

Skeletal muscle inflammation and atrophy in heart failure

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Published online: 14 January 2017
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Abstract Heart failure represents a systemic disease with profound effects on multiple peripheral tissues including skeletal muscle. Within the context of heart failure, perturbations in skeletal muscle physiology, structure, and function strongly contribute to exercise intolerance and the morbidity of this devastating disease. There is growing evidence that chronic heart failure imparts specific pathological changes within skeletal muscle beds resulting in muscle dysfunction and tissue atrophy. Mechanistically, systemic and local inflammatory responses drive critical aspects of this pathology. In this review, we will discuss pathological mechanisms that drive skeletal muscle inflammation and highlight emerging roles for distinct innate immune subsets that reside within damage muscle tissue focusing on the recently described embryonic and monocyte-derived macrophage lineages. Within this context, we will discuss how immune mechanisms can be differentially targeted to stimulate skeletal muscle inflammation, catabolism, fiber atrophy, and regeneration.

Keywords Macrophage · Heart failure · Skeletal muscle · Inflammation

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Skeletal muscle myopathy and inflammation It is now recognized that heart failure is a systemic disease with profound effects on multiple peripheral tissues including skeletal muscle. Several clinical studies have convincingly demonstrated that impairments in skeletal muscle physiology and function are largely responsible for exercise intolerance in patients with chronic systolic heart failure. Structurally, cachexia and skeletal muscle atrophy represent important comorbidities associated with poor prognosis [2]. Within the chronic heart failure population, skeletal muscle atrophy and intrinsic reductions in oxidative metabolism are tightly associated with reduced exercise capacity [55]. Patients with chronic heart failure not only have smaller peripheral muscle mass but also display reduced oxidative metabolism during exercise. Moreover, measurement of skeletal muscle lactate production during exercise demonstrated metabolic abnormalities in patients with chronic heart failure independent of tissue perfusion. Consistent with this, skeletal mitochondria density is reduced in patients with chronic heart failure and the extent of mitochondrial loss correlates with peak exercise capacity [24, 110].

These observations demonstrate that while reductions in tissue perfusion may contribute to skeletal muscle dysfunction in patients with chronic systolic heart failure, there is substantial evidence indicating that pathologic and metabolic abnormalities intrinsic to skeletal muscle beds are the primary mediators of muscle atrophy and dysfunction [53, 54, 90]. Examination of muscle biopsies has demonstrated that compared to control subjects, patients with chronic systolic heart failure display multiple pathological findings including fiber atrophy, myocyte apoptosis, and increased interstitial inflammatory cells. In addition, immunostaining studies have revealed evidence of muscle fiber reprogramming favoring anaerobic muscle fiber types, namely, reduced type I slow twitch fibers and increased type II fast twitch fibers. Consistent with

these observations, biochemical studies focused on mitochondrial function have revealed that subjects with chronic heart failure have significant deficits in oxidative metabolism and morphological studies have reported reduced capillary density [25, 40, 53, 55, 81, 90, 102, 110]. Together, these findings suggest that patients with heart failure display an intrinsic skeletal muscle myopathy, which likely contributes to the prominent muscle wasting, contractile dysfunction, and reduced exercise capacity observed in this patient population. While the molecular mechanisms that govern the development of heart failure-associated skeletal muscle myopathy have not yet been completely defined, recent findings have provided important and exciting insights.

Intriguingly, the pathology of heart failure-associated skeletal muscle myopathy closely resembles what has been observed in myopathies due to chronic inflammatory conditions, such as Crohn's disease. Examination of muscle biopsies obtained from patients with Crohn's disease demonstrated fiber atrophy, myocyte apoptosis, reduced type I fibers, increased type II fibers, and increased numbers of inflammatory cells. These findings were associated with elevated levels of the pro-inflammatory cytokines TNF α , sphingosine, and lipopolysaccharide (LPS) [17]. Importantly, numerous large studies have revealed that patients with systolic heart failure also have elevated serum levels of pro-inflammatory cytokines including TNF α , IL-1 β , IL-6, and IL-2 [22, 29, 73, 96]. These findings highlight a potentially shared pathogenesis of skeletal muscle atrophy in Crohn's disease and chronic systolic heart failure and implicate systemic and/or local inflammation as a potential causative mechanism in heart failure-associated skeletal muscle myopathy.

In this review, we will discuss pathologic mechanisms that drive skeletal muscle inflammation in the setting of chronic heart failure. In addition, we will highlight potential roles for distinct innate immune subsets that reside within damage muscle tissue focusing on the recently described embryonic-derived and monocyte-derived macrophage lineages. Specifically, we will discuss what these cell types represent and how they may differentially impact on skeletal muscle repair and inflammation. Finally, we will connect inflammatory mechanisms with pathways known to stimulate skeletal muscle atrophy, dysfunction, catabolism, and myokine production. Where appropriate, we will comment on potential contributions of aging to skeletal muscle inflammation and dysfunction.

Skeletal muscle injury and inflammation in heart failure

Whether due to systolic or diastolic dysfunction, the systemic syndrome of heart failure imparts multiple insults on peripheral tissues including skeletal muscle. Collectively, these perturbations contribute to heart failure-associated skeletal myocyte injury and dysfunction. Within the context of heart failure, skeletal muscle injury can be divided into primary and

secondary mechanisms. We will define primary injury mechanisms as those directly related to the syndrome of heart failure, namely, derangements in tissue perfusion, neurohormonal activation, disruption of skeletal muscle homeostasis, and systemic inflammation. Each of these primary mechanisms contributes to skeletal myocyte injury or death. Secondary injury mechanisms will be defined as the activation of local immune responses by injured or damaged skeletal muscle. In the following sections, we will outline the pathophysiological triggers of primary skeletal muscle injury in the setting of chronic heart failure (Fig. 1), describe the mechanisms by which these pathologies stimulate local inflammatory responses, and discuss the pathological and clinical implications of skeletal muscle inflammation as they relate to muscle atrophy and dysfunction.

Skeletal muscle insults in heart failure: primary injury mechanisms

Derangements in tissue perfusion Reduced cardiac output (particularly during exercise) and increased venous pressure are central to all etiologies of heart failure and result in reduced skeletal muscle blood flow. Failure to augment blood flow during exercise due to reduced forward flow and impaired vasodilation leads to inadequate skeletal muscle perfusion and production of lactate, a hallmark of tissue ischemia [89]. Similarly, increased central venous pressures not only result in microvascular congestion and tissue edema but also reduced perfusion pressure across skeletal muscle capillary beds [84, 89]. As a consequence, skeletal myocytes receive inadequate nutrient supply including oxygen and are either stressed, reversibly injured, or in more extreme conditions undergo apoptotic and/or necrotic cell death.

Neurohormonal activation In addition to episodic tissue ischemia, patients with heart failure display several systemic perturbations that contribute to skeletal muscle pathology including neurohormonal activation and systemic inflammation. Neurohormonal activation defined as exaggerated sympathetic tone and increased systemic epinephrine, norepinephrine, and angiotensin II levels are commonly observed in patients with acute and chronic heart failure [60]. In addition to promoting myocardial adverse remodeling, neurohormonal activation has direct effects on skeletal myocytes including induction of oxidative injury, sarcomere loss, and myocyte death. Chronic epinephrine and norepinephrine exposure is sufficient to promote oxidative stress, capillary rarefaction, and skeletal muscle atrophy. These effects appear to occur through a combination of chronic β 1-adrenergic stimulation and downregulation of β 2-adrenergic signaling [5, 107]. Moreover, norepinephrine may contribute to reduced tissue perfusion through exaggerated α -adrenergic-mediated vasoconstriction [67]. Lastly, increased local and systemic sympathetic nerve activity and reduced vagal tone have important effects on innate

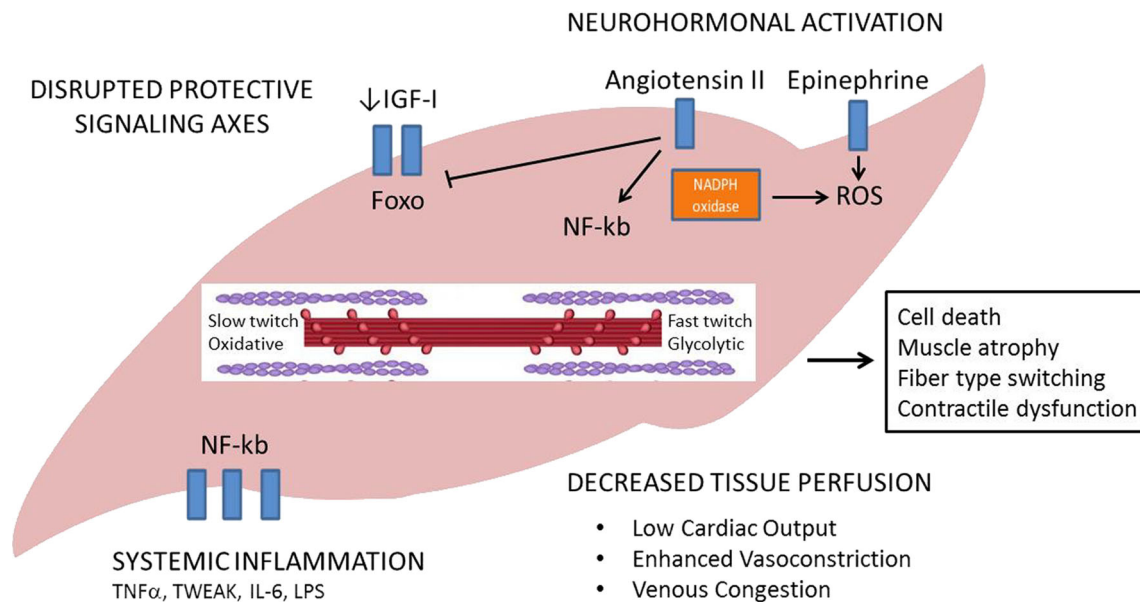


Fig. 1 Schematic depicting mechanisms of skeletal muscle injury in the context of chronic heart failure. *IGF-1* insulin-like growth factor 1, *IL-6* interleukin 6, *LPS* lipopolysaccharide, *NF-κB* nuclear factor kappa-light

chain-enhancer of activated B cells, *TNF α* tumor necrosis factor α , *TWEAK* TNF-related weak inducer of apoptosis

immune cell recruitment, pro-inflammatory signaling, and resolution of inflammatory responses. Sympathetic activation is an essential cue to mobilize monocytes from the bone marrow potentially through a β_3 -adrenergic mechanism, while parasympathetic signaling via nicotinic acetylcholine receptors is an important negative regulator of pro-inflammatory innate immune responses to sterile tissue injury [16, 26, 71].

Angiotensin II levels are also elevated in the setting of chronic heart failure and trigger the generation of damaging reactive oxygen species through direct stimulation of NADPH oxidase [38, 47]. In addition, angiotensin II signaling directly contributes to skeletal muscle inflammation through augmentation of inflammatory and inhibition of anti-inflammatory signaling mechanisms. Angiotensin II signaling activates canonical NF κ B-dependent pro-inflammatory gene expression in skeletal muscle myocytes. Importantly, angiotensin II also suppresses insulin-like growth factor 1 (IGF1) signaling in skeletal myocytes, a central anti-inflammatory signaling mechanism that governs skeletal muscle homeostasis and growth [6, 9, 47, 76, 113].

Disruption of the IGF1 signaling axis Patients with heart failure display reductions in circulating factors that are protective towards skeletal muscle, the most notable of which is IGF1 [7, 99]. Serum IGF1 levels are inversely associated with LV systolic dysfunction, neurohormonal activation, cytokine production, and muscle atrophy [3, 68, 74]. IGF1 is expressed by multiple tissues in the body including liver and skeletal and cardiac muscle. The exact mechanism by which systemic IGF1 is reduced in heart failure is not well defined. However, elevated angiotensin II activity may play an

important role [76]. IGF1 signaling represents a well-established mechanism to stimulate muscle growth and regeneration [64]. IGF transgenic mice are resistant to angiotensin II and heart failure-induced muscle atrophy, and local IGF1 treatment can reverse disuse atrophy [83, 87, 88]. These protective properties of IGF1 signaling are mediated through an AKT1, mTOR, and FoxO axis supporting cell survival, myofibril growth, and protein synthesis, while inhibiting protein degradation [7]. Importantly, IGF1 also possesses significant immunomodulatory activity. Specifically, IGF1 is a robust inhibitor of pro-inflammatory responses through IL10-dependent suppression of monocyte activation [34].

Systemic inflammation Numerous clinical studies have documented that patients with heart failure display signs of systemic inflammation [17, 22, 29, 73, 96]. Biomarker analysis of 1200 heart failure patients enrolled in the VEST trial demonstrated that serum levels of TNF α and IL6 are elevated in heart failure and prognostically important. Specifically, patients with elevated cytokine levels displayed higher mortality [22]. Moreover, serum TNF α and IL6 levels are predictive of the development of heart failure and are reduced in patients receiving optimal medical therapy for heart failure [97, 100]. The exact source of cytokines is not well established, but likely includes both the myocardium as well as peripheral tissues including but not limited to the gastrointestinal tract, liver, and circulating monocytes [49, 50, 100]. One proposed mechanism is that increased gut permeability leads to systemic inflammation through either systemic LPS exposure and/or dysregulated mucosal immune responses [69]. In either scenario, activation of innate immune cells results in elevated

systemic levels of TNF α , IL-1 β , IL-6, and IL-2 with deleterious effects on skeletal muscle. Cytokine signaling is sufficient to trigger skeletal myocyte injury, generation of reactive oxygen intermediates, and muscle atrophy [18, 59]. IL6 signaling via STAT3 has been reported to regulate myostatin, an important mediator of skeletal muscle catabolism [115]. In addition, muscle-specific TNF α signaling through NF- κ B results in a severe muscle wasting phenotype that is mediated by the ubiquitin ligase MuRF1 and suppression of IGF1 signaling [10, 20]. The TNF superfamily member, TNF-like weak inducer of apoptosis (TWEAK), induces a similar phenotype by binding to the Fn14 receptor and activating NF- κ B signaling [23].

Local skeletal muscle immune responses: secondary injury mechanisms While primary mechanisms that contribute skeletal muscle dysfunction and injury are well established, less is known regarding the role of skeletal muscle cell death and local inflammatory responses. In the following section, we will highlight the importance of local inflammation and discuss the mechanistic basis by which myocyte cell death contributes to local activation of the innate immune system. In addition, we will introduce the concept of macrophage diversity and propose a conceptual framework explaining why local inflammation paradoxically contributes to both tissue repair and collateral tissue injury.

Immune recognition of injured and dying skeletal myocytes In recent years, details have emerged clarifying the mechanisms by which tissue injury is recognized by the immune system and inflammatory responses are generated. It is now understood that cells that are injured or those that undergo cell death through necrosis, necroptosis, and aborted apoptosis release an array of intracellular signaling molecules with potent effects on tissue-resident immune cells [56]. Indeed, defective autophagocytic responses associated with skeletal muscle catabolism and atrophy also result in cell death and local inflammation [65]. Dying myocytes release an array of signals collectively referred to as danger-associated molecular patterns (DAMPs) that encompass a variety of mediators including alarmins (HMGB1, S100A8/9/12, S100B, IL1 α , HSPs), nucleotides (ATP, CpG, dsRNA), bioactive lipids, extracellular matrix fragments (glycans, heparin sulfate, hyaluronan), and lectins [13].

The majority of DAMPs are recognized by a set of germ line-encoded pattern recognition receptors (PRRs) most prominently expressed on leukocytes, endothelial cells, and fibroblasts. PRRs are well known for their roles in recognizing pathogen-derived products referred to as pathogen-associated molecular patterns (PAMPs). Examples of PAMPs include gram-negative bacterial lipopolysaccharides (LPS), gram-positive bacterial teichoic acids, yeast zymosans, mycobacterial glycolipids, and viral dsRNAs [65]. Classically, engagement of PRRs such as toll-like receptor 4

(TLR4) by pathogen-derived products (i.e., LPS) results in activation of mononuclear phagocytes and generation of profound inflammation responses aimed at eliminating both pathogens and infected cells [57, 61, 95].

An array of recent studies has provided substantial evidence indicating that recognition of DAMPs by PRRs is responsible for sterile injury-associated inflammation and, in some scenarios, tissue repair. PRRs implicated in sterile injury responses include toll-like receptors (TLR2, 3, 4, and 9), NOD-like receptors (NOD, NLRs, NLRP3), RIG-I-like receptors, C-type lectin receptors (CLRs), RAGE receptors, and formyl peptide receptors (FPRs) [92, 101], all of which are present in healthy and diseased skeletal muscle [93, 109]. TLRs are found on either the plasma membrane (TLR2, 4) or endosomes (TLR3, 9) and recognize an array of DAMPs including HMGB1, S100A/B, HSPs, ECM fragments, and dsDNA including mitochondrial DNA and CpG fragments [92]. Engagement of TLR receptors by various DAMPs leads to the activation of a well-described cascade of signaling events culminating in the release of pro-inflammatory chemokines and cytokines [72]. Activation of the NOD-like receptors NOD1, NOD2, and NLRP3 by nucleotides and other metabolites including uric acid results in inflammasome activation and generation of robust inflammatory responses [35]. Formyl peptide receptors recognize products released from damaged mitochondria and have been shown to trigger robust activation of neutrophils in the setting of sterile liver injury [58]. At this point in time, considerably less is known regarding the roles of RIG-like receptors, C-type lectin receptors, and RAGE receptors in sterile tissue injury. However, it is likely that much will be learned in the near future.

With respect to skeletal muscle, multiple DAMPs have been implicated in skeletal myocyte injury, inflammation, and tissue repair. Traumatic or ischemic skeletal muscle injury elicits the release of mitochondria-associated DAMPs including formyl peptides and mitochondrial DNA. In this context, formyl peptides are recognized by FPR1 present on neutrophils, while mitochondrial DNA is recognized by neutrophils, monocytes, and macrophages expressing TLR9. Collectively, mitochondrial DAMPs appear to drive local and systemic inflammatory responses [114]. In contrast to mitochondrial-derived DAMPs, high-mobility group box 1 protein (HMGB1) release from injured skeletal muscle is required for tissue repair and regeneration. HMGB1 is a ubiquitous multifunctional protein, which under homeostatic conditions functions within the nucleus to augment interactions between transcription factors and chromatin. However, following tissue injury, HMGB1 is released into the extracellular matrix by injured or dying cells where it activates mononuclear phagocytes through TLR4 and RAGE receptor signaling [1, 32, 108]. HMGB1 may also signal directly to satellite cells and endothelial cells [21]. Importantly, HMGB1 is required for revascularization and myocyte regeneration following skeletal

muscle injury [11, 21], suggesting that activation of local immune responses through a DAMP-mediated mechanism is a key determinant of not only inflammation but also tissue repair.

To date, no studies have investigated whether skeletal muscle DAMPs are activated in the setting of heart failure. Given data demonstrating increased skeletal myocyte death, inflammation, and the multiple insults imparted on skeletal muscle in the setting of chronic heart failure, it would not be surprising that heart failure-associated skeletal muscle inflammation is driven by DAMP signaling. Whether DAMP signaling contributes to heart failure-associated skeletal muscle atrophy, fiber type switching, metabolic derangements, fibrosis, and impaired microvasculature remains unclear. Moreover, whether DAMP signaling can be manipulated to favor satellite cell activation and regenerative responses is yet to be studied. Furthermore, the mechanistic determinants explaining why some DAMPs trigger inflammatory responses while others stimulate tissue repair is not fully understood; however, some clues are beginning to emerge.

Macrophage diversity Immune cells represent the predominate cell type that utilizes PRRs to recognize and respond to tissue injury. Macrophages, neutrophils, dendritic cells, and B cells harbor an array of PRRs poised to recognize the release of an array of DAMPs. Within muscular tissues, macrophages represent the most abundant resident innate immune cell. Macrophages are evolutionary conserved phagocytes that were first discovered late in the nineteenth century by Ilya Metchnikoff [15, 94]. In the 1960s, Van Furth proposed that tissue macrophages originated from circulating blood monocytes, which has been the prevailing view for the last 40 years. However, evolving evidence has challenged this dogma and suggested that tissue macrophages may exist independent of circulating monocytes [80, 98, 106].

More recently, a series of studies performed in model systems have drastically revised our understanding of macrophage origin. Collectively, these publications demonstrated that many tissue-resident macrophages are established during embryonic development and persist into adulthood independent of blood monocyte input [27, 36, 39, 42, 48, 82, 112]. This advancement in knowledge was dependent on the development and utilization of genetic lineage tracing and parabiotic systems. Several detailed review articles have been published describing different aspects of macrophage ontogeny and related functions [19, 86, 111]. However, few publications have explored macrophage ontogeny within the skeletal muscle. In the following section, we will describe the currently available knowledge regarding tissue-resident macrophage subsets, origins, and potential functions in injured skeletal muscle.

In the mouse, embryonic and adult monocyte-derived macrophages can be readily distinguished through genetic lineage

tracing. Adult monocyte-derived macrophages are derived from definitive hematopoietic stem cells, which express FLT3 as they differentiate. Based on this finding, a Flt3-Cre mouse was developed to track the progeny of adult definitive hematopoietic stem cells [8]. Using this genetic lineage tracing tool, several studies have identified embryonic-derived (Flt3-Cre negative) and adult monocyte-derived (Flt3-Cre positive) macrophages in multiple tissues including the brain, heart, lung, kidney, liver, and skin [28, 45]. Using a combination of immunostaining and genetic lineage tracing, we were able to similarly identify embryonic-derived and monocyte-derived macrophages in skeletal muscle (Fig. 2).

Collectively, studies utilizing Flt3-Cre mice have revealed that adult monocyte-derived macrophages do fully replace embryonic-derived macrophages during steady state conditions [27, 42, 82]. In fact, macrophages of embryonic and adult monocyte origin coexist within tissues. Intriguingly, in the context of aging, adult monocyte-derived macrophages increase in number and progressively replace embryonic-derived macrophages in some tissues including the heart [62]. Furthermore, detailed studies have better refined the composition of Flt3-Cre-negative embryonic-derived macrophages suggesting that this population consists of a combination of two lineages derived from progenitors located within the early yolk sac and those that migrate from the yolk sac to the fetal liver at later developmental stages [27].

Embryonic-derived macrophages are first observed during early gestation (embryonic day 6.5–8.5 in the mouse) in the extra-embryonic yolk sac where they arise from an early bipotent erythromyeloid progenitor. At this early stage of development, the yolk sac supports primitive hematopoiesis producing erythrocytes and yolk sac-derived macrophages [78]. In the mouse, primitive hematopoiesis can be distinguished from definitive hematopoiesis based on the requirement for the transcription factor MYB. *Myb*^{-/-} embryos have a selective deficiency in definitive hematopoietic stems and are unable to support definitive hematopoiesis. While *Myb*^{-/-} embryos lack definitive hematopoietic progeny (lymphocytes, granulocytes, monocytes, and megakaryocytes), their ability to produce early erythrocytes and yolk sac-derived macrophages is not perturbed [82]. Yolk sac-derived macrophages have a characteristic CX3CR1^{hi} F4/80^{hi} CD11b^{lo} expression pattern in the embryo and give rise to adult brain microglia, a subset of cardiac macrophages, and a transient population of skin Langerhans's cells [27, 36, 42, 44, 82, 112].

At later stages during embryonic development (embryonic day 8.5–10.5 in the mouse), definitive hematopoietic stem cells emerge from the aorta-gonades mesonephros, hemogenic endothelium, and yolk sac giving rise to definitive fetal immune lineages. Beginning at E10.5, HSCs migrate to the fetal liver, which then serves as the major hematopoietic organ during the remainder of embryonic development [36, 79]. During this period, fetal monocytes emigrating from the liver take residence within

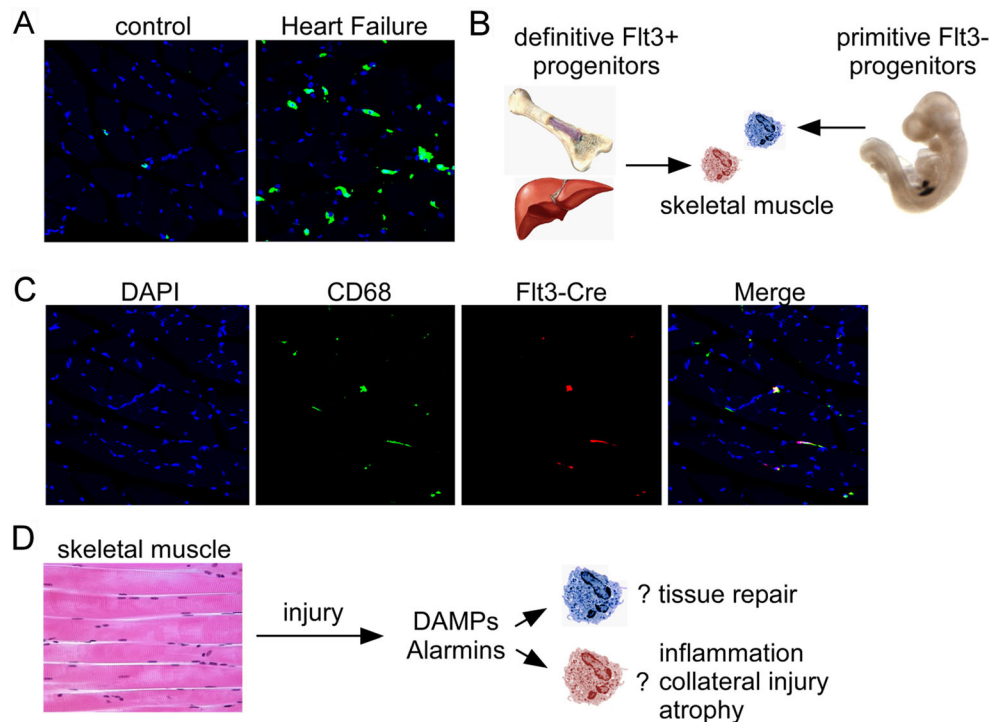


Fig. 2 Skeletal muscle macrophages in heart failure. **a** Immunostaining for CD68 (green) and DAPI (blue) in skeletal muscle obtained from controls and a mouse model of dilated cardiomyopathy demonstrating increased macrophage abundance. **b** Diagram illustrating that macrophages are derived from distinct lineages including primitive and definitive hematopoietic progenitors. **c** Genetic lineage tracing with Flt3-

Cre (red) revealing the presence of CD68+ macrophages derived from embryonic (Flt3-Cre-negative) and adult monocyte (Flt3-Cre-positive) origins. **d** Schematic describing the potential roles for embryonic-derived (blue) and monocyte-derived (red) macrophages in the context of skeletal muscle injury

multiple developing organs and likely constitute the primary origin of the majority of tissue-resident embryonic-derived macrophages [28, 45]. Within the skin, fetal monocytes out-compete yolk sac-derived macrophages and contribute to the overwhelming majority of adult Langerhans cells. Recent data suggests that a similar phenomenon occurs in the developing liver, kidney, and lung [39, 45, 48].

During the perinatal period, definitive hematopoietic stem cells take residence within the bone marrow where they establish the primary site of hematopoiesis for the remainder of life. Within this compartment, Flt3-Cre-positive definitive hematopoietic stem cells produce the full complement of immune lineages including adult monocyte-derived macrophages [70]. Adult monocytes arise from definitive hematopoietic stem cells through a well-characterized cascade involving the progressive differentiation of committed progenitor cells including the monocyte-macrophage dendritic cell progenitor (MDP) [30]. Recently, a Ly6C-positive monocyte-specific progenitor downstream of MDPs has been identified in the bone marrow and spleen [43]. In the mouse and human, there appear to be two principle monocyte subsets: classical Ly6C^{high} monocytes and nonclassical Ly6C^{low} monocytes [46]. Ly6C^{hi} monocytes are direct descendants of the Ly6C-positive monocyte progenitor and give rise to tissue-resident adult monocyte-derived macrophages [28, 48]. Nonclassical

Ly6C^{low} monocytes differentiate from Ly6C^{high} monocytes through an Nr4a1-dependent transcriptional program [41, 43, 112]. Within the vasculature, nonclassical Ly6C^{low} monocytes crawling over the endothelium in a LFA-1 integrin-dependent manner where they clear damaged endothelial cells and maintain vascular integrity (Auffray et al. 2007) [12]. While some have considered these monocytes to be “vascular macrophages,” they transcriptionally cluster with monocytes and do not express core macrophage transcripts, including Mer tyrosine kinase [33, 48].

Impact of local skeletal muscle immune responses As discussed above, innate immune cells (predominately macrophages) recognize skeletal muscle injury and drive both damaging inflammatory as well as reparative responses. Until recently, it has remained relatively unclear how activation of the innate immune system can trigger such divergent responses. In fact, there are numerous examples of seemingly contradictory reports claiming that inflammation is both harmful following injury and an essential mediator of tissue repair [37]. This paradox is well established in models of ischemic cardiac injury. Macrophages within the infarcted heart not only drive robust inflammatory responses and pathological remodeling but also are required for the resolution of inflammation, tissue repair, and coronary angiogenesis [31]. One explanation for

these findings is that distinct macrophage populations may mediate inflammatory (M1-like) and reparative (M2-like) macrophage behaviors [66]. Until recently, the exact identities of these proposed macrophage subsets have remained largely undefined.

Recently, we have demonstrated that distinct resident and recruited macrophage subsets derived from embryonic and definitive monocyte progenitors, respectively, govern tissue repair and inflammation in the context of acute cardiac injury [51]. Conceptually, whether these findings apply to other tissues such as skeletal muscle remains to be established. However, it is intriguing to postulate that in the context of chronic heart failure recognition of injured or stressed skeletal myocytes by resident and newly recruited inflammatory macrophages may similarly contribute to tissue repair and secondary pro-inflammatory responses.

In support of this concept, M2-like skeletal muscle macrophages are required for skeletal muscle regeneration following cardiotoxin injury through augmentation of satellite cell proliferation and angiogenesis [4, 91]. In distinction to the heart, monocyte recruitment was necessary for skeletal muscle regeneration [14, 85]. However, in this scenario, monocytes differentiated into anti-inflammatory M2-like macrophages through a mechanism involving phagocytosis [4]. How these M2-like macrophages compare to embryonic-derived macrophages resident in cardiac and skeletal muscle remains to be studied. These data do highlight the possibility that monocyte-derived macrophages can be instructed by tissue-derived factors to acquire a reparative phenotype and promote tissue regeneration. To date, it has not yet been explored whether macrophages resident within the skeletal muscle in the context of failure contribute to muscle regeneration.

Similar to following cardiac injury, monocyte-derived pro-inflammatory M1-like macrophages infiltrate injured skeletal muscle and secrete an array of inflammatory chemokines and cytokines including MCP1, IL1 β , and TNF α [4]. Each of these factors is sufficient to drive inflammation through recruitment of additional pro-inflammatory monocytes and collateral tissue injury. In addition, IL1 β and TNF α signaling to skeletal myocytes contribute to skeletal muscle atrophy and catabolism through reductions in oxidative metabolism and IGF1 signaling [20, 47, 52]. Furthermore, pro-inflammatory macrophages inhibit regeneration as persistence of these cells leads to ongoing damage and defective tissue healing [63, 75, 77]. Examination of a chronic model of skeletal muscle injury (i.e., muscular dystrophy) revealed the existence of pro-inflammatory M1-like and reparative alternatively activated “M2-like” macrophages [103–105], supporting the possibility that distinct macrophage subsets may also govern inflammation and regeneration in chronic skeletal muscle pathologies.

Could inflammation be a target for heart failure-associated skeletal muscle myopathy? Based on the above

findings, it is reasonable to postulate that manipulation of innate immune responses in the context of skeletal muscle injury or chronically disease may impact outcomes. With respect to heart failure, is it possible to bias the immune response to skeletal muscle injury in a manner that might slow the progression or reverse heart failure-associated skeletal muscle myopathy? Selective targeting of distinct macrophage subsets may represent one potential avenue for intervention. For example, manipulations favoring M2-like macrophages would likely bias the immune response towards muscle regeneration and ultimately restoration of skeletal muscle function. Such a manipulation may also minimize the collateral injury, metabolic perturbations, and muscle atrophy associated with excessive inflammation. At this point in time, the exact mechanisms that might be suitable for therapeutic intervention have not yet been identified. Future studies delineating specific mechanisms by which inflammatory M1-like and resident M2-like macrophages are recruited to sites of skeletal myocyte injury, become activated, and exert their functions will undoubtedly provide critical details that will likely be informative with respect to potential therapeutic intervention.

Conclusions It has long been known that skeletal muscle wasting represents an important pathology contributing to the morbidity of heart failure. Recently, important insights have been made mechanistically linking inflammation to muscle atrophy and dysfunction. In addition, paradigm shifting studies have revealed that distinct components of the innate immune system may govern inflammation and tissue repair following sterile injury. Together, these advances have raised the question of whether it is possible to develop therapeutics that target systemic and local inflammatory responses in an effort to restore muscle mass and function. Future studies will be required to determine whether these exciting opportunities represent a reality and new hope for patients crippled by chronic heart failure.

Acknowledgements Lavine is supported by funding from Children’s Discovery Institute of Washington University and St. Louis Children’s Hospital (CH2015-462), Foundation of Barnes-Jewish Hospital (8038-88), Burroughs Foundation Welcome Fund, and NIH K08 HL123519.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Andersson U, Wang H, Palmblad K, Aveberger AC, Bloom O, Erlandsson-Harris H, Janson A, Kokkola R, Zhang M, Yang H, Tracey KJ (2000) High mobility group 1 protein (HMG-1) stimulates proinflammatory cytokine synthesis in human monocytes. *J Exp Med* 192:565–570

2. Anker SD, Ponikowski P, Varney S, Chua TP, Clark AL, Webb-Peploe KM, Harrington D, Kox WJ, Poole-Wilson PA, Coats AJ (1997) Wasting as independent risk factor for mortality in chronic heart failure. *Lancet* 349:1050–1053
3. Anker SD, Volterrani M, Pflaum CD, Strasburger CJ, Osterziel KJ, Doehner W, Ranke MB, Poole-Wilson PA, Giustina A, Dietz R, Coats AJ (2001) Acquired growth hormone resistance in patients with chronic heart failure: implications for therapy with growth hormone. *J Am Coll Cardiol* 38:443–452
4. Arnold L, Henry A, Poron F, Baba-Amer Y, van Rooijen N, Plonquet A, Gherardi RK, Chazaud B (2007) Inflammatory monocytes recruited after skeletal muscle injury switch into antiinflammatory macrophages to support myogenesis. *J Exp Med* 204:1057–1069
5. Bacurau AV, Jardim MA, Ferreira JC, Bechara LR, Bueno CR Jr, Alba-Loureiro TC, Negrao CE, Casarini DE, Curi R, Ramires PR, Moriscot AS, Brum PC (2009) Sympathetic hyperactivity differentially affects skeletal muscle mass in developing heart failure: role of exercise training. *J Appl Physiol* (1985) 106:1631–1640
6. Bechara LR, Moreira JB, Jannig PR, Voltarelli VA, Dourado PM, Vasconcelos AR, Scavone C, Ramires PR, Brum PC (2014) NADPH oxidase hyperactivity induces plantaris atrophy in heart failure rats. *Int J Cardiol* 175:499–507
7. Bonaldo P, Sandri M (2013) Cellular and molecular mechanisms of muscle atrophy. *Dis Model Mech* 6:25–39
8. Boyer SW, Schroeder AV, Smith-Berdan S, Forsberg EC (2011) All hematopoietic cells develop from hematopoietic stem cells through Flk2/Flt3-positive progenitor cells. *Cell Stem Cell* 9:64–73
9. Brink M, Wellen J, Delafontaine P (1996) Angiotensin II causes weight loss and decreases circulating insulin-like growth factor I in rats through a pressor-independent mechanism. *J Clin Invest* 97:2509–2516
10. Cai D, Frantz JD, Tawa NE Jr, Melendez PA, Oh BC, Lidov HG, Hasselgren PO, Frontera WR, Lee J, Glass DJ, Shoelson SE (2004) IKKbeta/NF-kappaB activation causes severe muscle wasting in mice. *Cell* 119:285–298
11. Campana L, Santarella F, Esposito A, Maugeri N, Rigamonti E, Monno A, Canu T, Del MA, Bianchi ME, Manfredi AA, Rovere-Querini P (2014) Leukocyte HMGB1 is required for vessel remodeling in regenerating muscles. *J Immunol* 192:5257–5264
12. Carlin LM, Stamatiades EG, Auffray C, Hanna RN, Glover L, Vizcay-Barrena G, Hedrick CC, Cook HT, Diebold S, Geissmann F (2013) Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell* 153:362–375
13. Chan JK, Roth J, Oppenheim JJ, Tracey KJ, Vogl T, Feldmann M, Horwood N, Nanchahal J (2012) Alarmins: awaiting a clinical response. *J Clin Invest* 122:2711–2719
14. Contreras-Shannon V, Ochoa O, Reyes-Reyna SM, Sun D, Michalek JE, Kuziel WA, McManus LM, Shireman PK (2007) Fat accumulation with altered inflammation and regeneration in skeletal muscle of CCR2^{-/-} mice following ischemic injury. *Am J Physiol Cell Physiol* 292:C953–C967
15. Cooper MD, Alder MN (2006) The evolution of adaptive immune systems. *Cell* 124:815–822
16. Courties G, Herisson F, Sager HB, Heidt T, Ye Y, Wei Y, Sun Y, Severe N, Dutta P, Scharff J, Scadden DT, Weissleder R, Swirski FK, Moskowitz MA, Nahrendorf M (2015) Ischemic stroke activates hematopoietic bone marrow stem cells. *Circ Res* 116:407–417
17. Cuoco L, Vescovo G, Castaman R, Ravara B, Cammarota G, Angelini A, Salvagnini M, Dalla LL (2008) Skeletal muscle wastage in Crohn's disease: a pathway shared with heart failure? *Int J Cardiol* 127:219–227
18. Dalla LL, Ravara B, Gobbo V, Danieli BD, Germinario E, Angelini A, Vescovo G (2005) Skeletal muscle myofibrillar protein oxidation in heart failure and the protective effect of Carvedilol. *J Mol Cell Cardiol* 38:803–807
19. Davies LC, Jenkins SJ, Allen JE, Taylor PR (2013) Tissue-resident macrophages. *Nat Immunol* 14:986–995
20. de Alvaro C, Teruel T, Hernandez R, Lorenzo M (2004) Tumor necrosis factor alpha produces insulin resistance in skeletal muscle by activation of inhibitor kappaB kinase in a p38 MAPK-dependent manner. *J Biol Chem* 279:17070–17078
21. De Mori R, Straino S, Di CA, Mangoni A, Pompilio G, Palumbo R, Bianchi ME, Capogrossi MC, Germani A (2007) Multiple effects of high mobility group box protein 1 in skeletal muscle regeneration. *Arterioscler Thromb Vasc Biol* 27:2377–2383
22. Deswal A, Petersen NJ, Feldman AM, Young JB, White BG, Mann DL (2001) Cytokines and cytokine receptors in advanced heart failure: an analysis of the cytokine database from the Vesnarinone trial (VEST). *Circulation* 103:2055–2059
23. Dogra C, Changotra H, Wedhas N, Qin X, Wergedal JE, Kumar A (2007) TNF-related weak inducer of apoptosis (TWEAK) is a potent skeletal muscle-wasting cytokine. *FASEB J* 21:1857–1869
24. Drexler H, Riede U, Munzel T, Konig H, Funke E, Just H (1992) Alterations of skeletal muscle in chronic heart failure. *Circulation* 85:1751–1759
25. Duscha BD, Kraus WE, Keteyian SJ, Sullivan MJ, Green HJ, Schachar FH, Phippen AM, Brawner CA, Blank JM, Annex BH (1999) Capillary density of skeletal muscle: a contributing mechanism for exercise intolerance in class II-III chronic heart failure independent of other peripheral alterations. *J Am Coll Cardiol* 33:1956–1963
26. Dutta P, Courties G, Wei Y, Leuschner F, Gorbатов R, Robbins CS, Iwamoto Y, Thompson B, Carlson AL, Heidt T, Majumdar MD, Lasitschka F, Eitzrodt M, Waterman P, Waring MT, Chicoine AT, van der Laan AM, Niessen HW, Piek JJ, Rubin BB, Butany J, Stone JR, Katus HA, Murphy SA, Morrow DA, Sabatine MS, Vinegoni C, Moskowitz MA, Pittet MJ, Libby P, Lin CP, Swirski FK, Weissleder R, Nahrendorf M (2012) Myocardial infarction accelerates atherosclerosis. *Nature* 487:325–329
27. Epelman S, Lavine KJ, Beaudin AE, Sojka DK, Carrero JA, Calderon B, Brija T, Gautier EL, Ivanov S, Satpathy AT, Schilling JD, Schwendener R, Sergin I, Razani B, Forsberg EC, Yokoyama WM, Unanue ER, Colonna M, Randolph GJ, Mann DL (2014a) Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. *Immunity* 40:91–104
28. Epelman S, Lavine KJ, Randolph GJ (2014b) Origin and functions of tissue macrophages. *Immunity* 41:21–35
29. Ferrari R, Bachetti T, Confortini R, Opasich C, Febo O, Corti A, Cassani G, Visioli O (1995) Tumor necrosis factor soluble receptors in patients with various degrees of congestive heart failure. *Circulation* 92:1479–1486
30. Fogg DK, Sibon C, Miled C, Jung S, Aucouturier P, Littman DR, Cumano A, Geissmann F (2006) A clonogenic bone marrow progenitor specific for macrophages and dendritic cells. *Science* 311:83–87
31. Frantz S, Nahrendorf M (2014) Cardiac macrophages and their role in ischaemic heart disease. *Cardiovasc Res*
32. Gardella S, Andrei C, Ferrera D, Lotti LV, Torrisi MR, Bianchi ME, Rubartelli A (2002) The nuclear protein HMGB1 is secreted by monocytes via a non-classical, vesicle-mediated secretory pathway. *EMBO Rep* 3:995–1001
33. Gautier EL, Shay T, Miller J, Greter M, Jakubzick C, Ivanov S, Helft J, Chow A, Elpek KG, Gordonov S, Mazloom AR, Ma'ayan A, Chua WJ, Hansen TH, Turley SJ, Merad M, Randolph GJ (2012) Gene-expression profiles and transcriptional regulatory

- pathways that underlie the identity and diversity of mouse tissue macrophages. *Nat Immunol* 13:1118–1128
34. Ge RT, Mo LH, Wu R, Liu JQ, Zhang HP, Liu Z, Liu Z, Yang PC (2015) Insulin-like growth factor-1 endues monocytes with immune suppressive ability to inhibit inflammation in the intestine. *Sci Rep* 5:7735
 35. Geddes K, Magalhaes JG, Girardin SE (2009) Unleashing the therapeutic potential of NOD-like receptors. *Nat Rev Drug Discov* 8:465–479
 36. Ginhoux F, Greter M, Leboeuf M, Nandi S, See P, Gokhan S, Mehler MF, Conway SJ, Ng LG, Stanley ER, Samokhvalov IM, Merad M (2010) Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science* 330:841–845
 37. Glaros T, Larsen M, Li L (2009) Macrophages and fibroblasts during inflammation, tissue damage and organ injury. *Front Biosci (Landmark Ed)* 14:3988–3993
 38. Gomes-Santos IL, Fernandes T, Couto GK, Ferreira-Filho JC, Salemi VM, Fernandes FB, Casarini DE, Brum PC, Rossoni LV, de Oliveira EM, Negrao CE (2014) Effects of exercise training on circulating and skeletal muscle renin-angiotensin system in chronic heart failure rats. *PLoS One* 9:e98012
 39. Williams M, De Kleer I, Henri S, Post S, Vanhoutte L, De Prijck S, Deswarte K, Malissen B, Hammad H, Lambrecht BN (2013) Alveolar macrophages develop from fetal monocytes that differentiate into long-lived cells in the first week of life via GM-CSF. *J Exp Med* 210:1977–1992
 40. Hambrecht R, Fiehn E, Yu J, Niebauer J, Weigl C, Hilbrich L, Adams V, Riede U, Schuler G (1997) Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol* 29:1067–1073
 41. Hanna RN, Carlin LM, Hubbeling HG, Nackiewicz D, Green AM, Punt JA, Geissmann F, Hedrick CC (2011) The transcription factor NR4A1 (Nur77) controls bone marrow differentiation and the survival of Ly6C⁺ monocytes. *Nat Immunol* 12:778–785
 42. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, Becker CD, See P, Price J, Lucas D, Greter M, Mortha A, Boyer SW, Forsberg EC, Tanaka M, van Rooijen N, Garcia-Sastre A, Stanley ER, Ginhoux F, Frenette PS, Merad M (2013) Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. *Immunity* 38:792–804
 43. Hettlinger J, Richards DM, Hansson J, Barra MM, Joschko AC, Krijgsveld J, Feuerer M (2013) Origin of monocytes and macrophages in a committed progenitor. *Nat Immunol* 14:821–830
 44. Hoeffel G, Wang Y, Greter M, See P, Teo P, Malleret B, Leboeuf M, Low D, Oller G, Almeida F, Choy SH, Grisotto M, Renia L, Conway SJ, Stanley ER, Chan JK, Ng LG, Samokhvalov IM, Merad M, Ginhoux F (2012) Adult Langerhans cells derive predominantly from embryonic fetal liver monocytes with a minor contribution of yolk sac-derived macrophages. *J Exp Med* 209:1167–1181
 45. Hoeffel G, Chen J, Lavin Y, Low D, Almeida FF, See P, Beaudin AE, Lum J, Low I, Forsberg EC, Poidinger M, Zozzetti F, Larbi A, Ng LG, Chan JK, Greter M, Becher B, Samokhvalov IM, Merad M, Ginhoux F (2015) C-Myb(+) erythro-myeloid progenitor-derived fetal monocytes give rise to adult tissue-resident macrophages. *Immunity* 42:665–678
 46. Ingersoll MA, Spanbroek R, Lottaz C, Gautier EL, Frankenberger M, Hoffmann R, Lang R, Haniffa M, Collin M, Tacke F, Habenicht AJ, Ziegler-Heitbrock L, Randolph GJ (2010) Comparison of gene expression profiles between human and mouse monocyte subsets. *Blood* 115:e10–e19
 47. Inoue N, Kinugawa S, Suga T, Yokota T, Hirabayashi K, Kuroda S, Okita K, Tsutsui H (2012) Angiotensin II-induced reduction in exercise capacity is associated with increased oxidative stress in skeletal muscle. *Am J Physiol Heart Circ Physiol* 302:H1202–H1210
 48. Jakubzick C, Gautier EL, Gibbings SL, Sojka DK, Schlitzer A, Johnson TE, Ivanov S, Duan Q, Bala S, Condon T, van Rooijen N, Grainger JR, Belkaid Y, Ma'ayan A, Riches DW, Yokoyama WM, Ginhoux F, Henson PM, Randolph GJ (2013) Minimal differentiation of classical monocytes as they survey steady-state tissues and transport antigen to lymph nodes. *Immunity* 39:599–610
 49. Kapadia SR, Oral H, Lee J, Nakano M, Taffet GE, Mann DL (1997) Hemodynamic regulation of tumor necrosis factor-alpha gene and protein expression in adult feline myocardium. *Circ Res* 81:187–195
 50. Kapadia SR, Yakoob K, Nader S, Thomas JD, Mann DL, Griffin BP (2000) Elevated circulating levels of serum tumor necrosis factor-alpha in patients with hemodynamically significant pressure and volume overload. *J Am Coll Cardiol* 36:208–212
 51. Lavine KJ, Epelman S, Uchida K, Weber KJ, Nichols CG, Schilling JD, Ornitz DM, Randolph GJ, Mann DL (2014) Distinct macrophage lineages contribute to disparate patterns of cardiac recovery and remodeling in the neonatal and adult heart. *Proc Natl Acad Sci U S A* 111:16029–16034
 52. Li W, Moylan JS, Chambers MA, Smith J, Reid MB (2009) Interleukin-1 stimulates catabolism in C2C12 myotubes. *Am J Physiol Cell Physiol* 297:C706–C714
 53. Lipkin DP, Jones DA, Round JM, Poole-Wilson PA (1988) Abnormalities of skeletal muscle in patients with chronic heart failure. *Int J Cardiol* 18:187–195
 54. Mancini DM, Coyle E, Coggan A, Beltz J, Ferraro N, Montain S, Wilson JR (1989) Contribution of intrinsic skeletal muscle changes to 31P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation* 80:1338–1346
 55. Mancini DM, Walter G, Reichek N, Lenkinski R, McCully KK, Mullen JL, Wilson JR (1992) Contribution of skeletal muscle atrophy to exercise intolerance and altered muscle metabolism in heart failure. *Circulation* 85:1364–1373
 56. Mann DL (2015) Innate immunity and the failing heart: the cytokine hypothesis revisited. *Circ Res* 116:1254–1268
 57. Mann DL, Topkara VK, Evans S, Barger PM (2010) Innate immunity in the adult mammalian heart: for whom the cell tolls. *Trans Am Clin Climatol Assoc* 121:34–50
 58. McDonald B, Pittman K, Menezes GB, Hirota SA, Slaba I, Waterhouse CC, Beck PL, Muruve DA, Kubus P (2010) Intravascular danger signals guide neutrophils to sites of sterile inflammation. *Science* 330:362–366
 59. Meadows KA, Holly JM, Stewart CE (2000) Tumor necrosis factor-alpha-induced apoptosis is associated with suppression of insulin-like growth factor binding protein-5 secretion in differentiating murine skeletal myoblasts. *J Cell Physiol* 183:330–337
 60. Mentz RJ, O'Connor CM (2016) Pathophysiology and clinical evaluation of acute heart failure. *Nat Rev Cardiol* 13:28–35
 61. Mezzaroma E, Toldo S, Farkas D, Seropian IM, Van Tassel BW, Salloum FN, Kannan HR, Menna AC, Voelkel NF, Abbate A (2011) The inflammasome promotes adverse cardiac remodeling following acute myocardial infarction in the mouse. *Proc Natl Acad Sci U S A* 108:19725–19730
 62. Molawi K, Wolf Y, Kandalla PK, Favret J, Hagemeyer N, Frenzel K, Pinto AR, Klapproth K, Henri S, Malissen B, Rodewald HR, Rosenthal NA, Bajenoff M, Prinz M, Jung S, Sieweke MH (2014) Progressive replacement of embryo-derived cardiac macrophages with age. *J Exp Med* 211:2151–2158
 63. Mounier R, Theret M, Arnold L, Cuvellier S, Bultot L, Goransson O, Sanz N, Ferry A, Sakamoto K, Foretz M, Viollet B, Chazaud B (2013) AMPKalpha1 regulates macrophage skewing at the time of resolution of inflammation during skeletal muscle regeneration. *Cell Metab* 18:251–264

64. Musaro A, McCullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M, Barton ER, Sweeney HL, Rosenthal N (2001) Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nat Genet* 27:195–200
65. Muth IE, Zschuntzsch J, Kleinschnitz K, Wrede A, Gerhardt E, Balcarek P, Schreiber-Katz O, Zierz S, Dalakas MC, Voll RE, Schmidt J (2015) HMGB1 and RAGE in skeletal muscle inflammation: implications for protein accumulation in inclusion body myositis. *Exp Neurol* 271:189–197
66. Nahrendorf M, Swirski FK, Aikawa E, Stangenberg L, Wurdinger T, Figueiredo JL, Libby P, Weissleder R, Pittet MJ (2007) The healing myocardium sequentially mobilizes two monocyte subsets with divergent and complementary functions. *J Exp Med* 204:3037–3047
67. Nazare Nunes Alves MJ, dos Santos MR, Nobre TS, Martinez DG, Pereira Barretto AC, Brum PC, Rondon MU, Middlekauff HR, Negrao CE (2012) Mechanisms of blunted muscle vasodilation during peripheral chemoreceptor stimulation in heart failure patients. *Hypertension* 60:669–676
68. Niebauer J, Pflaum CD, Clark AL, Strasburger CJ, Hooper J, Poole-Wilson PA, Coats AJ, Anker SD (1998) Deficient insulin-like growth factor I in chronic heart failure predicts altered body composition, anabolic deficiency, cytokine and neurohormonal activation. *J Am Coll Cardiol* 32:393–397
69. Niebauer J, Volk HD, Kemp M, Dominguez M, Schumann RR, Rauchhaus M, Poole-Wilson PA, Coats AJ, Anker SD (1999) Endotoxin and immune activation in chronic heart failure: a prospective cohort study. *Lancet* 353:1838–1842
70. Orkin SH, Zon LI (2008) Hematopoiesis: an evolving paradigm for stem cell biology. *Cell* 132:631–644
71. Pereira MR, Leite PE (2016) The involvement of parasympathetic and sympathetic nerve in the inflammatory reflex. *J Cell Physiol*
72. Piccinini AM, Midwood KS (2010) DAMPening inflammation by modulating TLR signalling. *Mediat Inflamm*
73. Rauchhaus M, Doehner W, Francis DP, Davos C, Kemp M, Liebenthal C, Niebauer J, Hooper J, Volk HD, Coats AJ, Anker SD (2000) Plasma cytokine parameters and mortality in patients with chronic heart failure. *Circulation* 102:3060–3067
74. Ren J, Samson WK, Sowers JR (1999) Insulin-like growth factor I as a cardiac hormone: physiological and pathophysiological implications in heart disease. *J Mol Cell Cardiol* 31:2049–2061
75. Ruffell D, Mourkioti F, Gambardella A, Kirstetter P, Lopez RG, Rosenthal N, Nerlov C (2009) A CREB-C/EBPbeta cascade induces M2 macrophage-specific gene expression and promotes muscle injury repair. *Proc Natl Acad Sci U S A* 106:17475–17480
76. Russell ST, Wyke SM, Tisdale MJ (2006) Mechanism of induction of muscle protein degradation by angiotensin II. *Cell Signal* 18:1087–1096
77. Sag D, Carling D, Stout RD, Suttles J (2008) Adenosine 5'-monophosphate-activated protein kinase promotes macrophage polarization to an anti-inflammatory functional phenotype. *J Immunol* 181:8633–8641
78. Samokhvalov IM (2014) Deconvoluting the ontogeny of hematopoietic stem cells. *Cell Mol Life Sci* 71:957–978
79. Samokhvalov IM, Samokhvalova NI, Nishikawa S (2007) Cell tracing shows the contribution of the yolk sac to adult haematopoiesis. *Nature* 446:1056–1061
80. Sawyer RT, Strausbauch PH, Volkman A (1982) Resident macrophage proliferation in mice depleted of blood monocytes by strontium-89. *Lab Invest* 46:165–170
81. Schaufelberger M, Eriksson BO, Grimby G, Held P, Swedberg K (1997) Skeletal muscle alterations in patients with chronic heart failure. *Eur Heart J* 18:971–980
82. Schulz C, Gomez PE, Chorro L, Szabo-Rogers H, Cagnard N, Kierdorf K, Prinz M, Wu B, Jacobsen SE, Pollard JW, Frampton J, Liu KJ, Geissmann F (2012) A lineage of myeloid cells independent of Myb and hematopoietic stem cells. *Science* 336:86–90
83. Schulze PC, Fang J, Kassik KA, Gannon J, Cupesi M, MacGillivray C, Lee RT, Rosenthal N (2005) Transgenic overexpression of locally acting insulin-like growth factor-1 inhibits ubiquitin-mediated muscle atrophy in chronic left-ventricular dysfunction. *Circ Res* 97:418–426
84. Shiotani I, Sato H, Sato H, Yokoyama H, Ohnishi Y, Hishida E, Kinjo K, Nakatani D, Kuzuya T, Hori M (2002) Muscle pump-dependent self-perfusion mechanism in legs in normal subjects and patients with heart failure. *J Appl Physiol* (1985) 92:1647–1654
85. Shireman PK, Contreras-Shannon V, Ochoa O, Karia BP, Michalek JE, McManus LM (2007) MCP-1 deficiency causes altered inflammation with impaired skeletal muscle regeneration. *J Leukoc Biol* 81:775–785
86. Sieweke MH, Allen JE (2013) Beyond stem cells: self-renewal of differentiated macrophages. *Science* 342:1242974
87. Song YH, Li Y, Du J, Mitch WE, Rosenthal N, Delafontaine P (2005) Muscle-specific expression of IGF-1 blocks angiotensin II-induced skeletal muscle wasting. *J Clin Invest* 115:451–458
88. Stitt TN, Drujan D, Clarke BA, Panaro F, Timofeyeva Y, Kline WO, Gonzalez M, Yancopoulos GD, Glass DJ (2004) The IGF-1/PI3K/Akt pathway prevents expression of muscle atrophy-induced ubiquitin ligases by inhibiting FOXO transcription factors. *Mol Cell* 14:395–403
89. Sullivan MJ, Knight JD, Higginbotham MB, Cobb FR (1989) Relation between central and peripheral hemodynamics during exercise in patients with chronic heart failure. Muscle blood flow is reduced with maintenance of arterial perfusion pressure. *Circulation* 80:769–781
90. Sullivan MJ, Green HJ, Cobb FR (1990) Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation* 81:518–527
91. Summan M, Warren GL, Mercer RR, Chapman R, Hulderman T, van Rooijen N, Simeonova PP (2006) Macrophages and skeletal muscle regeneration: a clodronate-containing liposome depletion study. *Am J Physiol Regul Integr Comp Physiol* 290:R1488–R1495
92. Takeuchi O, Akira S (2010) Pattern recognition receptors and inflammation. *Cell* 140:805–820
93. Tamrakar AK, Schertzer JD, Chiu TT, Foley KP, Bilan PJ, Philpott DJ, Klip A (2010) NOD2 activation induces muscle cell-autonomous innate immune responses and insulin resistance. *Endocrinology* 151:5624–5637
94. Tauber AI (2003) Metchnikoff and the phagocytosis theory. *Nat Rev Mol Cell Biol* 4:897–901
95. Topkara VK, Evans S, Zhang W, Epelman S, Staloch L, Barger PM, Mann DL (2011) Therapeutic targeting of innate immunity in the failing heart. *J Mol Cell Cardiol* 51:594–599
96. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL (1996) Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: a report from the Studies of Left Ventricular Dysfunction (SOLVD). *J Am Coll Cardiol* 27:1201–1206
97. Tsutamoto T, Hisanaga T, Wada A, Maeda K, Ohnishi M, Fukai D, Mabuchi N, Sawaki M, Kinoshita M (1998) Interleukin-6 spillover in the peripheral circulation increases with the severity of heart failure, and the high plasma level of interleukin-6 is an important prognostic predictor in patients with congestive heart failure. *J Am Coll Cardiol* 31:391–398
98. Van Furth R, Cohn ZA (1968) The origin and kinetics of mononuclear phagocytes. *J Exp Med* 128:415–435
99. Vasan RS, Sullivan LM, D'Agostino RB, Roubenoff R, Harris T, Sawyer DB, Levy D, Wilson PW (2003a) Serum insulin-like growth factor I and risk for heart failure in elderly individuals

- without a previous myocardial infarction: the Framingham Heart Study. *Ann Intern Med* 139:642–648
100. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, Sawyer DB, Levy D, Wilson PW, D'Agostino RB (2003b) Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: the Framingham Heart Study. *Circulation* 107:1486–1491
 101. Venereau E, Ceriotti C, Bianchi ME (2015) DAMPs from cell death to new life. *Front Immunol* 6:422
 102. Vescovo G, Serafini F, Facchin L, Tenderini P, Carraro U, Dalla LL, Catani C, Ambrosio GB (1996) Specific changes in skeletal muscle myosin heavy chain composition in cardiac failure: differences compared with disuse atrophy as assessed on microbiopsies by high resolution electrophoresis. *Heart* 76:337–343
 103. Villalta SA, Nguyen HX, Deng B, Gotoh T, Tidball JG (2009) Shifts in macrophage phenotypes and macrophage competition for arginine metabolism affect the severity of muscle pathology in muscular dystrophy. *Hum Mol Genet* 18:482–496
 104. Villalta SA, Deng B, Rinaldi C, Wehling-Henricks M, Tidball JG (2011a) IFN-gamma promotes muscle damage in the mdx mouse model of Duchenne muscular dystrophy by suppressing M2 macrophage activation and inhibiting muscle cell proliferation. *J Immunol* 187:5419–5428
 105. Villalta SA, Rinaldi C, Deng B, Liu G, Fedor B, Tidball JG (2011b) Interleukin-10 reduces the pathology of mdx muscular dystrophy by deactivating M1 macrophages and modulating macrophage phenotype. *Hum Mol Genet* 20:790–805
 106. Volkman A, Chang NC, Strausbauch PH, Morahan PS (1983) Differential effects of chronic monocyte depletion on macrophage populations. *Lab Invest* 49:291–298
 107. Voltarelli VA, Bechara LR, Bacurau AV, Mattos KC, Dourado PM, Bueno CR Jr, Casarini DE, Negrão CE, Brum PC (2014) Lack of beta2-adrenoceptors aggravates heart failure-induced skeletal muscle myopathy in mice. *J Cell Mol Med* 18:1087–1097
 108. Wang H, Bloom O, Zhang M, Vishnubhakat JM, Ombrellino M, Che J, Frazier A, Yang H, Ivanova S, Borovikova L, Manogue KR, Faist E, Abraham E, Andersson J, Andersson U, Molina PE, Abumrad NN, Sama A, Tracey KJ (1999) HMG-1 as a late mediator of endotoxin lethality in mice. *Science* 285:248–251
 109. Warren GL, Hulderman T, Liston A, Simeonova PP (2011) Toll-like and adenosine receptor expression in injured skeletal muscle. *Muscle Nerve* 44:85–92
 110. Wilson JR, Mancini DM, Dunkman WB (1993) Exertional fatigue due to skeletal muscle dysfunction in patients with heart failure. *Circulation* 87:470–475
 111. Wynn TA, Chawla A, Pollard JW (2013) Macrophage biology in development, homeostasis and disease. *Nature* 496:445–455
 112. Yona S, Kim KW, Wolf Y, Mildner A, Varol D, Breker M, Strauss-Ayali D, Viukov S, Guillemins M, Misharin A, Hume DA, Perlman H, Malissen B, Zelzer E, Jung S (2013) Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis. *Immunity* 38:79–91
 113. Yoshida T, Semprun-Prieto L, Sukhanov S, Delafontaine P (2010) IGF-1 prevents ANG II-induced skeletal muscle atrophy via Akt- and Foxo-dependent inhibition of the ubiquitin ligase atrogin-1 expression. *Am J Physiol Heart Circ Physiol* 298:H1565–H1570
 114. Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ (2010) Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature* 464:104–107
 115. Zhang L, Pan J, Dong Y, Tweardy DJ, Dong Y, Garibotto G, Mitch WE (2013) Stat3 activation links a C/EBPdelta to myostatin pathway to stimulate loss of muscle mass. *Cell Metab* 18:368–379