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Skeletal Muscle Inflammation and Atrophy in Heart Failure

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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 the how immune mechanisms can be differentially targeted to stimulate skeletal muscle inflammation, catabolism, fiber atrophy, and regeneration.

Keywords

Macrophage; Heart Failure; Skeletal Muscle; Inflammation

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

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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;89]. Examination of muscle biopsies have 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;89;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 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 damaged 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 (Figure 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[90]. Similarly, increased central venous pressures not only results in microvascular congestion and tissue edema, but also, reduced perfusion pressure across skeletal muscle capillary beds[84;90]. 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 reduce vagal tone have important effects on innate 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, 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 possess 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 1,200 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[114]. In addition, muscle specific TNF α signaling through NF-kB 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, TWEAK (TNF like weak inducer of apoptosis), induces a similar phenotype by binding to the Fn14 receptor and activating NF-kB 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 receptor 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 proinflammatory 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 mitochondrial 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[115]. In contrast to mitochondrial derived DAMPs, HMGB1 (high mobility group box 1 protein) 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 utilize 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 19th 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 have 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 publication have explored macrophage ontogeny within 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;44]. Using a combination of immunostaining and genetic lineage tracing, we were able to similarly identify embryonic-derived and monocyte-derived macrophages in skeletal muscle (Figure. 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 compellation 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;45;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-gonads 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 multiple developing organs and likely constitute the primary origin of the majority of tissue resident embryonic-derived macrophages[28;44]. 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;44;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 maintaining 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 macrophages 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 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 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.

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Figure 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-kb: nuclear factor kappa-light chain-enhancer of activated B cells, TNFα: tumor necrosis factor α, TWEAK: TNF-related weak inducer of apoptosis.

Figure 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.