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Exploring the Potential of Stem Cells in Modulating Gut Microbiota and Managing Hypertension

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Hypertension, commonly known as high blood pressure, is a significant health issue that increases the risk of cardiovascular diseases, stroke, and renal failure. This condition broadly encompasses both primary and secondary forms. Despite extensive research, the underlying mechanisms of systemic arterial hypertension—particularly primary hypertension, which has no identifiable cause and is affected by genetic and lifestyle agents—remain complex and not fully understood. Recent studies indicate that an imbalance in gut microbiota, referred to as dysbiosis, may promote hypertension, affecting blood pressure regulation through metabolites such as short-chain fatty acids and trimethylamine N-oxide. Current antihypertensive medications face limitations, including resistance and adherence issues, highlighting the need for novel therapeutic approaches. Stem cell therapy, an emerging field in regenerative medicine, shows promise in addressing these challenges. Stem cells, with mesenchymal stem cells being a prime example, have regenerative, anti-inflammatory, and immunomodulatory properties. Emerging research indicates that stem cells can modulate gut microbiota, reduce inflammation, and improve vascular health, potentially aiding in blood pressure management. Research has shown the positive impact of stem cells on gut microbiota in various disorders, suggesting their potential therapeutic role in treating hypertension. This review synthesizes the recent studies on the complex interactions between gut microbiota, stem cells, and systemic arterial hypertension. By offering a thorough analysis of the current literature, it highlights key insights, uncovers critical gaps, and identifies emerging trends that will inform and guide future investigations in this rapidly advancing field.

Keywords: hypertension, gut microbiota, stem cells, mesenchymal stem cells, dysbiosis

Introduction

Hypertension, a prevalent global health concern, has long been associated with various cardiovascular complications and is typically classified into two forms: systemic (arterial) hypertension and secondary hypertension. Systemic hypertension includes primary (essential) hypertension, which accounts for 90–95% of cases and lacks a specific cause, and secondary hypertension, which arises due to underlying issues such as kidney disease, hormonal disorders, or the use of certain medications.[1–3] Statistically, hypertension affects roughly 116 million adults in the United States and exceeds 1 billion adults worldwide.[4] Among these individuals, resistant hypertension—a condition where elevated blood pressure continues even with the administration of three or more antihypertensive medications, including diuretics—is of particular concern.[5] This condition significantly elevates the risk of heart disease, stroke, kidney damage, and vision impairment. Persistent high blood pressure places excessive strain on the arteries, leading to their hardening and narrowing, which diminishes blood flow to critical organs.[6] With about 15% of cases being treatment resistant, there is a crucial demand for novel treatment strategies.[7] The underlying causes of essential hypertension are still not well understood.[8–10] Although unhealthy lifestyles

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and more than 900 genetic locations are linked to a higher risk of hypertension, widespread genetic susceptibility forms describe under 6% of the differences in systolic blood pressure.[10,11]

Hypertension typically emerges from a complex interplay of factors involving a combination of genetic elements and environmental influences.[12] The conventional development of hypertension involves heightened sympathetic nervous system (SNS) activity, stimulation of the renin–angiotensin–aldosterone system, impaired vascular function, insulin resistance, and an imbalance in neurohumoral factors.[13,14] In the past 10 years, studies have connected the gut microbiome with the management of blood pressure. More recently, within the last 5 years, the focus of research has evolved from identifying correlations to establishing causal relationships, using sterile animal models, antibiotic therapies, and the addition of microbial metabolites.[15] Both preclinical and clinical studies show a connection between hypertension and gut microbiota imbalance (dysbiosis).[9,16–18] A balanced gut microbiota is crucial for overall health, and its imbalance, as indicated by the ratio of *Firmicutes* to *Bacteroidete*s (F/B), is strictly associated with hypertension. Research has demonstrated that hypertensive conditions are often defined by an elevated F/B ratio, which reflects dysbiosis in the gut microbiome.[18–20] This microbial imbalance can lead to variations in the levels of short-chain fatty acids (SCFAs), such as butyrate, acetate, and propionate. SCFAs are crucial in controlling blood pressure and maintaining vascular health by interacting with G protein-coupled receptors (GPCRs), encouraging vasodilation, and influencing immune responses.[20–22] Furthermore, trimethylamine N-oxide (TMAO), another product influenced by gut microbiota metabolism, contributes to hypertension by promoting atherosclerosis and endothelial dysfunction (ED). Elevated TMAO levels enhance platelet aggregation, increase arterial stiffness, and induce inflammation, all exacerbating hypertension and vascular damage.[23,24] The intricate pathogenesis of hypertension, coupled with the challenges of managing it using current antihypertensive drugs, highlights the limitations in their effectiveness, potential drug resistance, and adherence issues.[25–27] These challenges emphasize the urgent requirement for creative therapeutic alternatives that not only manage the disease conditions but also enhanced the patient's overall wellness and life quality.

In recent years, significant advances in regenerative medicine have inspired researchers to explore innovative therapies for complex conditions like hypertension.[28,29] Stem cells are unique undifferentiated cells with the remarkable ability to self-renew, proliferate, and differentiate into a variety of distinct types of specialized cell.[28,29] Several stem cell varieties exhibit promise in treating hypertension, particularly pulmonary hypertension (PH). Notable examples include endothelial progenitor cells (EPCs), mesenchymal stem cells (MSCs), and induced pluripotent stem cells (iPSCs).[28] Research indicates that stem cells can modulate blood pressure through various mechanisms, including the inhibition of apoptosis, prevention of inflammation, induction of angiogenesis, suppression of inflammation, and regulation of gut microbiota.[28] Additionally, the positive impact of stem cells on gut microbiota in conditions like Crohn's and Parkinson's diseases have been established.[30,31] Stem cell interventions have led to decreased harmful bacteria, increased beneficial ones, reduced inflammation, and improved gut health. Additionally, stem cells were found to regulate inflammatory cytokines and support intestinal cell maintenance, indicating their potential therapeutic role in diverse gut-related disorders.[32]

Throughout this review, we will explore the complex relationship between stem cells and gut microbiota in the context of systemic arterial blood pressure regulation. Our focus is on dissecting the latest research to provide a detailed understanding of these connections, with an eye toward identifying critical gaps and potential research approaches that could drive this field forward.

Pathophysiology of Hypertension

Endothelial dysfunction

The vascular endothelium is an important component of cardiovascular physiology, acting as a vital interface between the bloodstream and surrounding tissues. It enables the transport of nutrients and metabolites and mediates interactions with circulating cells, hormones, and cytokines.[33] The endothelium responds to various stimuli, including hormonal, neural, and hemodynamic signals. It is essential for regulating platelet activity, inflammatory responses, the proliferation and movement of vascular smooth muscle cells, and alterations in the vascular extracellular matrix structure. Apart from these roles, it also controls blood vessel constriction by producing and secreting several blood vessel-modulating substances. These substances include nitric oxide (NO), prostacyclin I2, and endothelium-derived hyperpolarizing factor, which have vasodilatory influence, as well as thromboxane A2 and endothelin-1 (ET-1), which have vasoconstrictive effects.[34,35] This diverse role establishes the healthy endothelium as a guardian of organ and tissue balance, pivotal in blood pressure regulation, and overall homeostasis.[36,37] In hypertensive individuals, there is observed ED marked by a decrease in the secretion of endothelial-derived relaxing elements like NO and endothelial-derived hyperpolarizing factor, coupled with an elevation in the release of endothelial-derived contracting, inflammatory, thrombotic, and proliferative factors.[37,38] ED is primarily caused by increased oxidative stress due to reduced NO availability. Studies also suggest that blocking of endothelium-derived nitric oxide synthase (eNOS) can induce hypertension, implicating that impaired endothelial function might be a contributing element in hypertension onset.[39,40] Furthermore, patients with hypertension exhibit a decrease in circulating EPCs, which are essential for repairing and maintaining the inner lining of blood vessels. This reduction is even more prominent in those with resistant hypertension, where ED is more severe.[41] The correlation between ED and systemic arterial hypertension is important, with impaired endothelial function serving as indicator of inflammatory condition, oxidative damage, and vascular pathologies in hypertensive individuals.[37]

Renin–angiotensin–aldosterone system (RAAS) activation

One of the primary mechanisms underlying the development of hypertension is the triggering of the renin–angiotensin–aldosterone system (RAAS).[42] It is a key player in

keeping normal blood pressure and is stimulated by the SNS and glomerular underperfusion. These stimuli cause the secretion of renin, which changes angiotensinogen to angiotensin I. Angiotensin I is then cleaved by angiotensin-converting enzyme into angiotensin II, a strong vasoconstrictor and the active component of the RAAS.[40,43–45] Angiotensin II, through its effect on the angiotensin AT1 receptor, induces vasoconstriction, inflammation, and remodeling in blood vessels.[46] Aldosterone, another key hormone in RAAS, acts on the kidneys to enhance sodium reabsorption, causing a rise in blood volume and, subsequently elevated blood pressure.[47] On the other hand, the natriuretic peptide system, particularly atrial natriuretic peptide (ANP), plays a balancing role. ANP, secreted by the atria in reaction to atrial stretching due to hemodynamic strain, leads to increased sodium excretion and urine production, modestly reducing blood pressure and decreasing plasma renin and aldosterone levels. ANP facilitates its effects through the membrane-associated guanylate cyclase-linked receptor, natriuretic peptide receptor A (NPR-A), activating cellular processes regulated by cyclic guanosine monophosphate (cGMP). By decreasing peripheral vascular resistance, the natriuretic peptide system counterbalances the function of the SNS and the RAAS, aiding in blood pressure regulation.[40]

RAAS activation promotes left ventricular hypertrophy in the heart, salt and water retention in the kidneys and amplified SNS action in the brain. These combined effects contribute to vascular and cardiac hypertrophy, inflammation, fibrosis, and, ultimately, hypertension.[48,49] It is worth mentioning that hormonal imbalances among angiotensin II (ANG II), vasopressin (VP), and the SNS can also promote hypertension and disrupt the water–electrolyte balance, contributing to cardiovascular diseases.[50] Clinical trials have demonstrated that targeting the RAAS in patients with hypertension can reduce inflammation, fibrosis, morbidity, and mortality, extending benefits beyond merely controlling blood pressure.[51]

Sympathetic nervous system overactivity

Recent evidence has increasingly supported the idea that the SNS is a major participant in the onset and progression of hypertension, beginning in its early phases and extending to cardiovascular conditions associated with hypertension. Several pathophysiological mechanisms are involved. Multiple pathophysiological mechanisms contribute to the condition, including genetic predisposition, immune system involvement, and activation of the SNS.[52] The hypothalamus and brainstem regulate sympathetic nerve activity, impacting heart rate, vasoconstriction, and renal sodium retention, leading to high blood pressure. Interactions between SNS and neurohumoral factors, such as the RAAS, exacerbate hypertension, while elevated oxidative stress in the central nervous system (CNS) further disrupts sympathetic regulation, complicating the pathophysiology of the condition.[53] Additionally, overexcitation of glutamatergic neurons in the hypothalamic paraventricular nucleus elevates blood pressure by enhancing sympathetic outflow.[54] Furthermore, purinergic signaling through P2 receptors in the brainstem's rostral ventrolateral medulla region raises vascular tone, exacerbating sympathetic overactivity and hypertension.[55] Introducing another factor contributing to SNS overactivity in hypertension, baroreflex dysfunction stimulates the condition. When baroreceptors in the carotid arteries and aortic arch become less sensitive, they fail to regulate blood pressure effectively. Consequently, this impaired regulation leads to sustained SNS overactivity, characterized by heightened heart rate, vasoconstriction, and renal sodium retention.[56]

Role of inflammation and oxidative stress

Chronic inflammation is a major contributor in hypertension pathogenesis, triggering vascular inflammation and microvascular remodeling, eventually leading to elevated blood pressure. Hypertension is driven by mechanisms involving both the innate and adaptive arms of the immune system. In this context, M1 macrophages, neutrophils, and dendritic cells contribute to the condition by releasing inflammatory cytokines, whereas regulatory T cells and M2 macrophages may provide a protective effect.[57] Activated T lymphocytes produce IFN-γ and IL-17, promoting oxidative stress injury and ED in hypertension. Oxidative stress, acting as both a trigger and a consequence of inflammation and immune system imbalances, aggravates vascular injury and remodeling, further driving hypertension.[57,58] Additionally, inflammation directly activates the RAAS via cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), leading to elevated renin secretion, angiotensinogen production, and aldosterone release.[59] It also contributes to hypertension-associated ED through endothelial activation, marked by the upregulation of chemokines and cell adhesion molecules (CAMs) like ICAM-1 and VCAM-1[37,60] This process is triggered by circulating inflammatory cytokines, TNF-α, and reactive oxygen species (ROS). The elevated level of adhesion molecules and chemoattractants promotes the recruitment and activation of neutrophils, which generate more ROS, exacerbating inflammation. Neutrophils also produce neutrophil extracellular traps (NETs), further enhancing local endothelial inflammation.[61] Excessive generation of ROS and diminished antioxidant protection add to ED, vascular remodeling, and tissue damage, all of which are associated with hypertension.[62] The imbalance between ROS and NO levels, caused by oxidative stress, impairs vascular function, reduces NO availability, and promotes vasoconstriction, ultimately elevating blood pressure.[63] Chronic oxidative stress can induce and maintain inflammatory responses within the vascular system. Cytokines that promote inflammation, such as IL-6 and TNF-α, are upregulated in conditions of oxidative stress. These cytokines can promote vascular remodeling and stiffness, both of which are key determinants in the progression of hypertension.[64] ET-1 also mediates oxidative damage by activating its receptor, which increases ROS via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation. Inflammatory cells, especially T cells and monocytes/macrophages, exacerbate oxidative stress and ED through increased NADPH oxidase function.[65,66] Additionally, mitochondrial reactive oxygen species (mtROS) stimulate NADPH oxidase 2 (Nox2), resulting in the recruitment of myelomonocytes and stimulating T cells to produce TNF-α. ROS influence the generation of NETs with NADPH oxidase activity. Oxidative–reduction pathways also regulate transcription factors such as nuclear factor kappa B (NF-κB) and Nrf2, which are involved in inflammatory pathways.[65,66]

Impact of gut microbiota

Changes in gut microbiota composition can result in imbalances impacting blood pressure regulation through various mechanisms.[67–69] These include modulation of production like serotonin, dopamine, and norepinephrine, which directly influence blood pressure.[70,71] Additionally, gut microbiota metabolites such as p-cresol sulfate, indoxyl sulfate, TMAO, and SCFAs exert a substantial influence on cardiovascular health. Heightened levels of TMAO, for instance, are associated with chronic kidney disease and are affected by the microbial metabolism of dietary nutrients, including choline and carnitine. This microbial activity contributes to increased TMAO production, which has been shown to promote inflammation and ED.[68,72] Intestinal bacteria also influence kidney function, affecting sodium excretion and, thus blood pressure. Moreover, SCFAs interact with GPRs 41 and 43 (GPR41, GPR43) and olfactory receptor 78 (Olfr78), regulating blood pressure via renal sensory nerves.[73] Chronic low-grade inflammation induced by gut microbiota is another contributing factor to hypertension.[74,75] The impact of gut microbiota will be thoroughly discussed in the subsequent section.

Figure 1 shows the main pathophysiological causes that might be involved in the development and progress of hypertension.

The Interrelationship Between Gut Microbiota and Hypertension

Emerging research highlights a complex, bidirectional relationship between gut microbiota and hypertension. This interplay suggests that gut microbiota not only mediate the development and progression of hypertension but are also significantly affected by hypertensive conditions.[20,67] This section explores this intricate interrelationship, beginning with how gut microbiota impact hypertension and followed by how hypertension, in turn, affects gut microbiota.

Dysregulated gut microbiota impact on hypertension

Gut microbiota, a diverse community of trillions of microorganisms residing in the human gastrointestinal tract, is essential in preserving overall wellness. These microorganisms, including bacteria, viruses, fungi, and protozoa, contribute to numerous physiological functions including digestion, immune function, and metabolism.[20,67,76] Recent investigation has increasingly underscored the predominant impact of gut microbiota on cardiovascular health, particularly on hypertension.

Several bacteria have been identified as either beneficial or harmful to hypertension. Beneficial bacteria such as *Lactobacillus, Roseburia, Coprococcus, Akkermansia*, and *Bifidobacterium* are associated with reduced blood pressure.[77] On the other hand, harmful bacteria like Clostridiuminnocuum, Eubacteriumcoprostanoligenes, Eubacteriumfissicatena, Anaerostipes, and Lachnospiraceae *FCS020* group have been linked to elevated blood pressure.[78]

Dysbiosis of gut microbiota, characterized by disproportions in beneficial and harmful bacteria, tightly connected with hypertension development.[68,69] The gut barrier is crucial for maintaining low intestinal permeability, preventing the leakage of pathogens and toxins, and reducing inflammation,

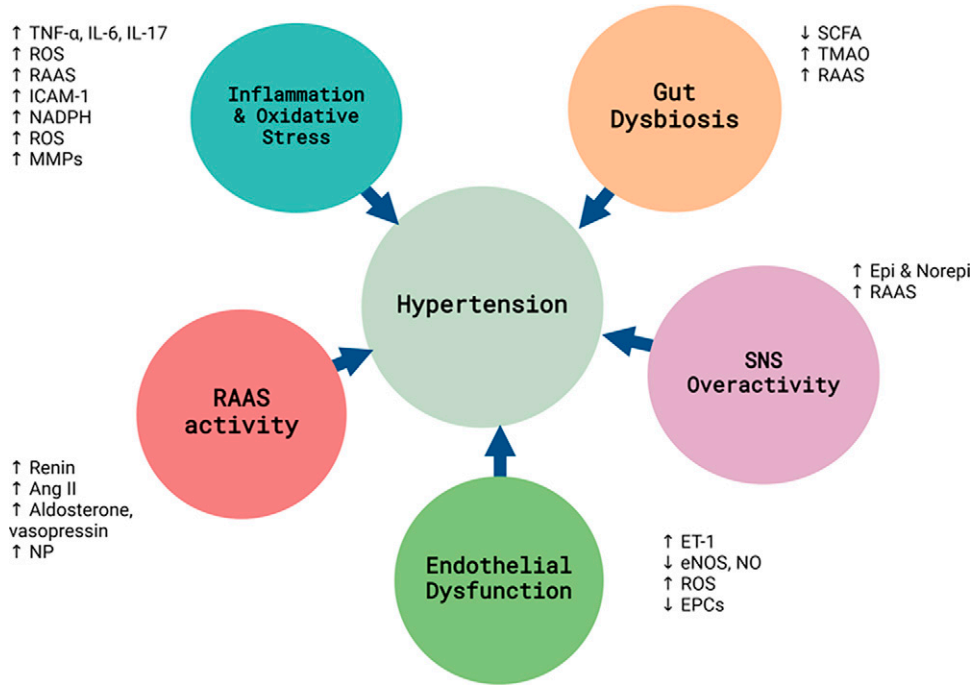

FIG. 1. Key pathophysiological elements that influence the onset and advancement of hypertension. (↑) increase, (↓) decrease. Ang II, angiotensin II; eNOS, endothelial nitric oxide synthase; EPCs, endothelial progenitor cell; Epi, epinephrine; ICAM-1, intercellular adhesion molecule 1; IL-6, interleukin 6; MMPs, matrix metalloproteinases; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NO, nitric oxide; Norepi, norepinephrine; NP, natriuretic peptide; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SCFA, short chain fatty acid; SNS, sympathetic nervous system; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor alpha. (Created with BioRender.com.)

which can lower blood pressure. Gut dysbiosis can disrupt tight junction proteins (such as ZO-1 and occludin) in the intestinal lining, raising intestinal permeability and allowing harmful bacteria and lipopolysaccharides (LPS) into the bloodstream. LPS activates TLR4 on immune cells, triggering pathways like NADPH/ROS/eNOS and MAPK/NF-κB. This leads to impaired endothelial function and blood vessel inflammation. LPS also causes damage to endothelial cells, promotes oxidative processes in monocytes and LDL oxidation, and stimulates inflammatory cytokine release, intensifying atherosclerosis progression.[20,79–81] Additionally, gut barrier dysfunction can hinder probiotic growth, further increasing the presence of pathogenic bacteria and LPS and exacerbating hypertension.[20,82]

Neuroinflammation in regions of the CNS implicated in sympathetic regulation, such as the PVN and nucleus of the solitary tract, is linked to hypertension.[83] Gut–brain communication can exacerbate sympathetic activation, with the gut transmitting physiological signals to the brain through the enteric nervous system and the vagus nerve. The vagus nerve serves as a crucial link in this communication, influencing neurogenesis and behavior. For example, vagotomy has been shown to prevent depressive-like behaviors associated with gut microbiota changes.[84] Additionally, vagal signaling plays a vital role in the immune response, modulating the microbiota–gut–brain axis and influencing anxiety-related behaviors.[85] The gut microbiota further contributes to this interaction by inducing serotonin production and affecting gut permeability through various mechanisms. Specifically, gut bacteria such as *Enterococcus* and *Escherichia* produce SCFAs that trigger enterochromaffin cells to secrete serotonin, a fundamental neurotransmitter for mood and gut motility.[86] Additionally, microbial metabolites, particularly SCFAs like butyrate, enhance intestinal barrier integrity by boosting the production of tight junction proteins, which maintain gut permeability.[87] Studies have shown that butyrate can enhance the synthesis of tight junction proteins, inhibit intestinal inflammatory pathways, and target toll-like receptor 4 signaling and the NLRP3 inflammasome, ultimately improving gut barrier function.[88,89] Gut dysbiosis can lead to reduced SCFA production and increased gut permeability, allowing endotoxins like LPS to enter the bloodstream.[90,91] This increased permeability triggers systemic inflammation and activates the SNS, leading to vasoconstriction, accelerated heart rate, and raised blood pressure.[23,92] SNS overactivity can also impact glucose metabolism, promote insulin resistance, affect renal function, increase fluid retention, and activate the RAAS.[23,78,93] Neuroinflammation in brain regions regulating blood pressure can maintain these effects, creating a feedback loop that worsens hypertension.[94]

In addition, dietary salt intake influences both the development of hypertension and the composition of gut microbiota. Increased salt consumption has been linked to changes in microbiota in various animal models, such as a rise in *Lachnospiraceae, Ruminococcus,* and *Parasutterella* species and a decline in *Lactobacillus* and *Oscillibacter* species.[95–97] Animal studies show that a high-salt diet reduces intestinal lactic acid bacteria and increases $CD4^+$, IL-17A+, and Th17 cells in the intestinal immune system, leading to salt-sensitive hypertension.[95,98]

Gut microbiota-derived metabolites are another essential factor contributing to hypertension. SCFAs, including acetate, propionate, and butyrate, generated through the fermentation of dietary fibers, affect blood pressure regulation by interacting with receptors on blood vessels and kidneys, influencing vascular tone and renal function.[99] SCFAs regulate blood pressure through multiple mechanisms. They activate GPCRs (GPR41, GPR43, and Olfr78), influencing vascular tone and blood pressure. SCFAs also inhibit histone deacetylases, resulting in anti-inflammatory effects and reduced proinflammatory cytokines. By inducing regulatory T cell production and upregulating Foxp3 gene expression, SCFAs help control inflammation.[100] They also interfere with the brain–gut and kidney–gut pathways, modulating metabolism, immunity, and inflammation to regulate blood pressure.[100] Additionally, SCFAs can impact NF-κB activation, as seen in studies where SCFA supplementation decreased systolic blood pressure and inhibited NF-κB-mediated inflammation.[101,102] On the other hand, TMAO, a gut microbiota-derived metabolite, exerts an adverse impact on blood pressure. TMAO has been shown to elevate systolic blood pressure and enhance vasoconstriction, exacerbating hypertension by facilitating Ang II-induced vasoconstriction through the (PERK) protein kinase RNA-like endoplasmic reticulum kinase/ROS/(CaMKII) calcium/calmodulin-dependent protein kinase II/(PLCβ3 axis) phospholipase C Beta 3 axis.[103]

Another significant factor in the link between gut microbiota and hypertension is bile acids, which mediate hypertension development through several mechanisms. Bile acids regulate lipid digestion and serve as messengers that impact metabolism and immune system response. Gut microbiota modify bile acids, which engage with receptors like farnesoid X receptor and G protein-coupled bile acid receptor.[104,105] These interactions can lead to metabolic disorders,[106] increased systemic inflammation,[105] compromised gut barrier function, elevated SNS activity, and disrupted lipid absorption, all contributing to hypertension.[20,23] Figure 2 illustrates the primary processes through which dysregulated gut microbiota can influence the onset and advancement of hypertension.

The effect of hypertension on gut microbiota

Hypertension negatively impacts gut microbiota through several mechanisms. Elevated blood pressure alters gut permeability, allowing harmful metabolites and inflammation-inducing agents to interact with gut microbes, disrupting their balance.[17,107,108] Hypertension-related biomarkers, such as heightened concentrations of inflammatory cytokines and oxidative strain, create an environment conducive to dysbiosis.[109,110] These inflammatory markers can directly damage gut epithelial cells, further compromising gut barrier integrity.[77,107,111] Additionally, hypertensive conditions elevate certain metabolites, such as TMAO, which aggravate microbial imbalances. TMAO levels are negatively associated with vascular reactivity index and endothelial function in hypertensive patients, indicating a correlation with ED.[112] TMAO can promote demyelination of white matter lesions in hypertension by inducing oligodendrocyte pyroptosis through ROS/NLRP3 inflammasome signaling and mitochondrial impairment.[113] Jiang et al. also

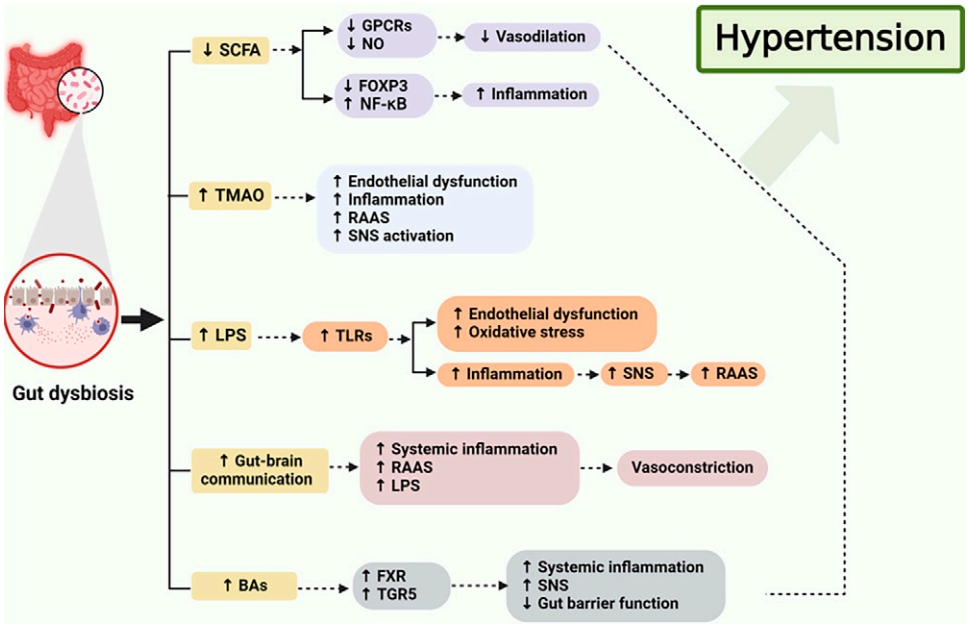

FIG. 2. Overview of gut microbiota dysregulation pathways affecting hypertension. (↑) increase, (↓) decrease. BA, bile acids; eNOS, endothelial nitric oxide synthase; FOXP3, Forkhead box P3; FXR, Farnesoid X receptor; GPCRs, G protein-coupled receptors; LPS, lipopolysaccharides; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NO, nitric oxide; ox-LDL, oxidized low-density lipoprotein; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SCFA, short chain fatty acid; SNS, sympathetic nervous system; TGR5, Takeda G protein-coupled receptor 5; TLRs, toll-like receptors; TMAO, trimethylamine N-oxide. (Created with BioRender.com.)

have revealed that TMAO levels were increased in severe PH, and reducing it can alleviate PH by suppressing macrophage production of proinflammatory cytokines and chemokines.[114] Research has shown that hypertensive individuals often exhibit a higher F/B ratio, reduced SCFA production, and increased presence of pathogenic bacteria like *Klebsiella* spp. and *Streptococcus* spp.[108] This dysbiosis not only reflects the impact of hypertension on gut health but also contributes to a feedback loop that exacerbates cardiovascular issues.[17,18,23,99,107,108]

In conclusion, the bidirectional link between gut microbiota and hypertension underscores the complexity of their interplay. Gut microbiota influence the development and progression of hypertension through various mechanisms, including metabolite production and immune modulation. Conversely, hypertensive conditions alter gut microbiota composition, further complicating the disease's pathology. Understanding this interrelationship enhances our overall comprehension of cardiovascular health and disease prevention.

Stem Cells: Basics and Therapeutic Potential

Overview of stem cells

Stem cells are unique, undifferentiated cells capable of self-renewal and differentiation into various specialized cell types.[115] It can be classified based on their differentiation potential into totipotent, pluripotent, multipotent, oligopotent, and unipotent cells.[116] From an origin perspectives, the primary categories of stem cells include embryonic stem cells (ESCs), adult stem cells (ASCs), and iPSCs.[117,118] ESCs, sourced from the inner cell mass of a blastocyst, are pluripotent, granting them the ability to differentiate into any cell type in the human body. ASCs, located in tissues such as bone marrow and adipose tissue, are typically multipotent and can differentiate into a limited range of related cell types. iPSCs are created by reprogramming adult somatic cells to revert to a pluripotent state, similar to ESCs.[118,119]

Stem cells exhibit several therapeutic properties that are highly beneficial to both hypertension and gut microbiota. They contribute fundamentally to regenerating damaged tissues in blood vessels and gut lining by differentiating into specific cell types and promoting tissue repair. Research has shown that stem cells, including intestinal stem cells and enteroblasts, are important for preserving tissue balance and promoting regeneration.[120,121] Also, the plasticity of stem cells, as demonstrated in various studies,[122,123] can have remarkable implications for blood vessels and gut microbiota. MSCs and EPCs have been shown to enhance blood capillary distribution and tight junction protein expression in the intestines, promoting vascularization and barrier function.[124] Besides, MSCs were also observed to restore gut microbiota diversity and function, revealing their versatility in modulating immune responses and improving microbiota composition.[125] Additionally, the homing ability of stem cells enables them to migrate to areas of injury or disease, targeting damaged blood vessels in hypertension and compromised gut tissues in gastrointestinal disorders.[126–128]

Conversely, the immune-modulating effect of stem cells, particularly MSCs, has gained traction as a therapeutic approach for cardiovascular diseases. MSCs effectively regulate immune cell subsets, orchestrating both local and systemic responses. This modulation fosters a stable inflammatory environment within damaged cardiac tissues, crucial for promoting effective repair and regeneration.[129] In the context of gut microbiota, MSCs have been discovered to engage with a

broad spectrum of enteric pathogens and commensal bacteria. This interaction leads to alterations in their immunomodulatory properties, enhancing the release of critical immunomodulatory factors such as prostaglandin E2 and interleukins.[130]

Modulation of gut microbiota by stem cells in inflammatory diseases

The gut microbiota impacts general health by modulating several physiological processes, including digestion, immune function, and even behavior. Dysbiosis, or the imbalance of gut microbial communities, has been linked to a range of diseases, such as inflammatory bowel disease (IBD), metabolic disorders, cardiovascular diseases, and neurodegenerative conditions.[131] This section explores how stem cells influence gut microbiota to restore microbial balance, enhance gut barrier integrity, and reduce inflammation. By examining preclinical and clinical studies, we aim to elucidate the therapeutic potential of stem cells in inflammatory diseases where gut dysbiosis plays a significant role. Understanding these mechanisms is important for developing effective stem cell-based treatments. This foundation will support further discussions on the direct effects of stem cells on hypertension, highlighting their multifaceted therapeutic potential.

Liu et al. demonstrated that adipose-derived stem cell (ASC) transplantation in aged mice has improved gut microbiota dysbiosis and reduced inflammation. Post-transplantation, there was increased gut microbiota diversity, including beneficial bacteria like *Akkermansia, Lactobacillus,* and *Prevotella*. Fecal sample analysis using 16sRNA sequencing confirmed these changes. Additionally, serum inflammatory markers (IL-6, TNF-α, and LPS) reduced, emphasizing the positive impact of ASC therapy on gut health and immune regulation.[132] This study highlights the ability of ASCs to rebalance gut microbiota and reduce inflammation, setting the stage for further exploration of their therapeutic potential in inflammatory conditions.

Supporting these findings, another study demonstrated the efficacy of MSCs in treating colitis in a 2,4,6-trinitrobenzene sulfonic acid-induced mouse model. The MSC treatment not only alleviated colitis symptoms and improved survival rates but also normalized gut microbiota dysbiosis by increasing alpha diversity and promoting beneficial bacteria such as *Bacteroidetes, Firmicutes*, and *Tenericutes*, while reducing harmful *Proteobacteria*. This study further elucidated that MSCs modulate metabolic pathways, reducing abnormal activities in sulfur and riboflavin metabolism.[133] These results align with Liu et al., suggesting a consistent pattern where stem cells enhance microbial diversity and reduce harmful bacterial populations, thereby alleviating inflammation and disease symptoms.

In this context, Wang et al. confirmed the effectiveness of MSCs in improving colitis symptoms. The findings indicated that MSC treatment decreased proinflammatory cytokine levels in a dextran sodium sulfate (DSS)-induced colitis mouse model, restored lymphocyte balance, and enhanced gut microbiota composition, specifically increasing beneficial bacteria such as *Firmicutes, Lactobacillus, Blautia, Clostridia,* and *Helicobacter*. Additionally, MSCs suppressed inflammatory pathways and upregulated the ferroptosis-related gene mucin-1 (MUC-1). This upregulation led to increased levels of SLC7A11 and GPX4, which are important for protecting cells from oxidative damage, and decreased levels of ACSL4, which is associated with promoting ferroptosis.[32] The findings from this study complement previous research, exhibiting how MSCs can influence both the immune system and gut microbiota to provide therapeutic benefits.

Affirming these results, MSCs have exhibited significant potential for addressing IBD due to their immune-regulating and survival-enhancing properties. Through the release of anti-inflammatory agents like IL-10, TGFβ, PGE2, and TSG-6, MSCs promote local tissue repair and modulate gut microbiota, enhancing the proliferation and differentiation of intestinal epithelial and stem cells to improve intestinal barrier integrity.[134]

In a combined approach, Zhu et al. observed that MSCs and EPCs improved intestinal repair and stabilized gut microbiota in BALB/c mice post-bone marrow transplantation. This treatment enhanced blood capillary distribution, increased tight junction protein (occludin), elevated IL-17A levels, and reduced IFN-γ levels. It also activated the p38 MAPK pathway and HSP27, promoting cell proliferation and reducing apoptosis. The therapy inhibited *Enterococcus* and stabilized *Akkermansia* populations, supporting intestinal health and microbiota stability.[135] These results suggest a synergistic effect when combining different stem cell types, enhancing both vascular and microbial health, and providing a more comprehensive approach to treating gut-related diseases.

Additionally, stem cells exert their effects through various pathways, linking gut microbiota alterations to immune modulation and inflammation reduction. In this context, human umbilical cord MSCs (HU-MSCs) have been shown to alleviate DSS-induced colitis by altering gut microbiota composition and increasing SCFA production. HU-MSCs reshaped T-cell immune homeostasis by upregulating SCFAs-producing bacteria like *Akkermansia, Faecalibaculum,* and *ClostridiaUCG-014*. These changes improved the Treg/Th2/Th17 balance in the intestinal mucosa. Gut microbiota depletion and fecal microbiota transplantation (FMT) experiments confirmed that HU-MSCs' protective effects were mediated via the microbiome-metabolite-immune axis, highlighting the critical role of microbiota-derived SCFAs in regulating immune responses and promoting recovery from colitis.[136]

Stem cells exhibit therapeutic potential in maintaining gut microbiota diversity and composition, which in turn supports intestinal health. Bu et al. confirmed this by demonstrating that human amniotic MSCs (HA-MSCs) effectively alleviated acute graft-versus-host disease (aGVHD) by rebalancing immune responses and restoring the intestinal barrier. Treatment with HA-MSCs enhanced gut microbiota diversity and composition, which was linked to improvements in tight junction proteins, immune cells, and cytokines. 16S rRNA sequencing revealed that HA-MSCs-treated mice had higher levels of beneficial bacteria like *Lachnospiraceae, Roseburia, Ruminococcaceae, Ruminiclostridium, Oscillibacter*, and *Clostridiales*, whereas harmful bacteria such as *Streptococcus* and *Delftia* were more abundant in the aGVHD group. Additionally, plasma levels of D-lactate and diamine oxidase confirmed the improved function of the intestinal barrier.[137]

Lastly, the administration of human intestinal MSCs (iMSCs) in a mouse model of colitis-associated cancer (CAC) has been shown to suppress tumor development and colitis through the reduction of IL-6 and COX-2 expression and inhibition of the IL-6/STAT3 and PI3K/Akt signaling pathways. This treatment also improved intestinal dysbiosis by increasing microbiota diversity and beneficial bacteria like *Akkermansia*, while reducing inflammatory genera such as *Alistipes* and *Turicibacter*.[138] Table 1 summarizes recent preclinical studies on the influence of stem cells on gut microbiota.

Emerging evidence suggests that exosomes, as key mediators of cell-to-cell communication, contribute to the modulation of gut microbiota composition and function. MSC-derived exosomes (MSC-exos) have been shown to restore the balance of gut microbiota in models of liver trauma and colitis, increasing beneficial bacteria such as *Bacteroides* and *Parabacteroides* while decreasing harmful species.[139] The exosomes also enhance the production of SCFAs, particularly butyrate, which is crucial for maintaining gut barrier integrity and immune homeostasis.[140,141] The regulatory effects of MSC-exosomes on gut microbiota and their metabolites highlight their potential as a novel therapeutic strategy for managing chronic gut diseases.[142,143]

Having explored the promising results from preclinical studies, the clinical applications of stem cells in modulating gut microbiota are still under investigation. In this context, Yang et al. have assessed the influences of MSC treatment on gut microbiota and fecal metabolites in refractory Crohn's disease (CD) patients, a condition strongly associated with gut dysbiosis. After eight MSC infusions (1×10^6 cells/kg), patients showed significant clinical improvements, including weight gain, reduced CDAI scores, and lower C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels, with no serious adverse effects. Endoscopic improvement was noted in two patients. Posttreatment analysis revealed increased levels of the beneficial bacteria *Cetobacterium* and decreased levels of the proinflammatory metabolite linoleic acid, suggesting a positive shift in gut microbiota composition and metabolic balance.[30] Another clinical study has investigated allogeneic donor MSCs for refractory aGVHD. Among 47 patients, the MSC group had a higher response rate (75% vs. 42.1%, P = .023) compared to those without MSCs. The treatment increased regulatory T cells (Tregs) and thymic function without raising infection or tumor relapse risks. Enhanced Treg levels suggest potential gut microbiota benefits.[144] Several clinical trials on MSC therapy for ulcerative colitis (UC) and CD have been conducted, but few are thoroughly documented, and clinical remission rates are unclear.[134,145] A meta-analysis of seven UC trials noted inconsistent definitions and a lack of control groups.[145–147] For CD, phase I trials with autologous and allogeneic MSCs showed limited success, with a remission rate of only 32% in severe cases.[148] A recent meta-analysis of 18 CD trials indicated MSC therapy can maintain remission and reduce severity but emphasized the necessity for additional high-quality randomized controlled trials to fully understand their impact on gut microbiota.[145,149]

These studies collectively highlight the significant potential of stem cells in modulating gut microbiota, which can lead to improved outcomes in various gastrointestinal and systemic diseases. The consistent findings across different studies suggest that stem cells can enhance microbial composition, mitigate gut barrier disruption, and reduce inflammation through multiple mechanisms. This understanding lays a crucial groundwork for developing new stem cell-based therapies aimed at targeting gut microbiota in diseases, including hypertension, as explored further in the interconnected relationship to be detailed in the subsequent section.

Stem cells in hypertension management

Stem cells have become a potential intervention for managing hypertension. By promoting vascular repair, reducing inflammation, and regenerating damaged tissues, stem cells offer a novel approach to controlling high blood pressure.[150] Several preclinical studies have shown the impact of stem cells on hypertension. Oliveira-Sales et al. have assessed the therapeutic benefits of primed MSCs (pMSCs) in spontaneously hypertensive rats (SHRs). Priming MSCs with endothelial growth medium (EGM-2) reduced cell death rates in vitro. Administering pMSCs to SHRs significantly lowered arterial pressure for 10 days, reduced cardiac hypertrophy, improved endothelium-dependent vasodilation, and increased skeletal muscle microvascular density. These benefits were attributed to the enhanced angiogenic and endothelial function of primed MSCs, despite the transplanted cells being rarely found in the hearts and kidneys.[151]

A research study has examined the impact of MSCs derived from human umbilical cord (HU-MSCs) on angiotensin receptor agonistic autoantibody (AT1-AA)-induced hypertension in pregnant rats. HU-MSC treatment significantly lowered systolic blood pressure (SBP) by gestational day 19, improved fetal weight, reduced kidney lesions, and enhanced spiral artery remodeling. HU-MSCs also modulated immune responses, lowering serum TNF-α levels, and increasing IL-10 level.[152] In an experimental model involving rats with pulmonary arterial hypertension, the infusion of MSCs from human (HUCB-MSCs) led to a substantial decline in right ventricular pressure. This effect was achieved umbilical cord blood by downregulating key biomarkers, including ET-1, endothelin receptor A (ERA), endothelial nitric oxide synthase (eNOS), and matrix metalloproteinase-2.[153] Furthermore, Wistar rats with pulmonary arterial hypertension (PAH) induced by monocrotaline were treated with adipose-derived MSCs (AD-MSCs). The treatment has significantly decreased right ventricular systolic pressure, lung collagen, smooth muscle cell proliferation, and inflammation markers (CD68+ macrophages, IL-6). It also increased proapoptotic mediator procaspase-3 and plasma vascular endothelial growth factor (VEGF) while decreasing antiapoptotic mediators (Bcl-2, survivin). AD-MSCs mitigated endothelial–mesenchymal transition in the pulmonary artery, showing their potential to reduce PAH symptoms through anti-inflammatory and antifibrotic mechanisms.[154] In this context, Oh et al. suggested that MSCs sourced from umbilical cord blood (UCB-MSCs) showed superior therapeutic benefits over adipose tissue (AD)- and bone marrow (BD)-derived MSCs in monocrotaline (MCT)-induced PH rat model. UCB-MSCs resulted in substantial progress in right ventricular function and reductions in

Table 1. Summary of Preclinical Studies on the Influence of Stem Cells on Gut Microbiota (2019–2024)

Type of cells	*Experimental model*	*Dose of injection*	*Duration of treatment*	*Results of the experiment/ general outcome of the study*	*References*
Adipose-derived stem cell	C57BL/6 J mice	NA	NA	↓ IL-6, TNF-α, and LPS ↑ *Akkermansia, Lactobacillus*, and *Prevotella* bacteria Reduced inflammation and improved gut health	132
HUC-MSC	TNBS-induced colitis BALB/c mice	1×10^6 cells/mouse, IP injection, passages 3–5	7 days	↑ *Bacteroidetes, Firmicutes, Tenericutes* bacteria ↑ Survival rate Improved gut health and enhanced survival rate	133
HUC-MSC	DSS-induced IBD colitis mice	1×10^6 cells/mouse, IV injection, passages 5	10 days	↑ *Firmicutes, Lactobacillus, Blautia, Clostridia,* and *Helicobacter* bacteria ↓ IL-1β, TNF-α, and IL-6 ↑ ferroptosis-related gene MUC-1 Reduced inflammation, improved gut microbiota diversity and enhanced cell survival and stress response	32
MSC+EPCs	BALB/c mice	1×10^6 MSC infusion, 5×10^5 EPCs, passages 3–9	15 days	↑ occludin, IL-17A ↓ IFN-γ ↑ p38 MAPK pathway and HSP27 ↓ *Enterococcus* ↑ *Akkermansia* Supported intestinal health and microbiota stability	135
HU-MSCs	DSS-induced colitis mice	1×10^6 cells/mouse, IP injection, passages 3–4	10 days	↑ SCFA production ↑ *Akkermansia, Faecalibaculum, and Clostridia_UCG_014* ↑ Treg/Th2/Th17 balance Regulated immune responses and promoting recovery from colitis	136
HA-MSCs	aGVHD mouse model	5×10^5 HAMSCs/mouse, IV injection, passages 3–6	3 days	↑ Lachnospiraceae, Roseburia, Ruminococcaceae, Ruminiclostridium, Oscillibacter, and Clostridiales ↓ *Streptococcus* and *delftia* ↑ Intestinal barrier functionality ↓ Inflammation Improved intestinal barrier function and reduced inflammation	137
iMSCs	AOM/DSS mouse model	0.5×10^6 cells/mouse, IP injection, passages 2–8	10 weeks	↓ IL-6 and COX-2 ↓ IL-6/STAT3 and PI3K/Akt signaling pathways ↑ Tregs and IFN-γ+CD8+ T cells ↓ IL-4+Th2 response ↑ *Bacillota/Bacteroidota* ratio, *Akkermansia* ↓ *Alistipes* and *Turicibacter* Improved gut microbiota balance, enhanced immune regulation, and reduced inflammation.	138

AOM, aGVHD, alleviated acute graft-versus-host disease; EPCs, endothelial progenitor cells B; HA-MSCs, human amniotic mesenchymal stem cells; IFN-γ, Interferon-gamma; IL-6, intereferon-6; iMSCs, intestinal mesenchymal stem cells; MSC, mesenchymal stem cell; MUC-1, SCFA, short-chain fatty acids; TNF-α, tumor necrosis factor alpha.

medial wall thickness, fibrosis around blood vessels, and proliferation of vascular cells. They also decreased immune cell recruitment and inflammatory cytokines. Gene expression and network analyses showed that UCB-MSCs most effectively reduced immune and inflammatory profiles and normalized classical PAH pathways, underscoring their potential in treating PH.[155] MSCs decreased pulmonary arterial pressure, collagen deposition, and vascular remodeling in rat models. They also reversed endothelial-to-mesenchymal transition (EndMT) by regulating CD31 (a protein primarily expressed on the surface of endothelial cells) levels and modulating key markers. Additionally, MSCs inhibited hypoxia-inducible factor-2α (HIF-2α), preventing EndMT.[156] It is worth mentioning that PH is a severe condition marked by elevated blood pressure in the pulmonary arteries, which may result in right-sided heart failure if left untreated. PH differs significantly from systemic or essential hypertension, which involves elevated blood pressure in the systemic arteries and is often linked to lifestyle factors and genetic predispositions. Despite their differences, both conditions involve vascular dysfunction and are areas where stem cell therapy shows promising potential.[150,157,158]

Stem cells, particularly MSCs, can mitigate hypertension through immunomodulation. The immunoregulatory characteristics of MSCs include their ability to influence both the innate and adaptive immune systems. MSCs interact with various immune cells, including T cells, B cells, natural killer cells, dendritic cells, and macrophages. They are able to suppress the growth and activation of T cells and B cells, alter the function of dendritic cells to promote a more tolerogenic state and modulate macrophages to adopt an anti-inflammatory phenotype. These interactions help reduce inflammation and promote tissue repair and regeneration.[129] In this context, skin MSCs (S-MSCs) significantly reduce AngII-induced hypertension in mice by lowering systolic blood pressure and vascular damage. They achieve this by inhibiting Th17 cell differentiation, decreasing IL-17 levels, and promoting macrophage M2 polarization, characterized by reduced TNF-α and increased Arg1 and IL-10 production. These effects involve the CXCR4/SDF-1 signaling pathway, highlighting the potential of S-MSCs for stem cell-based hypertension therapy.[159] A study on mixed-sex broilers with PAH, administration of MSCs at 15 days of age reduced PAH morbidity, and alleviated lung endothelial injury and plexiform lesions. MSC treatment also decreased lung inflammation by reducing TNF-α, IL-6, and IL-1β levels, while maintaining stable levels of paracrine angiogenic factors such as VEGF-A and TGF-β. Additionally, it enhanced the endothelial differentiation capacity of endogenous MSCs.[160] Chan et al. have studied the application of MSCs derived from Wharton's jelly (WJ-MSCs) as a treatment for metabolic syndrome (MetS) in rats fed a high-fat, high-fructose (HFHF) diet. While the primary results showed no notable alterations between the intervention group and the control group, the secondary analysis revealed that WJ-MSCs enhanced cardiopulmonary health and slowed the progression of metabolic decline. This improvement was evident in better histopathological findings in the lungs, liver, and heart. These findings suggest that WJ-MSCs may offer potential benefits for conditions associated with hypertension, given that metabolic syndrome often exacerbates hypertension by contributing to vascular inflammation and ED.[161] Table 2 summarizes recent preclinical studies on the impact of stem cells on hypertension.

The effects of stem cell-derived exosomes on hypertension and blood vessels are increasingly recognized as a promising therapeutic avenue. Exosomes from umbilical cord MSCs (hUC-MSC-EXO) and iPSCs have been shown to inhibit pulmonary vascular remodeling by regulating the NF-κB/BMP signaling pathway, leading to reduced right ventricular hypertrophy and improved pulmonary artery function.[162,163] iPSC-derived exosomes (iPSC-Exo) effectively reduce the proliferation and migration of pulmonary artery smooth muscle cells through pathways involving HIF-1α and Runx2, thereby preventing excessive vascular remodeling.[164] Additionally, exosomes from kidney stem cells (WKY-Exo) have been shown to improve arterial compliance and endothelial function in SHRs, suggesting a protective role against hypertension-induced vascular damage.[165]

However, limited clinical research has explored the impact of stem cells on hypertension. A Phase 1a clinical trial investigated autologous MSC infusion in 39 patients with atherosclerotic renovascular disease (ARVD), a condition linked to hypertension. Twenty-one patients received MSC infusions, and 18 received standard medical therapy. After three months, the MSC-treated group showed increased renal blood flow (164 to 190 mL/min), reduced inflammatory cytokines and hypoxia, lower SBP (144–136 mmHg), and a modest elevation in glomerular filtration rate (GFR) (53–56 mL/min), with the highest benefits seen in the high-dose group. No significant differences were detected in the medically treated group. These results suggest MSC therapy can improve kidney function and manage hypertension in patients with ARVD.[166] It is important to highlight that there is a notable scarcity of clinical studies exploring the potential of stem cells in managing hypertension. Therefore, there is a pressing need for comprehensive human studies to elucidate the potential therapeutic impact of stem cells on hypertension.

The Role of Stem Cells in Modulating the Interaction Between Gut Microbiota and Hypertension

The relationship between gut microbiota, hypertension, and stem cells is complex and interconnected. Research has exhibited that alterations in the gut microbiota are closely linked to the development and progression of hypertension.[20,167] Furthermore, gut microbiota dysbiosis can lead to gut barrier dysfunction, impacting blood pressure regulation.[168] Despite the emerging interest in the interplay between gut microbiota, hypertension, and stem cells, few studies have explored this relationship.

Due to the limited research specifically addressing this topic, we will review cases that illustrate the effect of stem cells on gut dysbiosis and hypertension biomarkers in different clinical conditions such as diabetes, atherosclerosis, and PH. These examples provide insight into the potential of stem cell therapy in modulating gut microbiota and improving hypertension management, indirectly highlighting the relevance of this emerging field.

In diabetic mice models (ACE2–/y-Akita and Akita), gut barrier disruption was linked to reduced bone marrow-

Table 2. Summary of Preclinical Studies on the Impact of Stem Cells on Hypertension

Type of cells	*Experimental model*	*Dose of injection*	*Duration of treatment*	*Results of the experiment/ General outcome of the study*	*References*
HU-MSCs	pregnant Sprague-Dawley rats	1×10^6 cells/mouse, IV injection, passages 3–5	4 months	↓ Kidney lesions ↑ spiral artery remodeling ↓ TNF-α ↑ IL-10 Improved kidney health, enhanced vascular remodeling and reduced inflammation	152
HUCB-MSCs	MCT-induced PAH Sprague-Dawley rats	3×10^6 cells/rat, IV injection, passages 5	4 weeks	↓ ET-1, ERA ↓ eNOS ↓ MMP-2 Improved vascular health and reduced vascular remodeling	153
AD-MSCs	MCT-induced PAH Wistar rats	1×10^5 cells/rat, IV injection, passages 5	4 weeks	↓ smooth muscle cell proliferation ↓ CD68+ macrophages, IL-6 ↑ procaspase-3, VEGF ↓ Bcl-2, surviving Improved vascular remodeling, reduced inflammation, enhanced apoptotic activity, and increased angiogenic potential	154
UCB-MSCs	MCT-induced PAH Sprague-Dawley rats	1×10^6 cells/rat, IV injection	2 weeks	↓ vascular remodeling ↓ inflammation Reduced structural changes of blood vessels and decreased inflammation	155
MSCs	Chronic hypoxia (CH)-induced PH and sugen hypoxia (SuHx)-induced PH	1×10^6 cells/rat, IV injection, passage 3–6	2 weeks	↓ vascular remodeling ↑ fibronectin and vimentin ↓ Endothelial markers (VE-cadherin, PECAM-1) ↓ HIF-2α Enhanced endothelial function and improved vascular structure	156
S-MSCs	C57BL/6 mice	0.5×10^6 cells/ mice, IV injection	3 weeks	↓ Th17 cell differentiation ↓ IL-17 levels ↑ macrophage M2 polarization ↓ TNF-α ↑ Arg1 and IL-10 Reduced inflammation with enhanced immune regulation and anti-inflammatory responses	159
MSCs	PAH-induction mixed-sex broilers model	2×10^6 cells/animal, IV injection, passage 2.	4 weeks	↓ TNF-α, IL-6, IL-1β ↑ VEGF-A and TGF-β Reduced inflammation and promote blood vessels growth and repair	160
WJ-MSCs	MetS Sprague-Dawley rats	3×10^6 cells/kg or 10×10^6 cells/kg	12 weeks	Improved cardiopulmonary health and slowed metabolic decline in rats with metabolic syndrome	161

AD-MSCs, adipose-derived mesenchymal stem cells; eNOS, endothelium-derived nitric oxide synthase; ERA, endothelin receptor A; ET-1, endothelin-1; HU-MSCs, human umbilical cord mesenchymal stem cells; HUCB-MSCs, human umbilical cord blood-mesenchymal stem cells; IL-10, interleukin-10; MMP-2, matrix metalloproteinase-2; MSCs, mesenchymal stem cells; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; S-MSCs, skin mesenchymal stem cells; TNF-α, tumor necrosis factor alpha; UCB-MSCs, umbilical cord blood-mesenchymal stem cells; VEGF, Vascular endothelial growth factor; WJ-MSCs, Wharton's jelly-mesenchymal stem cells.

derived myeloid angiogenic cells without increased inflammatory monocytes in the gut. Increased peptidoglycan-producing bacteria led to higher peptidoglycan and FABP-2 levels in diabetic human plasma, indicating systemic inflammation. Peptidoglycan activated a noncanonical TLR-2 signaling cascade in endothelial cells, leading to the disruption of p120-catenin and internal uptake of VE-cadherin, which caused ED. Administering bone marrow-derived myeloid angiogenic cells in diabetic mice decreased peptidoglycan biosynthesis genes, restored gut barrier integrity, and reduced systemic inflammation, mitigating ED.[169] These findings are relevant to hypertension as systemic inflammation and ED are key contributors to its pathogenesis, linking gut microbiota imbalances to vascular complications and elevated blood pressure.

In another study, HU-MSCs significantly reduced aortic plaque area in a high-fat diet rabbit model of atherosclerosis, indicating their potential to address hypertension by modulating gut microbiota. The treatment with human umbilical cord MSCs (UCSCs) ameliorates gut dysbiosis by normalizing the composition of the gut microbiota disrupted by a high-fat diet. It reduces levels of inflammatory cytokines such as IL-6 and TNF-α and raises anti-inflammatory molecules like IL-10 and TGF-β, thereby lowering systemic inflammation. Additionally, UCSCs down-regulate the gut microbiota-derived metabolite TMAO, which is associated with atherosclerosis, and improve peripheral blood flow, enhancing overall vascular health and mitigating the harmful effects of dysbiosis.[170]

Moreover, Lou et al. demonstrated that MSC intervention may reduce hypoxia-induced PH in mice by modulating gut microbiota equilibrium. In hypoxia-induced PH mice, gut microbiota disruptions included an augmented F/B ratio and elevated levels of harmful bacteria such as Marinifilaceae, Helicobacteraceae, and Lactobacillaceae, along with declined levels of beneficial bacteria like Bacteroidaceae, Prevotellaceae, Tannerellaceae, and Lachnospiraceae. MSC treatment reversed these changes, reducing harmful microbiota and increasing anti-inflammatory and immunomodulatory bacteria. Specific gut microbiota biomarkers associated with hypoxia-induced PH (Erysipelotrichaceae, Alphaproteobacteria) and MSC treatment (Micrococcales, Nesterenkonia) were identified. These findings suggest that MSC therapy alleviates PH by altering gut microbiota composition and metabolic pathways, linking gut microbiota modulation to hypertension management.[167]

In summary, gut microbiota significantly influences blood pressure regulation, and dysbiosis can lead to gut barrier dysfunction, resulting in systemic inflammation and ED, each of which plays a part in hypertension. Stem cells have an impact on both gut dysbiosis and ED, resulting in reduced high blood pressure. MSCs restore gut barrier integrity, modulate gut microbiota composition, and decrease harmful metabolites like TMOA reducing systemic inflammation. They also enhance endothelial function by promoting endothelial cell repair and regeneration, stabilizing cell junctions, and reducing apoptosis. Figure 3 demonstrates the hypothesized complex link between gut dysbiosis and ED. It illustrates how stem cells can positively affect both and highlights their synergistic potential in managing hypertension through multiple pathways.

Challenges and Future Directions

Despite the promising potential of stem cells in modulating gut microbiota and addressing hypertension, significant

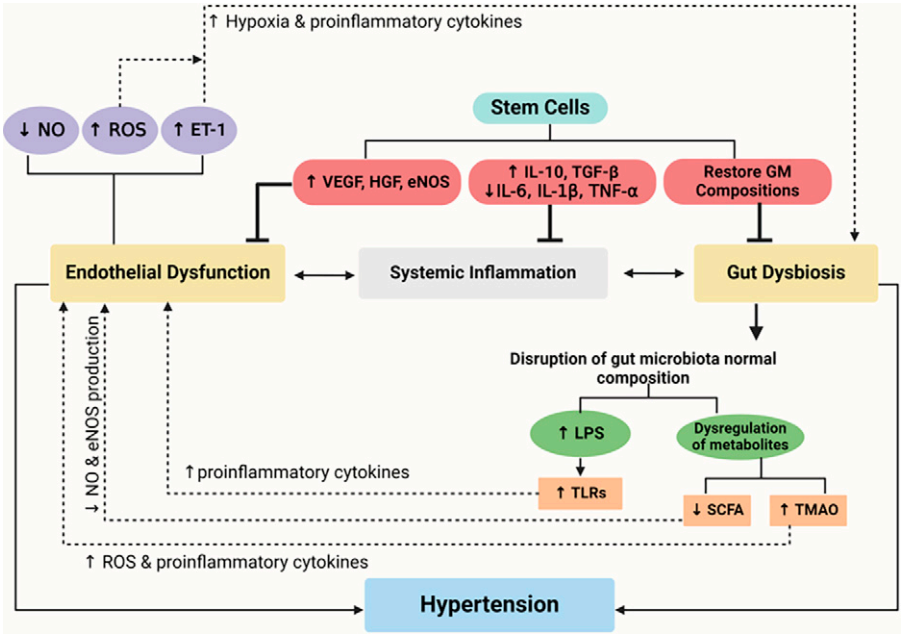

FIG. 3. The hypothesized complex link between gut dysbiosis and endothelial dysfunction and how stem cells can positively affect both. (→) activation, (⊤) inhibition (↔) bidirectional affect. eNOS, endothelial nitric oxide synthase; ET-1, endothelin-1; GM, gut microbiota; HGF, hepatocyte growth factor; IL-1β, interleukin 1 beta; IL-6, interleukin 6; NO, nitric oxide; ROS, reactive oxygen species; SCFA, short chain fatty acid; TGF-β, transforming growth factor-beta; TLRs, toll-like receptors; TMAO, trimethylamine N-oxide; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor. (Created with BioRender.com.)

challenges and future directions remain. One of the major difficulties is the intricacy of the gut microbiota and its function in hypertension, which requires detailed and longitudinal studies to fully understand how stem cells interact with and modulate the microbiome to influence blood pressure regulation.[171] A detailed mechanistic understanding is still lacking, requiring further research into the specific pathways involved. Variability in stem cell sources, such as bone marrow or umbilical cords, also affects therapeutic consistency, necessitating standardization.[172] Safety concerns, including potential tumorigenesis and immune reactions, further complicate the clinical application of stem cells, requiring extensive preclinical and clinical trials to ensure their safety and efficacy.[173–175] Regulatory barriers further complicate the translation of research findings into clinical practice, thereby slowing down the adoption of innovative stem cell therapies for hypertension.[28,176] Future directions for using stem cells to treat gut microbiota in the context of hypertension include personalized medicine approaches and leveraging advanced omics technologies for deeper insights. Personalized medicine can customize stem cell therapies based on individual genetic, environmental, and lifestyle factors, potentially improving therapeutic outcomes by providing more targeted and effective treatments. Advanced omics approaches, including genomics, proteomics, and metabolomics, can provide comprehensive data on the molecular mechanisms underlying hypertension and gut dysbiosis. These technologies aid in identifying new biomarkers and therapeutic targets, enhancing the precision and effectiveness of stem cell treatments. Various interventions, including stem cell therapy, dietary changes, probiotics, and FMT, could enhance therapeutic outcomes by addressing gut dysbiosis and potentially reducing hypertension. This combined strategy offers a promising approach for future research and clinical application, seeking a more thorough and effective management of hypertension through modifications in the gut microbiota.

Conclusion

Collectively, the complex connection between hypertension, gut microbiota, and stem cells presents a promising approach for new therapeutic strategies. The pathophysiology and global impact of hypertension underscore the need for novel interventions. Research has shown that gut microbiota significantly influence blood pressure regulation, and stem cells, with their regenerative and immunomodulatory potential, can impact both gut microbiota and blood vessels. Stem cells can restore microbial balance, improve gut barrier function, and repair damaged vessels, aiding in better blood pressure control. This interplay suggests a synergistic relationship that could inspire new treatments. Upcoming research should concentrate on elucidating the precise mechanisms of interaction between these elements and overcoming the challenges associated with translating preclinical findings into clinical practice. Understanding these dynamics will be crucial in developing targeted therapies that leverage the gut microbiota and stem cell interface to manage and treat hypertension more effectively. The integration of multidisciplinary approaches and advanced technologies will be vital in addressing these challenges and advancing this promising field.

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Availability of Data and Material

This review article synthesizes data and findings from previously published studies. No new data or materials were generated or analyzed in this study. All the datasets referenced in this article are publicly available and can be accessed through the original publications as cited in the article.

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