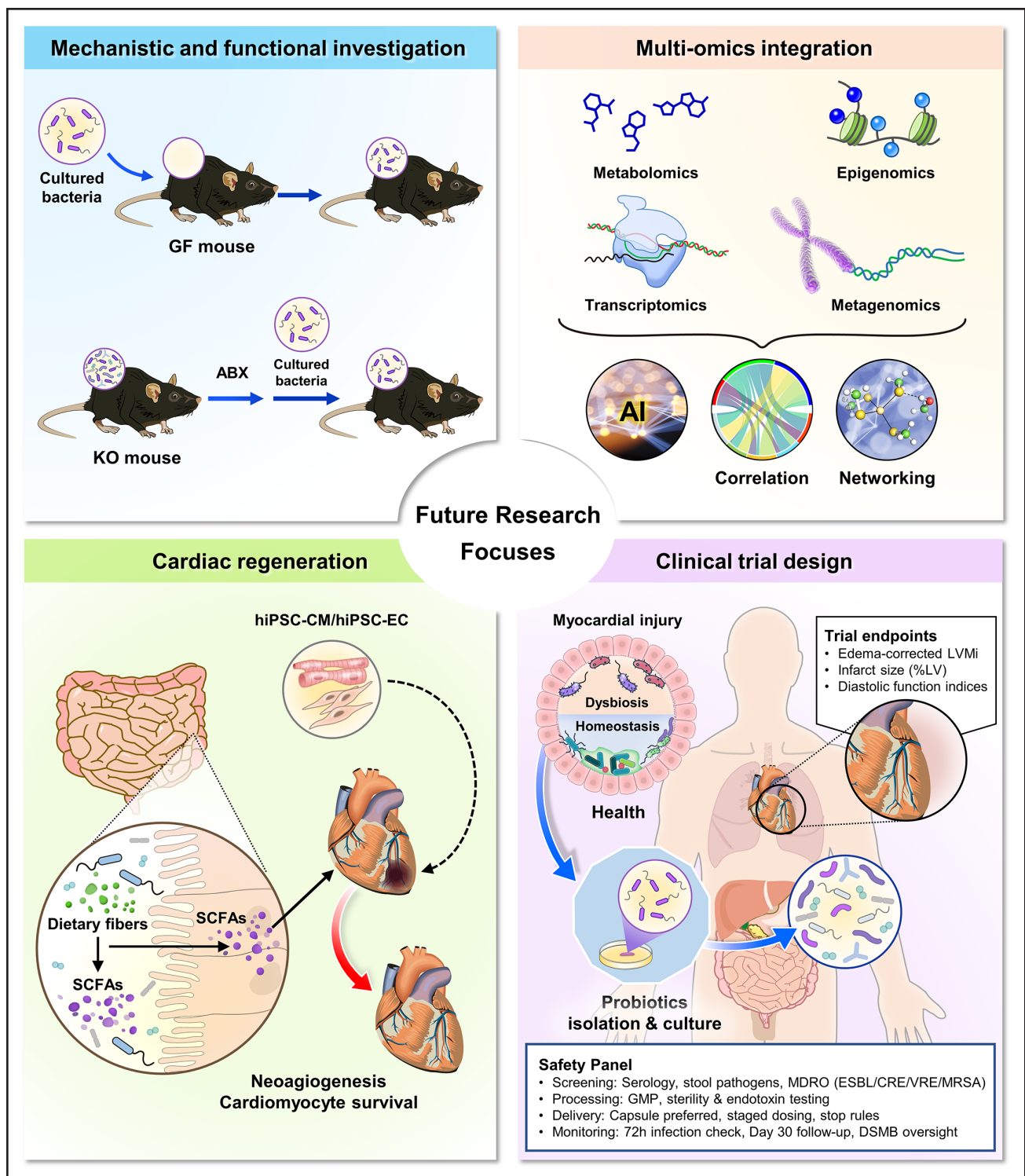


Figure 4. Future directions in microbiota-based cardiovascular research and therapeutics.

Advancing microbiota research in myocardial health requires a multifaceted approach that integrates mechanistic and functional investigation, multiomics analysis, regenerative medicine, and clinical translation. Mechanistic and functional studies using gnotobiotic models, including transplantation of defined bacterial strains into germ-free (GF) or genetically knockout (KO) mice, enable causal interrogation of microbiota-host interactions. Integrative multiomics analysis, combining metagenomics, epigenetics, transcriptomics, and metabolomics, provides system-level insights into microbial regulations of cardiac function. Microbial metabolites influence the efficacy of cell-based therapies, including human induced pluripotent stem cell (hiPSC)-derived cardiomyocytes (CMs) and endothelial cells (ECs), highlighting a role of microbiome in cardiac regeneration. Isolation and cultivation of functionally relevant probiotics facilitate microbiota-informed clinical trial designs, supporting precision and personalized therapies for myocardial diseases. CRE indicates carbapenem-resistant *Enterobacterales*; DSMB, data and safety monitoring board; ESBL, extended-spectrum β -lactamase; LVMI, left ventricular mass index; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; and VRE, vancomycin-resistant *Enterococci*.

Further mechanistic dissection can be achieved by mapping microbial effects to specific cardiac cell types. For instance, acetate and propionate attenuate cardiac fibrosis, vascular dysfunction, hypertrophy, and hypertension via GPR41 and GPR43-mediated inhibition of myofibroblast activation and collagen deposition in the ECM under pressure-overload conditions, thereby preserving myocardial mechanical resilience after injury.^{20,21} Conversely, phenylacetic acid, a phenylalanine-derived metabolite of *Clostridium sp.*, induces oxidative stress and mitochondrial dysfunction in endothelial cells, leading to premature senescence.⁵⁹ Notably, acetate can counteract phenylacetic acid-induced endothelium senescence and restore endothelial function.⁵⁹ A key priority for future research will be to translate these preclinical insights into the human population through large-scale, randomized clinical trials while, in parallel, identifying the precise cardiac cell targets of microbes or their secreted metabolites and decoding the downstream pathways they engage. Such integrative efforts will not only confirm causal mechanisms but also reveal novel therapeutic opportunities. By linking specific microbes or metabolites to distinct cardiac cellular responses, future research can move beyond association to mechanistically guided microbiota-based interventions in cardiovascular diseases.

Multomics Integration

The development of high-throughput technologies has enabled multiomics strategies to comprehensively profile gut microbiota, host metabolism, and cell type-specific gene expression. Approaches such as shotgun metagenomics, liquid chromatography-mass spectrometry-based metabolomics, and single-cell transcriptomics now allow unprecedented resolution in characterizing microbial communities and their functional impact on the host. The decreasing cost of shotgun metagenomics and metabolomics has expanded their application, enabling strain-level identification of disease-associated microbial shifts and detailed mapping of host metabolic alterations.^{35,60} For example, metagenomic analysis from the Human Microbiome Project profiling 300 healthy adults aged 18 to 40 years has provided a valuable reference for characterizing human microbiota across multiple body sites.⁶¹

Longitudinal multiomics studies in chronic cardiac conditions, such as HFpEF, are emerging as powerful tools to capture temporal changes in gut microbiota during disease progression, offering insights into the bidirectional dynamics of host-microbiota interactions. Integrating gut microbiota metagenomics with host metabolomics can pinpoint the microbial pathways and metabolites influencing cardiac physiology, as illustrated by the cardioprotective effects of IPA via SIRT3 activation in HFpEF.¹⁰ Single-cell transcriptomics adds an additional layer of resolution, allowing mapping of microbiota-induced changes to specific cell types and elucidating

the molecular mechanisms involved (Figure 4). Applying such multiomics approaches longitudinally in patients can validate animal-derived mechanistical insights and accelerate translation to clinical trial design.

Artificial intelligence and machine learning are poised to accelerate the translation of multiomics data into clinical tools. Early studies have demonstrated that gut microbiota signatures can aid in the diagnosis of ST-segment-elevation MI.²² With the continued expansion of large-scale, multiomics databases, integrating artificial intelligence-driven analysis could enable the development of microbiota-based diagnostics, personalized interventions, and precision nutrition strategies, advancing the era of precision cardiovascular medicine.

Microbiota in Cardiac Regeneration

The growing demand for cell-based therapies to treat heart failure and promote postinjury cardiac repair has prompted increasing interest in the role of the gut microbiota in modulating regenerative interventions. Emerging evidence indicates that gut microbiota-targeted modulation can enhance the efficacy of transplantation strategies, including mesenchymal stem cells and human induced pluripotent stem cell-derived cardiomyocyte therapies (Figure 4).⁶² These improvements are frequently accompanied by shifts in host metabolism, particularly toward amino acid and lipid biosynthesis, supporting cell proliferation and tissue repair.⁶² The beneficial effects of gut microbiota are largely mediated by bioactive microbial metabolites. SCFAs such as acetate and butyrate, derived from dietary fiber fermentation by commensal bacteria, exert broad effects on host metabolism, immune tone, and vascular function.^{17,22}

Butyrate, a potent HDAC inhibitor, reprograms immune and stromal cells toward reparative phenotypes.^{25,63} In cardiac repair, butyrate suppresses TGF- β /Smad-mediated myofibroblast activation, thereby attenuating fibrosis, preserving ventricular geometry, and improving myocardial performance.²⁷ Acetate, another SCFA, functions as an epigenetic regulator by serving as a substrate for acetyl-CoA (coenzyme A) via ACSS2 (acetyl-CoA synthetase 2). This enables HAT (histone acetyltransferase)-mediated transcription activation while also influencing HDAC activity, thus fine-tuning chromatin accessibility.⁶⁴ In cardiomyocytes, class II HDACs (HDAC4, HDAC5, HDAC7, HDAC9) interact with MEF2 (myocyte enhancer factor 2) to suppress transcriptional activity of GATA (GATA-binding transcription factor) and NFAT (nuclear factor of activated T cells), a key mechanism that prevents pathological hypertrophy under hemodynamic stress.⁶⁵

Beyond SCFAs, β -hydroxybutyrate, a microbiota-influenced ketone body with emerging epigenetic roles, also contributes to myocardial regeneration. Lysine β -hydroxybutyrylation of PHD2 (pyruvate dehydrogenase E1 component subunit beta) enhances HIF-1 α

(hypoxia-inducible factor 1 α) stability, leading to VEGF-A (vascular endothelial growth factor A) in macrophages.⁶⁶ This promotes neovascularization and helps preserve cardiac function following ischemic injury.⁶⁶

Collectively, these findings highlight a previously underappreciated role of gut microbial metabolites as epigenetic and metabolic regulators of cardiac regeneration. Targeting the gut microbiota, through dietary interventions, prebiotics, or probiotics, represents a promising adjunct to regenerative therapies, with potential to enhance cell engraftment, mitigate fibrosis, and improve long-term outcomes after myocardial injury.

Microbiota-Informed Clinical Trial Design

Since its successful use in treating recurrent or refractory *Clostridium difficile* infection, fecal microbiota transplantation (FMT), the transfer of microbiota from a healthy donor to a recipient, has gained attention for its potential in other diseases.^{67–69} In mouse models of MI and transverse aortic constriction, FMT from healthy donors preserved cardiac functions, improving left ventricular ejection fraction, fractional shortening, and myocardial mechanical properties.^{21,22} Despite the therapeutic promise of FMT, its clinical application has been tempered by safety concerns. The US Food and Drug Administration has issued safety alerts documenting transmission of multidrug-resistant organisms and pathogenic *Escherichia coli* strains, including ESBL (extended-spectrum β -lactamase)-producing, enteropathogenic, and Shiga toxin-producing variants, in recipients of investigational FMT.^{69,70} To address these risks, emerging strategies emphasize oral capsule-based microbiota transfer, rigorous donor and product screening, and the selective use of defined bacterial consortia with established safety profiles (Figure 4). These safeguards are critical to minimize potential contamination and ensure patient safety, providing a necessary foundation for any future cardiology trials evaluating FMT efficacy.

Dietary modulation offers another rapid, noninvasive, and scalable approach to reshape gut microbiota. High-fiber diets promote SCFA-producing bacteria, such as *Bacteroides acidifaciens*, and can prevent hypertension and heart failure in animal models, effects comparable to direct SCFA administration.⁷¹ Notably, maternal consumption of a fiber-rich diet during pregnancy in mice has been shown to influence offspring gut microbial composition and confer cardiovascular protection into adulthood.⁷² These findings highlight the transgenerational influence of diet-microbiota interactions on myocardial health.

In the context of heart failure or postinjury cardiac repair trials, stratifying patients according to microbiota composition or leveraging microbiota-based biomarkers to identify dysbiosis could enable more precise targeting of interventions. Moreover, therapeutically modulating the microbiome using inhibitors of key enzymes that

result in detrimental products (eg, trimethylamine-lyase and urocanate reductase) opens a new avenue for promoting myocardial health. Companion diagnostics, paired with dietary, prebiotic, or probiotic strategies, have the potential to improve efficacy, support greater personalization, and enhance safety in microbiota-informed cardiovascular clinical trials.

CONCLUSIONS

The recognition that the gut microbiota is an integral regulator of cardiovascular health marks a conceptual shift in how we understand, prevent, and treat heart disease. Far from being a passive bystander, the gut microbiome emerges as a dynamic, adaptable organ system that engages in continuous bidirectional dialogue with the heart, shaping systemic metabolism, immunity, vascular function, and regenerative capacity.

The growing convergence of microbiology, cardiology, immunology, and systems biology is dismantling traditional disciplinary boundaries, giving rise to a more unified view of host-microbe-organ interactions. Advances in longitudinal cohort studies, gnotobiotic modeling, and high-resolution multiomics are now enabling researchers to move beyond association toward causal, mechanistic, and cell type-specific insights. The next frontier lies in translating these insights into precision interventions, whether through diet, targeted probiotics, engineered microbial consortia, metabolite supplementation, or microbiota-informed regenerative strategies.

As this field matures, the gut-heart axis will likely expand into an interconnected network of organ-microbe axes, revealing shared molecular languages that govern systemic health and disease. In this vision, cardiovascular medicine will not only repair the failing heart but also restore the symbiotic equilibrium between the host and its microbial partners. Achieving this will require sustained multidisciplinary collaboration, large-scale integrative data sets, and a deliberate path from bench discovery to bedside application.

The promise is profound: a future in which modulating the microbiota becomes a cornerstone of cardiovascular prevention, therapy, and regeneration, transforming patient care and redefining the boundaries of cardiology for decades to come.

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Disclosures

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