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Cardio-Hematopoietic Axis in Cardiac Injury and Repair: From Adaptation to Maladaptation

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ABSTRACT: The cardiovascular and hematopoietic systems are functionally interconnected through the cardio-hematopoietic axis, a dynamic signaling network that governs hematopoietic responses following cardiac injury. Traditionally viewed primarily as a unidirectional pathway in which cardiac damage mobilizes bone marrow–derived cells to facilitate myocardial repair, emerging evidence now suggests a bidirectional model wherein cardiac-derived cues reciprocally influence hematopoietic stem and progenitor cell fate decisions within the bone marrow niche. This review synthesizes current insights into the mechanistic crosstalk between the injured heart and bone marrow, highlighting the mechanisms by which myocardial injury activates emergency hematopoiesis and immune cell mobilization to support cardiac repair, as well as how cardiac-derived inflammatory and neurohumoral signals remodel the bone marrow niche and reprogram hematopoietic stem cell lineage commitment toward a myeloid-biased, proinflammatory output that amplifies systemic inflammation that contributes to increased cardiovascular risk.

Key Words: bone marrow ■ clonal hematopoiesis ■ hematopoietic stem cell ■ inflammation ■ stromal cells

The cardiovascular system and the hematopoietic system are closely connected through a dynamic communication network termed the cardio-hematopoietic axis. Whereas this network was previously conceptualized primarily as a unidirectional communication in which cardiac injury resulted in the mobilization of bone marrow–derived cells that home to the heart to initiate tissue repair, there is increasing evidence that suggests that the cardio-hematopoietic axis is bidirectional. This review explores the complex interactions between the heart and the bone marrow microenvironment in the setting of cardiac injury, focusing on 3 major themes: (1) myocardial tissue injury activates emergency hematopoiesis and immune cell trafficking to the heart that is essential for initiating myocardial repair; (2) cardiac-derived signals remodel the bone marrow niche and inform hematopoietic stem cell (HSC) lineage decisions; and (3) dysregulation of the bone marrow niche leads to persistent maladaptive innate immune memory in HSCs, and promotes the emergence of clonal hematopoiesis (CH), which is characterized by the abnormal expansion of blood cell clones bearing 1 or more somatic mutations within hematopoietic stem and progenitor cells, thereby contributing to chronic systemic inflammation and elevated cardiovascular risk.

Bone Marrow

The bone marrow is a specialized tissue located within the cavities of long bones, vertebrae, sternum, pelvis, and ribs. It comprises a complex architecture of stromal cells, extracellular matrix, and vascular networks that support hematopoiesis.[1,2] There are 2 main regions: the endosteal niche, adjacent to the inner bone surface, and the central (or perivascular) marrow, surrounding the sinusoidal blood vessels.

The marrow is highly vascularized, with a dual supply from nutrient arteries and periosteal capillaries forming a network of sinusoids that drain into central veins. These sinusoidal vessels are fenestrated, allowing for

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Nonstandard Abbreviations and Acronyms

C/EBPβ	CCAAT/enhancer-binding protein beta
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcomes Study
CCR2	C-C chemokine receptor 1
CH	clonal hematopoiesis
CXC	C-X-C motif chemokine ligand
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	C-X-C chemokine receptor type 4
H3K27ac	histone 3 at lysine 27
HSC	hematopoietic stem cell
HSPC	hematopoietic stem progenitor cell
IL	interleukin
LEPR	leptin receptor
SCF	stem cell factor
SNS	sympathetic nervous system
STAT	signal transducer and activator of transcription
TLR	toll-like receptor
TNF	tumor necrosis factor
VWF	von Willebrand Factor

Highlights

- Acute myocardial tissue injury activates emergency hematopoiesis and immune cell trafficking to the heart, which is essential for initiating myocardial repair. The activation of emergency hematopoiesis and immune cell trafficking to the heart is transient (1–2 weeks).
- Cardiac-derived signals remodel the bone marrow niche and inform hematopoietic stem cell lineage decisions.
- Both cardiac-derived signals and chronic sympathetic nervous system signaling can lead to dysregulation of the bone marrow niche, with persistent maladaptive trained innate immune memory in hematopoietic stem cells and the emergence of clonal hematopoiesis, thereby contributing to chronic systemic inflammation, cardiac dysfunction, and elevated cardiovascular risk.

the exchange of cells and factors between the marrow and circulation.[1] The proximity of hematopoietic cells to these vessels enables efficient trafficking of newly formed blood cells. Both myelinated and unmyelinated sympathetic and sensory fibers are distributed throughout the marrow, often in close association with arteries and arterioles, and their density can vary by bone and region within the marrow. These sympathetic nerve fibers enter the bone marrow alongside nutrient blood vessels, thereby providing extensive innervation of the bone marrow. Both sensory (afferent) and motor (efferent) sympathetic fibers are located near the bone marrow vasculature.[3] Sympathetic nerve fibers release a diverse array of signaling molecules, including catecholamines such as norepinephrine and dopamine, as well as various neuropeptides, neurotransmitters, and neurotrophic factors.[4] Sympathetic neurons form synaptic connections with perivascular stromal cells, and play a vital role in maintaining bone marrow homeostasis by regulating HSC quiescence and self-renewal (see below).[5] In contrast, the role of parasympathetic innervation in bone marrow remains less clearly defined. Recent studies suggest that certain sympathetic fibers may acquire the capacity to transmit cholinergic signals after birth. These fibers, which have been identified surrounding hematopoietic clusters in rat bone marrow, appear to act through α7-nicotinic receptors within the bone marrow environment.[6] Neuropeptides such as substance P, neuropeptide Y, and calcitonin gene-related peptide, released from sensory fibers, also play a regulatory role in hematopoiesis and immune modulation within the marrow microenvironment.[7] The sympathetic nervous system (SNS) mediates both acute responses during emergency hematopoiesis (see below), as well as chronically in the setting of heart failure. In chronic heart failure, heightened sympathetic activity has been linked to bone marrow abnormalities, including impaired hematopoietic progenitor cell function, diminished clonogenic potential across erythroid, myeloid, and lymphoid lineages, increased progenitor cell apoptosis, and remodeling of the bone marrow microenvironment toward a catabolic state favoring increased bone reabsorption. The severity of bone marrow dysfunction correlates with the clinical and biochemical severity of heart failure, independent of anemia status.[8,9]

Hematopoiesis

Hematopoiesis is the process by which blood cells are generated from a small pool of multipotent stem and progenitor cells. In humans, hematopoiesis is initiated in the yolk sac, subsequently transitions to the aorta-gonad-mesonephros region, and then shifts to the placenta, fetal liver, and spleen, before localizing to the diaphyseal region of the bone marrow at ≈10.5 weeks of gestation, with hematopoietic activity becoming more established and widespread by 12 weeks.[10] Single-cell RNA sequencing and functional assays confirm that functional HSCs capable of long-term, multilineage reconstitution are present in the fetal bone marrow by week 12 post-conception. HSCs possess both self-renewal capacity and multilineage differentiation potential. HSCs give rise to multipotent progenitors, which lack self-renewal but retain the ability to differentiate into all myeloid and lymphoid blood cell types (reviewed in[1]).

HSCs and lineage-restricted hematopoietic stem progenitor cells (HSPCs) occupy specialized and spatially distinct microenvironments within the bone marrow, referred to as niches. Insofar as this topic has been thoroughly covered in prior reviews ([1,10–12]), it is summarized here only briefly to provide context for the discussion that follows. Briefly, HSCs are predominantly localized adjacent to sinusoidal vasculature throughout the marrow cavity,[13] where endothelial cells and stromal populations, including periarteriolar nestin–GFP^{high} cells, CXCL12 (C-X-C motif chemokine ligand 12)-abundant reticular cells, LEPR (leptin receptor)–positive stromal cells, NG2-expressing pericytes, MYH11+ smooth muscle cells, perisinusoidal nestin–GFP^{low} cells support HSC quiescence and self-renewal by producing key factors, such as SCF (stem cell factor),[14] CXCL12,[15] and other regulatory signals (Figure 1).[1,12,18] SCF is produced primarily by mesenchymal stromal cells and endothelial cells, and is critical for HSC survival and self-renewal within the niche.[19] CXCL12, also known as stromal cell-derived factor-1, is abundantly secreted by CXCL12-abundant reticular cells and other niche stromal cells.[20] CXCL12 acts through its receptor, CXCR4 (C-X-C chemokine receptor type 4), on HSCs to mediate their retention, localization, and quiescence within the bone marrow microenvironment. Deletion of CXCL12 from perivascular niche cells disrupts HSC localization and reduces HSC numbers, while CXCL12 gradients direct HSC homing and retention in the niche.[20] CXCL12 is also critical for the maintenance of lymphoid-biased HSCs and supports B-lineage differentiation.[10] Osteoblasts have also been linked to HSC regulation, particularly of lymphoid progenitors, although their precise molecular contributions remain unclear. By contrast, adipocytes may exert inhibitory effects on HSC maintenance.[12] Distinct spatial niches have been described for different HSC subtypes: platelet- or myeloid-biased VWF (von Willebrand Factor)–GFP$^+$ HSCs are often found near megakaryocytes,

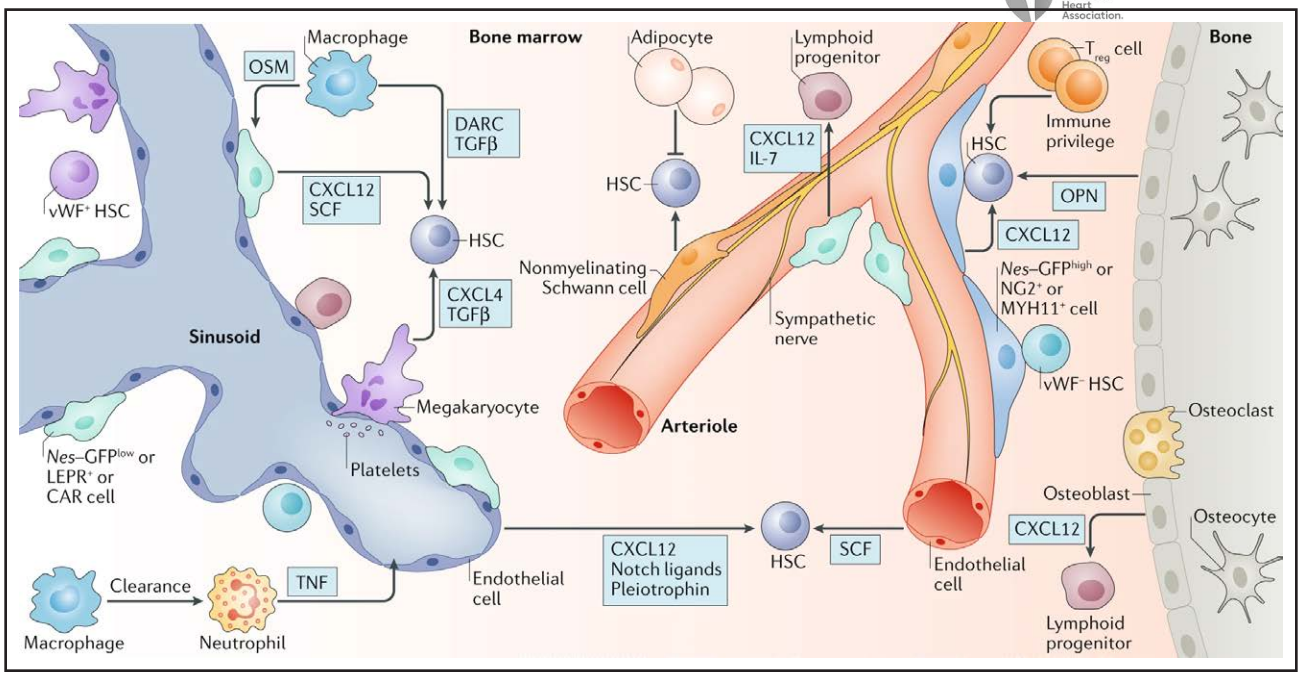

Figure 1. The hematopoietic stem cell niche under homeostatic conditions.
The bone marrow niche constitutes a tightly coordinated microenvironment in which hematopoietic and nonhematopoietic cells interact to govern hematopoietic stem cell (HSC) maintenance, self-renewal, and differentiation. As shown, the vascular network and its stromal populations, including periarteriolar nestin (Nes)–GFP^{high} cells, NG2-expressing pericytes, MYH11+ smooth muscle cells, perisinusoidal Nes–GFP^{low} cells, CXCL12-abundant reticular (CAR) cells, and LEPR (leptin receptor)–positive stromal cells, play an important role in sustaining HSC maintenance. Nes-GFP^{high} and Nes-GFP^{low} cells refer to 2 populations of Nes-expressing cells identified in Nestin-GFP (green fluorescent protein) transgenic reporter mice, which were engineered to express GFP under the control of the Nestin promoter. These populations help distinguish key stromal and perivascular cell subsets that regulate HSCs.[16] Sympathetic nerve fibers modulate HSC mobilization, while nonmyelinating Schwann cells are thought to help preserve HSC quiescence. Osteoblasts have also been linked to HSC regulation, particularly of lymphoid progenitors, although their precise molecular contributions remain unclear. By contrast, adipocytes may exert inhibitory effects on HSC maintenance. Several hematopoietic progeny–including macrophages, neutrophils, regulatory T (Treg) cells, and megakaryocytes–can provide feedback signals that influence HSC retention or release. Distinct spatial niches have been described for different HSC subtypes: platelet- or myeloid-biased VWF (von Willebrand Factor)–GFP$^+$ HSCs are often found near megakaryocytes, whereas VWF–GFP$^-$ HSCs are more commonly associated with arteriolar regions. The terms VWF-GFP$^-$ and VWF-GFP$^+$ refer to 2 subpopulations of HSCs distinguished by expression of a VWF promoter–driven GFP reporter.[17] Key regulatory factors in these microenvironments include Duffy antigen receptor for chemokines (DARC), IL (interleukin)-7, OPN (osteopontin), OSM (oncostatin M), SCF (stem cell factor), TGFβ (transforming growth factor-β), and TNF (tumor necrosis factor). Reprinted from Pinho et al[12] with permission. Copyright ©2019, Springer Nature BV.

whereas VWF-GFP^{-} HSCs are more commonly associated with arteriolar regions.[12]

HSC quiescence is important for preserving hematopoietic homeostasis, insofar as quiescence preserves the long-term self-renewal capacity of HSCs and prevents functional exhaustion. In adults, HSCs replicate on average once every 40 weeks (range, 25–50 weeks depending on age), which is ≈1.3× per year.[21] Quiescent HSCs are protected from accumulating DNA damage and cellular stress that can occur during repeated cell division, thereby maintaining the integrity of the stem cell pool over the lifetime of an individual. Loss of quiescence leads to increased proliferation, which can result in HSC depletion, impaired hematopoiesis, and increased risk of developing CH or malignant transformation.[22,23] Additional regulators of HSC homeostasis include sympathetic adrenergic fibers,[5,7] nonmyelinating Schwann cells,[24] resident macrophages,[25] and osteoclasts.[26] Components of the extracellular matrix[27] and ionic factors such as calcium[28] further modulate HSC behavior.

The microenvironment of the bone marrow niche exerts extrinsic control over HSCs through cell-cell interactions, secreted factors, and metabolic cues that can lead to long-lasting epigenetic changes in HSCs and progenitor cells. For example, mesenchymal stromal cells, osteoblasts, and endothelial cells within the niche secrete cytokines and growth factors that activate signaling pathways in HSCs, leading to the recruitment of epigenetic modifiers (eg, DNA methyltransferases, histone deacetylases) to specific chromatin regulatory sites. This results in the maintenance of HSC quiescence or the induction of differentiation depending on the physiological context. Additionally, metabolic changes in the niche, such as hypoxia, can alter the activity of epigenetic regulators, further influencing HSC fate.

HSCs and HSPCs continuously circulate at low levels in peripheral blood, and their numbers rise in response to physiological or pharmacological stimuli. After egress, these cells can home back to the bone marrow, which is critical for maintaining hematopoietic homeostasis. Homing is mediated by specific interactions between chemokines (notably CXCL12) and their receptors, as well as adhesion molecules and the bone marrow microenvironment.[29] Although activated T and B cells are also known to return to the bone marrow and form long-lived memory populations, their potential involvement in cardio-hematopoietic interactions has not been clearly established at the time of this writing.[30,31]

The Cardio-Hematopoietic Axis in Acute Myocardial Injury

The initial response of the heart to tissue injury is characterized by the rapid activation of cardiac-specific innate immune responses, as well as by the rapid mobilization of bone marrow-derived neutrophils and monocytes that home to the heart to facilitate myocardial repair and restore tissue homeostasis. Typically, this acute response occurs over hours to days, whereas chronic responses evolve over weeks to months. Given that the topic of emergency hematopoiesis has been extensively discussed elsewhere (reviewed in[1,32–35]), it is addressed here only briefly to provide a framework for the subsequent discussion. Although we focus here on the canonical acute ischemic injury models that have been studied for innate immune responses in the heart, it is important to recognize other forms of myocardial injury. Including pressure overload, neurohormonal activation, and infection (eg, viral myocarditis), also elicit similar, evolutionarily conserved innate immune responses.[36]

Following acute myocardial tissue injury, necrotic cardiac myocytes and degraded extracellular matrix proteins release danger-associated molecular patterns, which in turn activate TLRs (toll-like receptors) on multiple cell types in the heart, including cardiac myocytes.[36] This triggers de novo synthesis and release of proinflammatory cytokines (eg, TNF [tumor necrosis factor], IL-1β [interleukin-1β], IL-6 [interleukin-6]) and chemokines (eg, monocyte chemoattractant protein-1 [CCL2] and CXCL12) that facilitate recruitment of immune cells to the heart.[34,37] The release of danger-associated molecular patterns also activates the complement system by binding to complement pattern recognition molecules (eg, C1q and mannose-binding lectin), which in turn initiate the classical and lectin complement activation pathways, which further amplify the inflammatory signal.[38]

During the early phase following myocardial injury, substantial numbers of neutrophils and proinflammatory CCR2^{+} (C-C chemokine receptor 1) Ly6C^{hi} monocytes are rapidly recruited to the damaged myocardium, where the infiltrating monocytes differentiate into macrophage subsets characterized by robust phagocytic capacity and elevated proteolytic activity, which facilitates the clearance of necrotic debris and matrix remodeling. Neutrophil numbers decline after 3 days and are largely absent by 1 week, whereas CCR2^{+} monocyte recruitment continues for several days. By day 4, the initial inflammatory phase begins to transition to a reparative healing phase with rapidly decreasing neutrophil numbers and a phenotypic switching of CCR2^{+} monocyte-derived macrophages towards a reparative CCR2- Ly6C^{low} phenotype.[39]

In response to myocardial tissue injury, bone marrow HSCs exit their quiescent state and initiate emergency hematopoiesis, a stress-induced process characterized by accelerated proliferation and myeloid-lineage differentiation that results in the enhanced production and mobilization of neutrophils and CCR2^{+} monocytes.[1,32] This homeostatic adaptive response ensures rapid replenishment of mature myeloid effector cells that are consumed during the acute immune response to tissue injury. The reprogramming of the bone marrow niche is driven, in part, by activation of the SNS,[5] along with

the direct and indirect sensing of danger-associated molecular patterns, reactive oxygen species, and inflammatory cytokines secreted by stromal cells, endothelial cells, and HSPCs in the niche.[1] The molecular pathways that are activated in the bone marrow microenvironment are mediated by TLRs, NF-κB activation, STAT (signal transducer and activator of transcription), and C/EBPβ (CCAAT/enhancer-binding protein beta) signaling.[40] The SNS plays an important role in coordinating the immediate response to myocardial injury, through cardiac sympathetic afferent fibers that are activated by molecules released during tissue injury (bradykinin, adenosine, and reactive oxygen species), as well as by myocardial stretch. These afferent signals are integrated in the nucleus tractus solitarius of the medulla oblongata, leading to increased sympathetic efferent activation of the bone marrow (reviewed in Maestroni et al).[5] SNS activation releases norepinephrine from nerve terminals in the bone marrow niche that binds to β_3-adrenergic receptors on perivascular cells, decreasing CXCL12 levels in the niche, which leads to increased HSC proliferation, enhanced myelopoiesis, and mobilization of myeloid cells.[5,16]

The spleen serves as an important site for extramedullary hematopoiesis during cardiac injury and repair. Experimental and clinical data demonstrate that splenic extramedullary hematopoiesis is upregulated following myocardial infarction and in chronic atherosclerosis, with the spleen acting as a reservoir and production site for inflammatory leukocytes that exacerbate cardiac inflammation and tissue remodeling.[41] Inhibition of splenic extramedullary hematopoiesis in animal models reduces leukocytosis and limits inflammatory cell infiltration into the heart and vasculature, supporting a causal role for splenic extramedullary hematopoiesis in sustaining chronic inflammation in cardiac disease. Together, these observations suggest that the spleen is an ancillary site for emergency hematopoiesis that supplements bone marrow output by generating myeloid progenitors and mature immune cells.

Under normal homeostatic conditions, emergency hematopoiesis is a tightly regulated process that is carefully timed to ensure a rapid but controlled immune response to initiate and facilitate cardiac repair. The factors that lead to quiescence of the bone marrow following an acute myocardial infarction are primarily the result of negative feedback from inflammatory cytokines, functional exhaustion and impaired clonogenic potential of bone marrow progenitor cells, and transcriptional reprogramming of the bone marrow microenvironment that is orchestrated by a coordinated decrease in inflammatory signals, upregulation of anti-inflammatory and pro-resolving signaling pathways, and restoration of niche retention signals, which allows the HSC pool to return to quiescence and steady-state hematopoiesis.

Maladaptive Changes in the Cardio-Hematopoietic Axis in Response to Cardiac Injury

Recent studies have highlighted the importance of the bidirectional nature of the cardio-hematopoietic axis, whereby cardiovascular injury reprograms the bone marrow niche, disrupts the homeostatic equilibrium between HSC self-renewal and differentiation, and promotes myeloid-biased hematopoiesis that contributes to residual systemic inflammation and increased cardiovascular risk. Many of the same stimuli that trigger acute emergency myelopoiesis (eg, danger-associated molecular patterns, exosomes, proinflammatory cytokines) can also lead to functional reprogramming of stromal cells, endothelial cells, and HSCs in the bone marrow niche, with potential long-term effects on immune cell memory and functionality, as well as the development of CH of indeterminate potential.[42]

Trained innate immunity refers to the long-lasting functional reprogramming of innate immune cells triggered by a brief external or internal stressor. This reprogramming alters the response of the innate immune system to a subsequent second challenge, either amplifying the response (priming and trained immunity) or dampening the response (innate immune tolerance).[43] Importantly, trained immunity is devoid of specificity and can be triggered by the same (homologous) or different (heterologous) stimuli. Although gene expression profiles typically return to baseline between exposures, trained immunity is maintained by metabolic reprogramming and epigenetic modifications that lead to chromatin unfolding of enhancer and promoter regions of immune-related genes.[43] This distinguishes trained immunity from immune priming, where gene transcription remains elevated after the initial stimulus and the second challenge amplifies the first response, or cell differentiation, in which an immature immune cell undergoes functional programming leading to long-term changes in cell morphology and function (Figure 2).[44] At the time of this writing, it remains unclear whether the myeloid-biased hematopoiesis that sustains residual systemic inflammation arises from immune priming, trained immunity, or a combination of both processes. Immune training can occur centrally within the bone marrow, where HSPCs and innate immune progenitor cells undergo long-term epigenetic and metabolic reprogramming after exposure to exogenous or endogenous ligands. Training of mature immune cells can also occur peripherally, when circulating monocytes or tissue macrophages are exposed to stimuli in their environment (Figure 3).[45]

The epigenetic reprogramming that establishes innate immune memory involves alterations in DNA methylation, changes in chromatin accessibility, and context-specific histone modifications (eg, acetylation, methylation) at regulatory regions that control HSC quiescence,

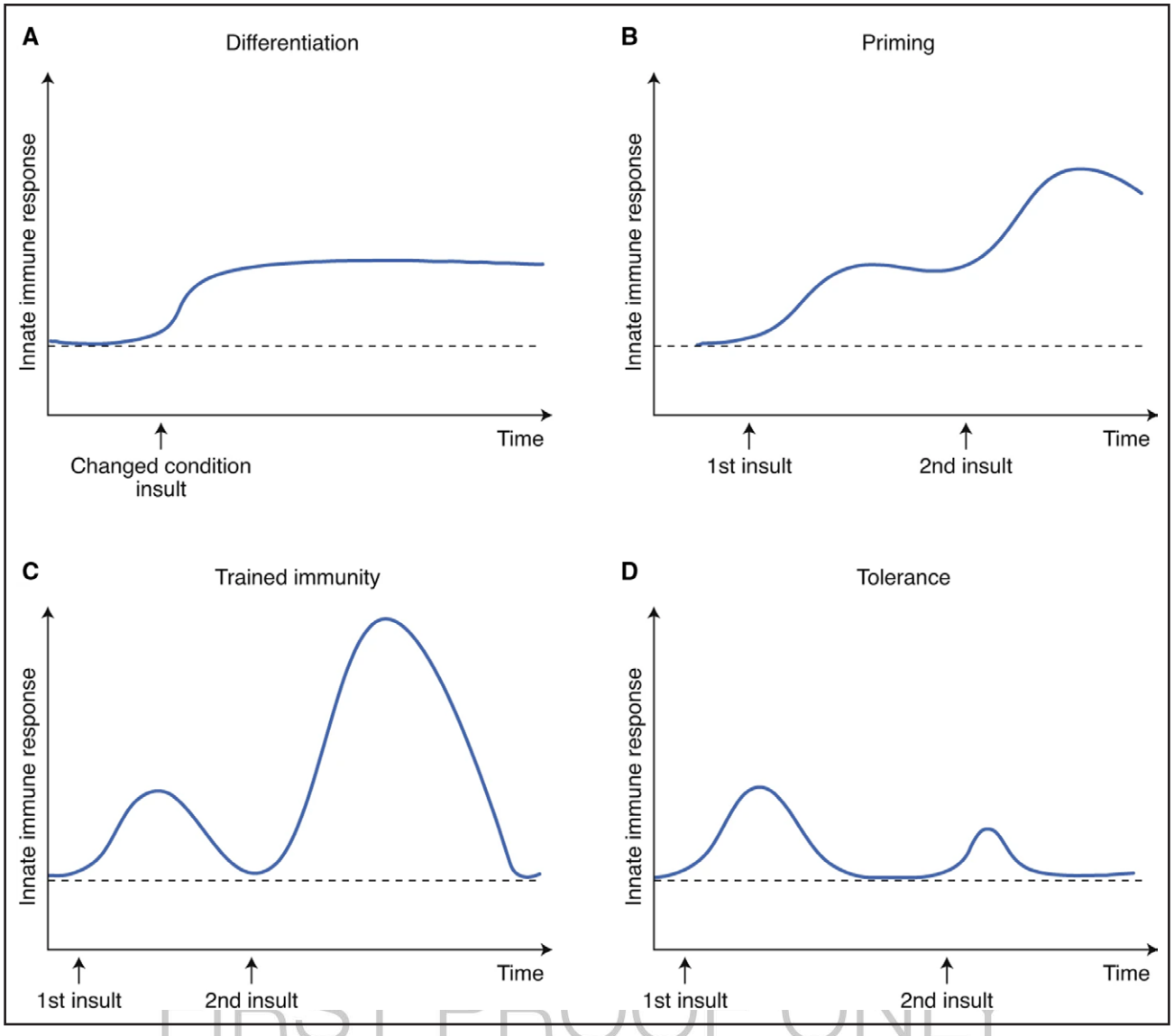

Figure 2. Innate immune responses during different adaptive programs are induced in innate immune cells.
A, Differentiation. **B**, Priming. **C**, Trained immunity (innate immune memory). **D**, Tolerance. Reproduced with permission from Divangahi et al[44] with permission. Copyright ©2021, Springer Nature BV.

self-renewal, and lineage commitment. The most well-established epigenetic marks include increased trimethylation of histone 3 at lysine 4 (H3K4me3) at promoters of key proinflammatory genes such as *IL-1β*, *IL-6*, and *TNF*, which is associated with open chromatin and increased gene transcription, and increased acetylation of H3K27ac (histone 3 at lysine 27), which further promotes chromatin accessibility and transcriptional readiness.[44,46] Emerging evidence also implicates histone lactylation, particularly H3K18la, as a stable epigenetic mark that links immunometabolic shifts, such as increased glycolytic flux and lactate accumulation, to long-term transcriptional memory.[47] Metabolite-driven modulation of histone-modifying enzymes by intermediates such as fumarate and lactate provided a mechanistic link between changes in metabolism with the changes in chromatin architecture that are responsible for the trained innate immune response. Notably, these epigenetic marks persist long after the initial stimulus, which explains the durability of the trained phenotype. DNA methylation changes in trained innate immunity typically involve promoter-specific hypomethylation at key inflammatory loci, which allows access of transcription factors (eg, NF-κB, AP-1, STATs) that lead facilitate the sustained expression of proinflammatory genes. Long noncoding RNAs function as molecular scaffolds that recruit and spatially organize chromatin-modifying enzymes, including histone acetyltransferases, deacetylases, methyltransferases, and ATP-dependent remodelers, thereby facilitating targeted alterations in chromatin structure and DNA accessibility through histone modification and nucleosome repositioning.[48] Monocytes and

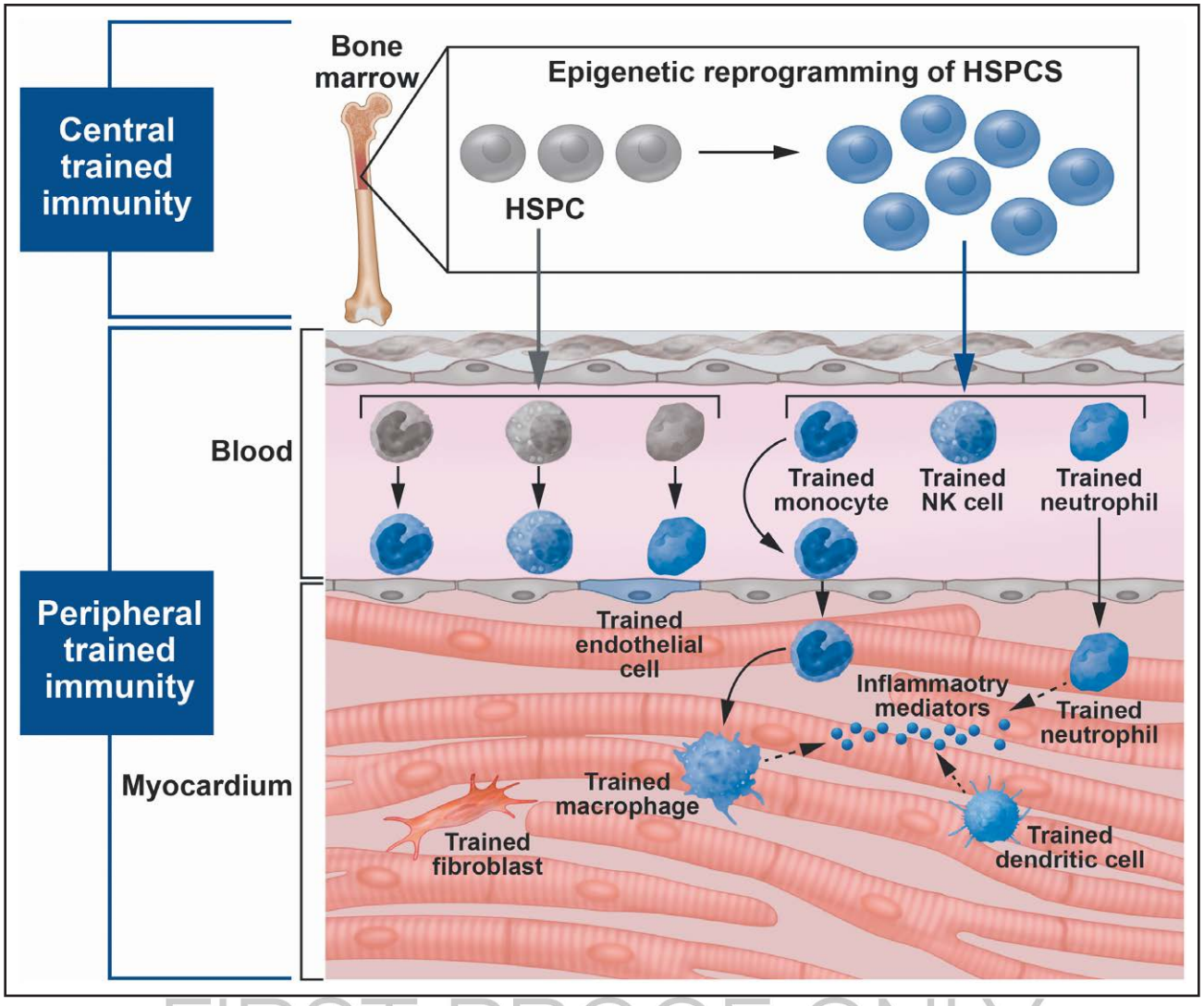

Figure 3. Central and peripheral trained immunity and Inflammation in cardiovascular disease.
Trained immunity may be initiated centrally within the bone marrow through the epigenetic and metabolic reprogramming of hematopoietic stem (HSC) and progenitor cells (HSPCs) in the bone marrow niche. The epigenetic reprogramming of the HSCs and HSPCs generates a pool of proinflammatory neutrophils, monocytes, and natural killer (NK) cells that have an enhanced inflammatory phenotype. These trained myeloid and NK cells are released from the bone marrow into the peripheral circulation and can infiltrate the arterial vessel wall as well as the myocardium, thereby expanding the pool of cardiac immune cells that have heightened inflammatory responses. Trained immunity can also be induced in circulating immune cells or cardiac resident cells, including macrophages, endothelial cells, and vascular smooth muscle cells, which can also undergo functional reprogramming to perpetuate systemic and myocardial Inflammation.

macrophages are the prototypical innate immune cells in which trained immunity has been most extensively characterized; however, other cell types, including natural killer cells, dendritic cells, neutrophils, endothelial cells, fibroblasts, and even HSCs, can also acquire a trained phenotype.[49]

The importance of central trained immune responses was demonstrated in a recent experimental study, in which the bone marrow from mice that had undergone transaortic constriction was transplanted into naive mice, leading to spontaneous cardiac remodeling, LV dysfunction, myocardial fibrosis, and increased susceptibility to injury in skeletal muscle and the kidneys in the naive mice.[50] Bone marrow HSCs from transaortic constriction mice exhibited increased skewing toward proinflammatory monocytes and macrophages, suggesting that epigenetic reprogramming of HSPCs alone is sufficient to provoke a heart failure phenotype.[51] In addition to directly causing myocardial tissue injury, the SNS can trigger the proliferation and mobilization of HSPCs with enhanced myelopoietic activity. In murine models subjected to environmental stress, augmented SNS activity suppressed CXCL12 expression within the HSC niche, resulting in enhanced HSC proliferation, increased myelopoiesis, and elevated production of neutrophils and monocytes. This signaling cascade facilitated the mobilization of inflammatory leukocytes into the peripheral circulation, thereby aggravating vascular

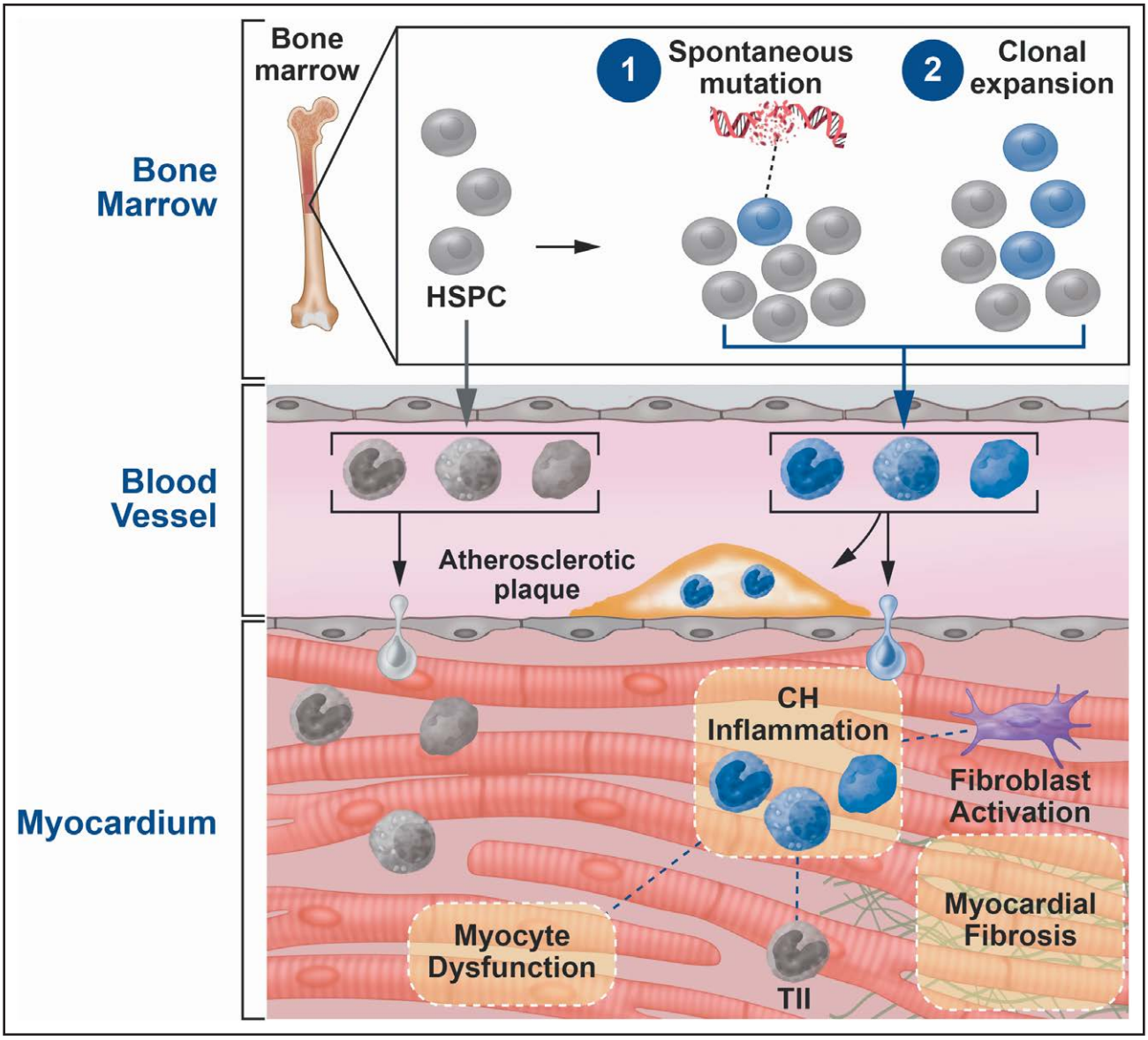

Figure 4. Clonal hematopoiesis (CH) and cardiovascular disease.
Hematopoietic stem cells (HSCs) that harbor certain somatic driver mutations gain a fitness advantage in the bone marrow niche that allows them to expand clonally. Proinflammatory immune cells derived from mutated myeloid precursors enter the circulation, where they can infiltrate atherosclerotic plaques in the coronary vasculature, thereby exacerbating atherosclerosis, or migrate into the myocardium, where the proinflammatory immune cells contribute to cardiomyocyte dysfunction, cell death, fibroblast activation, and myocardial Inflammation. CH can also contribute to central and peripheral trained immune responses through cell-cell interactions. This can further exacerbate vascular Inflammation, atherosclerotic plaque destabilization, myocyte dysfunction, myocardial fibrosis, and adverse cardiac remodeling. TII indicates trained innate immunity.

plaque inflammation in apolipoprotein E–deficient mice (*ApoE*$^{-/-}$). Remarkably, treatment with a β3-adrenergic receptor antagonist attenuated disease progression, highlighting the importance of sustained sympathetic signaling and disrupting the CXCL12-CXCR4 signaling axis in the bone marrow niche.[52] After acute myocardial infarction, cardiomyocyte-derived exosomes are preferentially taken up by bone marrow mononuclear cells, where they downregulate CXCR4 expression, resulting in the mobilization of bone marrow progenitor cells into the peripheral circulation.[53] Although the process of recruiting bone marrow-derived hematopoietic cells to the heart is essential for initial tissue repair, excessive or prolonged recruitment of inflammatory cells can exacerbate tissue damage, promote fibrosis, and drive adverse cardiac remodeling, ultimately increasing the risk of incident heart failure. In addition to cardiac injury. Ischemic stroke provokes a sustained proinflammatory response across multiple organ systems through the induction of innate immune memory.[54] This study identified IL-1β–driven epigenetic reprogramming within the myeloid as the mechanism responsible for the development of

cardiac fibrosis and diastolic dysfunction following cerebral ischemic injury.[54]

A second cardiovascular consequence of sustained inflammation and disruption of the bone marrow microenvironment following cardiovascular injury is the emergence of CH. James DeGregori and colleagues proposed that the development of tumors (oncogenesis) was driven not only by the accumulation of gene mutations in cells, but also by changes in the tissue microenvironment that altered the selective pressures on cells, favoring the expansion of mutant clones that were better adapted to the altered environment, which the authors termed adaptive oncogenesis.[55] This evolutionary framework is also germane to the development of CH in cardiovascular disease, wherein tissue injury caused by ischemic damage, hemodynamic pressure overload (eg, hypertension), or chronic metabolic stress (eg, diabetes, obesity) alters the bone marrow microenvironment and hematopoietic regulatory networks leading to the development of CH.[56]

Whereas normal HSCs are susceptible to exhaustion (ie, functional decline and loss of regenerative capability) or apoptosis when exposed to inflammatory cytokines (eg, IFN-γ, TNF, IL-6), HSCs harboring specific somatic driver mutations gain a fitness advantage that allows them to undergo clonal expansion within the dysregulated proinflammatory milieu of the niche. Furthermore, the proinflammatory milieu within the bone marrow niche not only facilitates the initial expansion of mutant clones but also establishes a self-amplifying mechanism whereby sustained myelopoiesis and elevated proinflammatory cytokine drive the further expansion of additional mutant clones, while also potentiating central and peripheral trained immune responses that contribute to vascular inflammation, plaque destabilization, and adverse cardiac remodeling.[45] Additionally, recent studies of CH in human heart failure suggest that paracrine signaling occurs between mutant and wild-type monocytes and T cells that would be expected to amplify and expand inflammatory signaling networks among cardiac resident immune cells.[56]

Clinical studies have shown that CH is independently linked to increased cardiovascular risk, including increased risk of coronary artery disease, myocardial infarction, ischemic stroke, heart failure with preserved and reduced ejection fraction, arrhythmias, and increased cardiovascular mortality (reviewed in Kallikourdis et al).[57] CH is also associated with a higher incidence of type 2 diabetes and cardiometabolic disease.[58] The most common CH driver mutations associated with increased risk for cardiovascular disease occur in genes involved in epigenetic regulation (*ASXL1*), DNA methylation (*TET2, DNMT3A*), and inflammatory signaling (*JAK2*).[57] The adverse effects of CH on cardiovascular outcomes likely involve both systemic paracrine effects that contribute to low-grade systemic inflammation, as well as local tissue effects that are secondary to the infiltration of myeloid cells derived from HSPs that harbor proinflammatory driver mutations. Murine studies have demonstrated that genetic deletion of *Tet2* in bone marrow–derived cells increased NLRP3 inflammasome activity and systemic IL-1β levels, fostering increased plaque formation and instability in atherosclerotic models.[59] Similar systemic inflammatory effects have been implicated in the progression of heart failure, where mutant clones amplify neurohumoral stress and endothelial dysfunction, predisposing the myocardium to adverse remodeling.[45,60] There is also compelling evidence that monocytes and macrophages with CH driver mutations are actively recruited to sites of vascular and myocardial injury, where they can exert local effects. For example, after myocardial infarction or pressure overload, *Tet2*-deficient macrophages accumulate within the heart and vasculature, promoting local inflammasome activation, leading to fibrosis, adverse cardiac remodeling, and worsening LV function.[61] Viewed together, these findings suggest a feed-forward (ie, self-reinforcing) mechanism for cardiovascular disease wherein inflammatory cells derived from CH clones drive cardiovascular disease through systemic paracrine effects, as well as by directly infiltrating atherosclerotic plaques, leading to increased coronary events and strokes that in turn promote adverse cardiac remodeling and LV dysfunction. The clinical relevance of these findings is underscored by the results of a subset analysis of the CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), in which patients harboring TET2 mutations who were receiving canakinumab had a reduced risk of nonfatal myocardial stroke, nonfatal stroke, and CV death when compared with placebo-treated controls.[62]

Therapeutic Implications

A deeper appreciation of the complexities of the cardiohematopoietic signaling axis may provide a roadmap for developing new therapies to prevent and treat cardiovascular disease, including strategies that target maladaptive trained innate immune responses, as well as CH. Current therapeutic approaches under development to treat maladaptive trained innate immunity focus on reversing or modulating the epigenetic and metabolic reprogramming that is responsible for the persistent proinflammatory state of innate immune cells. The most promising strategies include but are not limited to (1) cytokine pathway inhibitors (eg, IL-1β)[63]; (2) small molecule inhibitors of histone-modifying enzymes (eg, histone methyltransferases or deacetylases) to reverse maladaptive epigenetic marks (reviewed in Tough et al[64]); and (3) modulating immunometabolism using small molecule inhibitors that interfere with key metabolic pathways such as glycolysis, the mevalonate pathway, and glutaminolysis (reviewed in Mulder et al[65]). However, at the time of this writing, the in vivo application of agents that suppress trained immunity remains limited by challenges such as systemic toxicity,

immune-mediated side effects, and insufficient bioavailability at sites where myeloid cells and their progenitors reside. It should also be remembered that trained immunity plays a critical role in host defense. Although inhibition of IL-1β in the CANTOS trial improved outcomes in patients with high risk of cardiovascular disease, the incidence of infection-related adverse events, although low overall, was increased ≈1.7-fold in the canakinumab treatment arm (0.31 versus 0.18 events per 100 person-year; $P<0.02$).[63] To overcome some of the limitations associated with conventional approaches, emerging strategies are focusing on the development of antibody-based therapies, RNA interference molecules, and advanced nano-immunotherapeutic platforms designed to deliver trained immune inhibitors to HSPCs residing in the bone marrow microenvironment.[65]

There are currently no disease-modifying therapies specifically indicated for patients with CH. The mainstay of management is observation and risk factor modification. The clinical consensus is that individuals with CH should undergo regular monitoring for hematologic progression (eg, development of cytopenia or overt hematologic malignancy) and aggressive management of modifiable cardiovascular risk factors, given the increased risk of both hematologic neoplasms and cardiovascular disease associated with CH. Preclinical and early translational studies suggest that anti-inflammatory therapies (eg, cytokine antagonists [IL-1β and IL-6], NLRP3 inflammasome inhibitors), interventions targeting specific mutant clones (eg, *TET2* and *JAK2* mutations), or lifestyle interventions associated with reducing CH expansion may have future therapeutic potential. However, at present, these approaches remain investigational and are not part of standard care.

Finally, biomarkers of bone marrow activity, trained immunity, or CH could serve as predictors of cardiovascular outcomes and guide personalized therapy. Circulating cell-free DNA, single-cell RNA sequencing of peripheral blood, or advanced imaging of hematopoietic organs may allow real-time assessment of the hematopoietic axis in humans.

CONCLUSIONS

The cardio-hematopoietic axis constitutes a critical bidirectional homeostatic network that modulates adaptive healing responses in the heart following tissue injury. Myocardial injury activates the mobilization of bone marrow–derived immune cells, initiating physiological inflammatory cascades that are necessary for effective tissue repair. However, the same injury-associated inflammatory signals can also remodel the bone marrow niche, epigenetically reprogram HSCs, and establish a long-lasting trained immune response in the bone marrow niche that has context-dependent consequences. That is, whereas trained immunity enhances host defenses against recurrent infections and, in some settings, tolerizes (ie, protects) the heart against recurrent injury,[66] long-lasting trained immunity of HSPCs in the bone marrow is also associated with increased myelopoiesis and enhanced numbers of circulating myeloid cells with heightened inflammatory responses, as well as the development of CH. Importantly, myeloid-biased HSCs also generate fewer lymphoid progeny with reduced lymphopoiesis, leading to diminished host adaptive immune responses. Moreover, the maladaptive trained innate immune state may also provide a mechanistic link between cardiometabolic disorders such as obesity and type 2 diabetes and the heightened risk of cardiovascular disease. Sustained immune memory in stromal cells in the bone marrow niche and HSCs may also lead to enhanced CH that promotes increased cardiovascular disease, chronic inflammatory disorders, type 2 diabetes, as well as the potential for progression to hematologic malignancies in a minority of patients. The evidence in support of Inflammation as a driver or innate immune training of HSCs within the bone marrow microenvironment in the context of previous ischemic cardiac injury and residual low-level Inflammation is supported by the CANTOS trial, in which IL-1β inhibition with canakinumab reduced atherosclerotic events,[63] heart failure events,[67] as well as incident lung cancer and lung cancer mortality in patients with a prior myocardial infarction.[56]

Current Gaps in the Field

A more comprehensive understanding of the cardio-hematopoietic axis and the adaptation of HSCs within the bone marrow niche in response to proinflammatory stimuli triggered by cardiac injury has the potential to transform our therapeutic approach to treating cardiovascular disease. As the field moves forward, integrating insights from basic research in cardioimmunology coupled with insights from cardiovascular clinical trials in concert with hematology and stem cell biology research and systems biology will be essential to fully elucidate the complex biologic interaction networks between the heart and other organ systems (eg, kidney, liver, gut) with the hematopoietic system in health and disease.

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