Am J Physiol Endocrinol Metab 304: E453–E465, 2013.
First published December 31, 2012; doi:10.1152/ajpendo.00553.2012.

Review

Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications

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Submitted 5 November 2012; accepted in final form 26 December 2012

Pillon NJ, Bilan PJ, Fink LN, Klip A. Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications. *Am J Physiol Endocrinol Metab* 304: E453–E465, 2013. First published December 31, 2012; doi:10.1152/ajpendo.00553.2012.—Skeletal muscles contain resident immune cell populations and their abundance and type is altered in inflammatory myopathies, endotoxemia or different types of muscle injury/insult. Within tissues, monocytes differentiate into macrophages and polarize to acquire pro- or anti-inflammatory phenotypes. Skeletal muscle macrophages play a fundamental role in repair and pathogen clearance. These events require a precisely regulated cross-talk between myofibers and immune cells, involving paracrine/autocrine and contact interactions. Skeletal muscle also undergoes continuous repair as a result of contractile activity that involves participation of myokines and anti-inflammatory input. Finally, skeletal muscle is the major site of dietary glucose disposal; therefore, muscle insulin resistance is essential to the development of whole body insulin resistance. Notably, muscle inflammation is emerging as a potential contributor to insulin resistance. Recent reports show that inflammatory macrophage numbers within muscle are elevated during obesity and that muscle cells in vitro can mount autonomous inflammatory responses under metabolic challenge. Here, we review the nature of skeletal muscle inflammation associated with muscle exercise, damage, and regeneration, endotoxin presence, and myopathies, as well as the new evidence of local inflammation arising with obesity that potentially contributes to insulin resistance.

inflammation; injury; skeletal muscle; macrophage; cytokines; chemokines; obesity; type 2 diabetes

THE IMMUNE SYSTEM IS CONSTITUTED by circulating cells in the blood and lymph, their collection in lymphoid organs, and cells scattered within most tissues. In physiological conditions, peripheral tissues contain mainly macrophages and dendritic cells, but other leukocytes (monocytes, neutrophils, lymphocytes) can transiently infiltrate tissues during pathological situations. Tissue resident macrophages originate in the bone marrow as monocytes that differentiate once settled in a tissue (39). The functions of resident macrophages are multiple: Phagocytosis of foreign particles (microbes, antigens, injured or dying cells) and antigen-presentation; secretion of enzymes and oxidative derivatives to fight pathogens; production of cytokines and growth factors that affect the parenchymal tissue and recruit additional immune cells. The role of monocyte/macrophage is consequently fundamental to combat pathogens in the case of infection, and to assist in tissue repair following muscle injury.

To complete these tasks, macrophages exhibit a wide range of activation states. In response to bacterial compounds [e.g., lipopolysaccharide (LPS)], macrophages become "classically activated" (typically designated as M1 phenotype) characterized by the expression of iNOS and proinflammatory cytokines (e.g., TNFα, IL-1β, IL-6) (80, 135). The "alternatively activated" macrophages (typically designated M2 phenotype) are more diverse and are characterized by the expression of arginase-1, CD163, and mannose receptor (usually in noninflammatory, repair conditions) and/or anti-inflammatory cytokines (e.g., IL-10) (80, 135). However, beyond these broad definitions, macrophages exhibit a wide variety of intermediate phenotype, M1 and M2 being the extremes of a continuum in activation states (80, 86, 135).

Like most tissues, skeletal muscle contains a population of resident immune cells, and additional immune cells infiltrate during pathophysiological conditions such as contraction or reperfusion-induced insult and injury, endotoxemia, or inflammatory myopathies and have been recently detected during obesity and diabetes. For immune cells to reach tissues and shift to the adequate polarization, the injured or infected site must produce factors with attracting and activating properties. On the other hand, once the tissue is repaired or the infection resolved, immune cells must leave the tissue or senesce. These events require a carefully orchestrated, regulated cross-talk between tissue and immune cells, involving paracrine/autocrine communication and contact interactions.

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Here, we briefly analyze the molecular aspects of muscle inflammation and its effects on the immune system. Subsequently, we review the immune cell-muscle fiber cross-talk during muscle regeneration, exercise, endotoxin excess, and inflammatory myopathies. Finally, we discuss muscle inflammation during obesity and diabetes, in the hope that lessons learned from other pathologies might be instructive in understanding this emerging connection.

Molecular Aspects of Skeletal Muscle Inflammation

Factors released by skeletal muscle cells. Muscle fiber-derived cytokines and other secreted factors (collectively named myokines) produced during physiological and pathological situations play key roles in muscle repair from various insults, exercise/contraction, and in selective myopathies (103, 151). In addition to their local autocrine effects, myokines can reach the circulation and impinge on other tissues. In the case of exercise, muscle contraction induces IL-6 release to the circulation, which subsequently impacts on hepatic glucose production and adipose tissue lipolysis (102). The range of myokines was the subject of recent reviews (103, 151) and will be referred to only succinctly here.

In addition to chemokines, muscle also produces low-molecular-weight molecules such as lactate and ATP, which are released during exercise (85, 137). Extracellular ATP released by contraction activates purinergic receptors that elevate Ca^{2+} influx, potentiating the contraction force (122). Similarly, extracellular ATP rises 30-fold in the medium after tetanic stimulation or K^+ depolarization of rat skeletal muscle myotube cultures (16). Such ATP release involves pannexin-1 hemichannels present in T-tubules of skeletal muscle (16, 31) that allow diffusion of small molecules (ATP, NAD^+, prostaglandin E_2) (20). Interestingly, stimulating isolated rat myotubes with ATP increases glucose uptake (96) and IL-6 expression (16), so ATP may exert autocrine effects. Muscle pathologies such as muscular dystrophy and atrophy are associated with alterations in extracellular ATP metabolism, sensitivity toward ATP, and elevated expression of purinergic receptors (6, 171), revealing that extracellular ATP and its receptors are important factors in muscle activity and plasticity (20). Presumably, muscle necrosis caused by acute muscle injury would lead to release of ATP, as observed in other tissue necrosis models of sterile inflammation (83). ATP is also released from primary human monocytes stimulated with microbial components and in turn induces autocrine liberation of IL-1β and IL-18 by stimulating purinergic receptors and activating the inflammasome (105). Notably, extracellular ATP per se can attract monocytes in vitro (56). Collectively, these findings raise the possibility that ATP may mediate communication between muscle cells and monocytes, a prediction that requires experimental verification.

Hyperlactatemia is commonly observed during exercise in vivo (147) and during severe inflammation such as sepsis (2). Indeed, muscle cells subjected in vitro to electrical pulse stimulation release lactate (90), and IL-1β infusion in rats results in hyperlactatemia due to increased lactate production from skeletal muscle (but not liver) (155). Plasma lactate is also increased during type 2 diabetes and is associated with higher fasting glucose among nondiabetic adults (29). Lactate affects macrophages, and genes induced by lactate overlap with most of those induced by LPS. Although the effect of lactate on these genes is less potent than that of LPS, lactate significantly potentiates the effect of LPS, notably the expression IL-1β (elevated 3-, 7-, and 60-fold by lactate, LPS, and lactate+LPS, respectively) (121) and TNFα (53). Furthermore, lactic acid secreted by tumor cells enhances transcription of the proinflammatory cytokine IL-23 in human blood-derived monocytes/macrophages (133) and can enhance responsiveness to LPS-induced inflammation (58). The mechanism of the lactate-LPS synergy involves activation of the NF-κB pathway, as LPS reduced IκBα levels whereas lactate reduced IκBβ levels. Accordingly, LPS and lactate exhibit synergistic effects on NF-κB and AP-1 transcriptional activity (88, 121). A possible explanation for the effect of lactate is its ability to elevate ROS production that activates the NF-κB pathway and stimulation of expression of MD-2, a TLR4 coreceptor, eventually augmenting LPS signaling and downstream expression of inflammatory genes (121). Collectively, these results suggest the possibility that lactate produced by muscle may potentiate responses of resident or recruited macrophages within this tissue.

Other small molecules may be involved in muscle autonomous inflammation. For instance, mouse C_2C_{12} myotubes exposed to palmitate exhibit an increase in expression of cyclooxygenase (COX)-2 (27), the enzyme responsible for the synthesis of prostaglandins, prostacyclin, and thromboxane, important mediators of the inflammatory response. Indeed, skeletal muscle can produce significant amounts of PGE1, PGE2, PGF2α (111), and notably, inhibition of COX-2 exacerbates palmitate-induced inflammation and insulin resistance in skeletal muscle cells, implying that muscle produces lipid derivatives that have autocrine, anti-inflammatory properties (27). Table 1 presents a succinct list of factors that are released from whole muscle, in vivo, under different pathophysiological conditions and indicates when they are also released from various macrophage and muscle cell systems in vitro.

Signaling pathways within muscle cells. Muscle cells detect and respond to inflammatory molecules secreted by immune cells and neighbouring muscle cells. Specifically, skeletal muscle fibers express receptors to IL-1, IL-6, and IFNγ (173) as well as the chemokine (C-C motif) receptors CCR2, CCR4, and CCR10 (129). Transcript levels of some of these receptors rise markedly in response to a combination of TNFα, IFNγ, and endotoxin in L6 myotubes, and in rat skeletal muscle in vivo following intraperitoneal administration of endotoxin (173). Similarly, the expression of CCR2 is upregulated in human skeletal myocytes rendered insulin resistant by treatment with TNFα (129). Hence, skeletal muscle cells can sense the inflammatory status of their extracellular environment, allowing them to mount a response that culminates in the release of muscle-endogenous factors.

Most inflammatory cytokine and chemokine receptor-signaling pathways lead to nuclear migration of the transcription factor NF-κB, which controls the expression of a host of proinflammatory proteins, and this pathway is active within skeletal muscle tissue (see later).

Cross-Talk Between Muscle and Innate Immune Cells in Physiological and Pathogenic Conditions

Acute skeletal muscle injury and regeneration. It is well established that muscle repair and regeneration following acute

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Table 1. *Factors released by skeletal muscle under pathophysiological conditions*

Produced by	Conditions	References
Lactate		
Muscle cells	Electrical pulse stimulation	(68)
	Lipids	(104)
Macrophages	N/A	
Muscle tissue	Sepsis (LPS)	(2)
	Obesity/Diabetes	(29, 112)
ATP		
Muscle cells	Exercise	(167)
	Electrical pulse stimulation	(16, 122)
	Cell damage	(26)
Macrophages	LPS	(105)
	Chemotaxis	(66)
Muscle tissue	Exercise	(72, 85)
Eicosanoids		
Muscle cells	Muscle repair	(111)
	Palmitate exposure	(27)
Macrophages	LPS	(91, 142)
Muscle tissue	Exercise	(150)
IL-6		
Muscle cells	Electrical pulse stimulation	(68, 97)
	Palmitate	(27, 106)
	LPS, TNFα, IL-1β	(38, 50)
Macrophages	LPS	(82, 117)
	Palmitate	(82, 120)
Muscle tissue	Exercise	(108)
	High fat feeding	(70)
TNFα		
Muscle cells	LPS	(50, 120)
	Palmitate	(106)
	Differentiation	(23)
Macrophages	LPS	(117, 120)
	Palmitate	(120)
Muscle tissue	Exercise	(108)
	Myopathies	(110)
	High fat feeding	(70)
CCL2		
Muscle cells	LPS, TNFα, IL-1β	(45, 50, 57)
	Palmitate	(106)
Macrophages	LPS	(169)
Muscle tissue	Acute injury	(73)
	Endotoxemia	(67)
	Myopathies	(109, 115)
	High fat feeding	(70)

Muscle cells: C_2C_{12}, L6, or primary muscle cells in culture stimulated in vitro. Macrophages: RAW 264.7 cells, bone marrow-derived or peritoneal macrophages stimulated in vitro. Muscle tissue: in vivo experiments with whole tissue analysis.

muscle injury involves a growth-promoting, local inflammation. Experimental models of damage to muscle in rodents include exposure to muscle-targeting toxins (cardiotoxin, notexin, bupivacaine), barium chloride, freeze injury, or ischemia (149). The repair process from initiation to resolution in these muscle injury models includes an initial proinflammatory phase during which the muscle releases cytokines and chemokines (myokines) and the site of damage is infiltrated by immune cells that coordinate the removal of dead muscle cells. Upon positive resolution, this period of muscle regeneration involves muscle satellite cell differentiation and growth that give rise to myoblasts, which in turn form myofibers (40). However, if conditions are not propitious, a prolonged period of inflammation, fibrosis, and accumulation of intramuscular adipose ensues.

The initial inflammatory response is required for a positive outcome of muscle repair (5, 18, 22, 71). Following crush-induced injury, TNFα is released by mast cell degranulation, and then neutrophils begin to accumulate in the muscle bed and release more TNFα, followed by monocyte infiltration (28, 114). Resident macrophages in the epimysium and perimysium interstitial spaces that surround the entire muscle and muscle fascicles, respectively, also play a critical role during the early stages of acute muscle injury in various models, by producing chemokines that attract bone marrow-emigrant immune cells to the tissue (21). Within days of muscle toxin-induced injury, macrophages/immature dendritic cells become the major immune cell types (Ly-6C^{low}/CX3CR1^{high}/CD11c^{intermediate}) at the site of injury, aiding in tissue repair (10).

Monocyte infiltration and conversion to macrophages is necessary to induce the beneficial inflammation that further activates the surrounding cells (T lymphocytes, mesenchymal stem cells, muscle satellite cells, myoblasts, and endothelial cells and their progenitors) to support muscle regeneration. Infiltrating macrophages phagocytose necrotic or apoptotic muscle cells and acquire anti-inflammatory phenotypes that express arginase and produce IL-10 and TGFβ1 (21). The best-characterized chemokine released by injured muscle is CCL2/MCP-1 [chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1], which has an important function in initiating and maintaining the inflammatory phase of various types of muscle injury that precedes muscle regeneration (11). Mice deficient in CCR2 [chemokine (C-C motif) receptor 2] have severely impaired monocyte infiltration (whereas the migration of neutrophils and lymphocytes is normal) along with halted angiogenesis, muscle regeneration, and accumulation of pockets of adipocytes at the site of toxin-induced muscle injury (81). Intriguingly, muscle regeneration is completely restored when CCR2-null mice receive bone marrow transplantation from wild-type mice, suggesting that CCL2 release from the muscle mobilizes monocytes directly from the bone marrow (140). Accordingly, intravenously injected GFP-expressing bone marrow-derived monocytes can enter the injured muscle in CCR2-null mice (140).

On the other hand, mice deficient in the CCR2 ligand, CCL2 have a milder defect in muscle regeneration following toxin-induced muscle injury compared with CCR2-null mice (81), suggesting that CCL2 is not essential and that other CCR2 ligands such as CCL7 and CCL12 or other small molecules could participate in mediating immune cell attraction during muscle regeneration (73, 140). Nevertheless, monocyte infiltration requires CCL2 expression in the bone marrow, circulating monocytes, and injured muscle fibers (73). Resident macrophages are most likely the major source of CCL2 from injured muscle, with a smaller contribution from endothelial cells, since mice depleted of resident macrophages (achieved through transgenic expression of CD11b promoter-driven diphtheria toxin receptor and treated with diphtheria toxin prior to toxin-induced muscle injury) have marked reductions in muscle CCL2 expression and in monocyte and macrophage infiltration (10). Thus, the CCL2/CCR2 system is required for the efficient and timely resolution of acute muscle injury, but the CD11b-positive cells responsible for the implicated CCL2 are still poorly defined.

In addition to CCL2, a number of cytokines participate in the muscle response to muscle toxin-induced injury. IL-6-null mice have impaired recovery, marked by less monocyte/macrophage infiltration shortly following muscle injury and re-

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duced myofiber size during regeneration, accompanied by increased tissue fibrosis (172). Of note, infiltrating monocytes/macrophages produce the majority of IL-6 within the muscle tissue in the first 24 h, leading to significant autocrine/paracrine expression and secretion of CCL2 and CCL3 that contributed to the full monocyte/macrophage infiltration. In addition, IL-6 along, with IL-6-dependent production of G-CSF from macrophages, was necessary for normal satellite cell proliferation and myofiber growth during the muscle regeneration phase (172). Thus, IL-6 may have a newly appreciated role in the early inflammatory response induced by muscle injury in addition to its well-known role in satellite cell proliferation and muscle tissue hypertrophy(130, 165).

Importantly, the proinflammatory M1 macrophages of the initial infiltration phase subsequently attain an M2 polarization profile that promotes muscle growth and regeneration. In hindlimb unloading muscle injury, hindlimb reloading (weight bearing) initiates macrophage infiltration and muscle regeneration (32). However, in IL-10-null mice, this transition is markedly impaired as is muscle regeneration. Furthermore, myoblast proliferation is enhanced in coculture with macrophages preactivated with IL-10 to an M2 polarization (32). Thus, IL-10 is a key mediator of the M1-to-M2 conversion of macrophages in muscle injury that drives myoblast proliferation and myofiber growth.

Fractalkine (CX3CL1) and vascular endothelial growth factor (VEGF) are additional muscle-derived products important for vascular remodeling in response to various types of tissue injury (125, 160), and as such may be regarded as chemokines. Fractalkine and its receptor CX(3)CR1 direct leukocyte infiltration into the site of tissue injury and increase smooth muscle cell expansion (125).

Muscle regeneration involves muscle satellite cell and myoblast growth and differentiation (40). Satellite cells reciprocally interact with neighbouring endothelial cells to promote angiogenesis while proliferating in response to endothelial-derived growth factors such as IGF I, HGF, bFGF, PDGF-BB, and VEGF (25). Anti-inflammatory macrophages also produce high amounts of IGF I, and muscles from CCR2-null mice do not mount a significant IGF I production and have markedly reduced infiltration with bone marrow-derived macrophages following acute skeletal muscle injury induced with barium chloride (74). VEGF produced by anti-inflammatory macrophages contributes to mesenchymal-endothelial cross-talk during tissue repair, helping create blood vessels to supply blood flow to the new muscle tissue (160). This interesting finding highlights that macrophages supply factors that help resolve muscle tissue damage by promoting IGF I-induced myoblast proliferation.

The urokinase-type plasminogen activator (uPA) is the major plasmin-generating system activated during muscle repair, promoting extracellular matrix deposition by activating matrix metalloproteinases and through proteolytic activation of TGFβ1 (40). Mice genetically depleted of uPA present tapered macrophage infiltration in injured muscle and very poor muscle regeneration (15). Significantly, bone marrow-derived macrophages produce the uPA needed for muscle repair, since muscle regeneration is rescued in uPA-null mice transplanted with wild-type bone marrow (15). By contrast, mice lacking the uPA inhibitor PAI-1 have increased neutrophil and macrophage accumulation at sites of toxin-induced muscle injury and present with modestly accelerated muscle repair (62). Thus, macrophages utilize systems that regulate extracellular matrix deposition and remodelling to aid in muscle tissue repair.

In summary, diverse insults used to provoke muscle damage and repair triggers rapid and significant leukocyte recruitment to the afflicted site. Muscle cells (myoblasts and myofibers) may produce some of the chemoattracting and activating factors, but other resident cell types such as tissue macrophages are probably more dominant generators of chemokines and inflammatory and growth factors. Additional contribution arises from endothelial, mesenchymal stem (e.g., pericytes), and satellite cells. The produced factors in turn draw in monocytes/macrophages to clear debris and further promote growth and differentiation of myoblasts and endothelial and smooth muscle cells required for tissue regeneration.

Mesenchymal stem cells are increasingly recognized as key mediators of muscle regeneration, and they can further modulate numerous immune responses within tissues. The reader is referred to an excellent recent review on this topic (84).

Exercise and muscle contraction. Exercise-induced skeletal muscle damage is thought to be necessary for long-term muscle strengthening adaptations and protection against further damage through its induction of muscle gene expression programs, protein turnover, autonomous inflammation, and tissue regeneration. The type of experimental exercise is an important consideration when one is comparing studies, with eccentric contraction (muscle elongation while under tension, e.g., downhill running) being the most damaging to muscle (126). The postexercise sampling period is also worthy of consideration, as in some studies it is delayed 24–48 h with the aim to capture events coincident with the peak of monocyte/macrophage infiltration observed in mouse acute muscle injury studies. In an extensive study with humans performing single bouts of eccentric exercise that induced severe muscle soreness, Malm et al. observed that muscle adaptations to physical exercise were fundamentally different from muscle repair mechanisms induced by acute damage resulting from various insults to muscle used in animal models (78). Nevertheless, they recorded an elevation in several immune cell and inflammatory markers (CD11b, CD3, and HIF-1β) in the muscle epimysium space, though not within the muscle fibers, at 6 h and 48 h after eccentric exercise (78). A comprehensive literature review concluded that if damage occurs it must be severe enough to induce a marked reduction in force-generating capacity in order to induce immune cell infiltration of the muscle (100). On the other hand, a proteomic analysis failed to detect changes in inflammation indexes in human muscle biopsies taken 48 h posteccentric exercise (79); similarly, no changes were observed in global cDNA microarray analyses of human muscle biopsies taken at 3, 24, or 48 h posteccentric, -endurance, or -concentric exercise (63, 75, 76). The unbiased nature of these analyses did reveal changes in structural and metabolic genes and proteins, questioning whether inflammation is an obligatory response of the muscle to exercise.

Supporting a role of inflammation in muscle recovery from exercise, a comprehensive cDNA array analysis of muscles from 35 subjects with the more focused goal of identifying changes in gene networks shortly after eccentric exercise (3 h) identified changes in dozens of gene products regulated by the NF-κB pathway such as CCL2, IL-18, CXCL1, LIF, and TGFβ1 (51). This study further confirmed the activation of

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NF-κB in muscle nuclei and made the unexpected finding that more than 65% of the NF-κB-positive nuclei in cross-sectional tissue samples were within pericytes and not macrophages, satellite cells, or myofibers. Pericytes are mesenchymal stem cells that are intimately associated with microvessels (14), and in the analysis by Hyldahl et al., pericytes and satellite cells represented ~7% and 4% of the nuclei in each cross-sectional field of the muscle biopsies, respectively (51). Pericyte abundance increases in muscle following eccentric exercise, and these cells may support the postexercise repair of muscle by recruiting satellite cells in the region of injury (153). The latter was demonstrated when $Sca1^+CD45^-$ pericyte transplantation into mouse muscle led to an increase in $Pax7^+CD56^+$ satellite cells and muscle fiber formation, especially if transplantation of pericytes was performed prior to eccentric exercise (151, 153). Pericytes themselves did not become myogenic or form myofibers but rather played a supporting role in myofiber growth, possibly through production of satellite growth factors such as LIF. The presence of pericytes imparts resistance to muscle injury, aids in muscle regeneration, and favors less tissue fibrosis (153). Thus, future studies understanding whether pericytes affect macrophage polarization would be of interest.

From the above, it follows that, immediately after undergoing muscle-damaging exercise, there is a significant proinflammatory NF-κB-mediated response in the mesenchymal stem cell compartment of muscle tissue. The NF-κB involvement in exercise-induced muscle inflammation is further evinced during high-intensity resistance (156) or aerobic (e.g., cycling) exercise (145), which cause transient increases in NF-κB phosphorylation, promoter binding, and mRNA expression of NF-κB-regulated cytokine genes (CCL2, IL-6, IL-8); however, the physiological relevance of NF-κB activation in muscle tissue following exercise has not been tested, and it is noteworthy that other inflammatory signaling pathways also mediate cytokine gene expression in exercised muscle. Indeed, the MAPK pathways are activated during exercise/contraction (reviewed by Ref. 65), and transcriptional regulation of IL-6 gene expression is signaled through the JNK/c-Jun/AP-1 pathway in electrically stimulated cultured muscle cells and mouse muscle shortly following treadmill running (166). In electrically stimulated muscle cell cultures, IL-6 expression was independent of the NF-κB pathway, since it was not blocked by an IKK inhibitor and the expression of IL-6 in exercised mouse muscle was blocked by muscle-specific JNK1 knockout, highlighting a role of JNK1 in exercise-induced IL-6 expression/production (166). Production of IL-6 within exercise-stimulated myofibers was shown by immunohistochemistry (108) and microdialysis catheterization and sampling of muscle beds in humans (116). Hence, myofibers produce IL-6 under regulation of JNK1/AP-1, whereas pericytes or macrophages may rely on NF-κB signaling to produce cytokines.

In summary, inflammatory pathways within rodent and human muscle are transiently activated shortly after exercise protocols that induce reproducible exercise-induced muscle injury such as eccentric or high-intensity resistance exercise. Inflammatory factors released by exercised muscle exert autocrine and paracrine actions, and it is becoming increasingly clear that skeletal muscle is also an endocrine organ, bringing new light on the contribution of muscle inflammation to whole body metabolism. During the ensuing repair period (24–48 h postexercise), modest immune cell infiltration takes place, and inflammatory read-outs taper off. The precise contribution of the transient inflammatory responses to the process of muscle repair, adaptation, and physiological activity following exercise is largely unknown (101, 159). Readers are referred to an in-depth review on exercise-induced muscle damage and inflammation (100).

Ischemia/reperfusion. Reperfusion injury is the damage caused when blood flow returns to the tissue after a period of ischemia, and it is associated with oxidative stress and inflammation in rats (77). Remote ischemia/reperfusion of mouse limbs induces muscle expression of chemokines CXCL1 and CXCL2 (49) and triggers systemic inflammation with significant elevation in plasma IL-6 levels, TNFα, IL-1, and thromboxane B2 (43, 170). The transcription factor NF-κB appears to be involved in this response, as blocking its activation with proteasome inhibitor attenuates muscle reperfusion injury (98).

Interestingly, ischemia/reperfusion results in priming of circulating phagocytic cells in pigs (43), induction of leukocyte rolling, and adherence associated with enhanced CD11b and ICAM-1 expression in rats (141), and finally recruitment of neutrophils to mouse muscle (8). Strikingly, hindlimb ischemia/reperfusion can remotely induce acute lung damage through pulmonary leukosequestration and edema in pigs (43), demonstrating that cytokines produced by skeletal muscle can affect immune cells in the circulation and consequently induce systemic and remote effects on immune cells in other tissues.

Even though ischemia/reperfusion can be deleterious to the muscle, transient ischemic preconditioning (repeated short episodes of ischemia/reperfusion) of the limb elicits local and systemic anti-inflammatory effects in rats (136), protects against local muscle damage, and confers remote cardiac and liver protection from subsequent acute ischemia of these tissues (24, 161). This suggests that skeletal muscle produces anti-inflammatory factors that can systemically protect itself and other tissues from the deleterious effects of inflammation. One of these factors may be extracellular Bcl2 that is released from muscle, since treatment of mice with recombinant Bcl2 reduces apoptosis and skeletal muscle tissue injury following acute ischemia/reperfusion (52). Because such beneficial action involves the innate immune receptor complex constituted by TLR2 and MyD88, extracellular Bcl2 may operate as a cytoprotective danger-associated molecular pattern (DAMP) recognized by elements of the innate immune pathway. If muscle also releases Bcl2 in the course of exercise, this molecule could potentially affect other tissues (e.g., liver, adipose) to improve their metabolic action (44).

In summary, ischemia/reperfusion provokes muscle autonomous inflammation with a signature reminiscent of the muscle's response to exercise, in particular the release of IL-6. Moreover, this experimental strategy has highlighted the distinct ability of muscle to induce or reduce inflammation at remote sites. These observations may be instructive in understanding how exercise exerts some of its systemic anti-inflammatory action.

Endotoxemia. Endotoxins form an integral part of the cell wall of bacteria, and LPS is the major endotoxin constituent of Gram-negative bacteria. Cells of a bacterially infected host recognize bacterial and other foreign components through one or more families of pattern recognition receptors [TLRs, Nods, and Nod-like receptors (NLRs)]. Each of these recognizes selective varieties of pathogen-associated molecular patterns

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(PAMPs), and several studies show expression and induction of TLRs and NLRs in skeletal muscle tissue and in myoblasts and myotubes in culture (35, 37, 144, 152). In skeletal muscle cells, LPS and fatty acids activate the NF-κB pathway, and these effects are blocked by inhibition/deletion of TLR4 (50, 113), demonstrating that skeletal muscle can indeed respond to bacterial products through this pathway. These receptors then signal within muscle to produce cytokines independently of any participation of immune cells, so that isolated quadriceps muscle or C_2C_{12} myotubes respond to LPS by expressing and producing TNFα, IL-6, and IL-10 (54, 93, 131).

Peptidoglycan and LPS also elicit expression of the chemokines CCL2 and CXCL1 in C_2C_{12} myotubes, signaled through the NF-κB pathway (9, 57). Similarly, in vivo, inoculation with low doses of LPS provokes an increase in TNFα and IL-6 mRNA in human skeletal muscle (4) and causes CCL2 expression in mouse diaphragm (67). LPS administration to mice in vivo activates muscle tissue proteolysis, induced by a systemic rise in glucocorticoids and independent of muscle TNFα expression or NF-κB signaling (123). Collectively, these studies show that muscle cells and tissue respond acutely to endotoxin (LPS) with a proinflammatory response that includes release of CCL2 and cytokine expression, which may in turn contribute to immune cell chemoattraction.

Myopathies. Skeletal muscle inflammation is evident in diverse myopathies, characterized by the presence of innate immune cells within the muscle beds. Typically, immune cell infiltration of skeletal muscle is more markedly noted in autoimmune myopathies (118), but genetic dystrophies also involve an inflammatory component, evoked by sustained muscle fiber damage during muscle contraction, that leads to fiber degeneration accompanied by inflammation and immune cell infiltration (11). In response to fiber damage, restorative progenitor cell activation competes with an ongoing fibrotic process that eventually curbs restoration of muscle function. Repeated cycles of damage, repair, and fibrosis lead to satellite cell exhaustion and fiber degeneration (40). In the case of experimental myasthenia gravis elicited by injection of anti-acetylcholine receptor antibodies in rats, local production of the chemokine CCL2 is observed (115), whereas opposite effects are achieved in mice with the NF-κB inhibitor bindarit (119). In Duchenne muscular dystrophy, gene/protein expression patterns reveal the induction of several chemokines and their receptors during the cycles of damage and repair (109), supporting the idea that locally secreted chemokines from muscle may promote migration and chemotaxis of monocytes and other leukocytes.

M1-polarized macrophages (iNOS positive) are found in muscle of 4-wk-old dystrophin-deficient *mdx* mice, and these cells cause muscle cell lysis via an NO-dependent mechanism; conversely, iNOS gene knockout markedly reduce soleus muscle damage (158). Similarly, immune-mediated necrotizing myopathy is characterized by a strong type 1 helper T cell (Th1)/classically activated macrophage M1 response, with significant increase in IFNγ, TNFα, and IL-12 levels (110). Therefore, an effective approach to treat myopathies may rely on targeting the inflammatory immune cell populations within skeletal muscle. Interestingly, M2-polarized macrophages also rise within *mdx* mouse muscle by 12 wk of age, responding to a local production of IL-4 and IL-10 (158), and it will be interesting to identify the cells that produce these cytokines. These M2 anti-inflammatory (CD206-positive) macrophages express arginase and are able to reduce NO production and muscle cytotoxicity. This may be accomplished through competition for the common substrate arginine, as was indeed observed in cocultures of M2 and M1 macrophages (158). Although arginine supplementation to *mdx* mice for 2–6 wk reduced M1 macrophage number, muscle inflammation, and muscle fiber damage, more prolonged supplementation (17 wk) induced muscle tissue fibrosis (162). These results are consistent with observations that M2 macrophages are profibrotic in muscle (11). Thus, the fate of muscle growth and regeneration relies greatly on the inflammatory polarization of macrophages during progression of myopathies. In addition, the profile of inflammatory markers differs in the invading macrophages from muscle with chronic injury compared to muscle with acute injury (148).

On the basis of these considerations, an alternative therapeutic approach to target inflammatory cells could rely on muscle-specific transgenic expression of nNOS, which in the *mdx* background vastly prevented muscle macrophage infiltration. In addition to effects on the immune cell populations, low levels of NO promote survival, activation, enhanced energy generation, and differentiation of satellite cells and muscle stem cells, helping them resist the oxidative environment of dystrophic muscle (12). Another therapeutic target, in Duchenne muscular dystrophy, could be the NF-κB/IKKβ signaling system. This is predicated on the basis that NF-κB activity is persistently elevated in immune cells and myofibers of *mdx* mice (1). Conversely, muscle tissue from *mdx* mice with reduced NF-κB signaling (p65 NF-κB heterozygous for one null allele, conditional deletion of IKKβ in monocyte/macrophages or conditional deletion of IKKβ in skeletal muscle) shows reduced macrophage infiltration and proinflammatory cytokines and improved regeneration of new muscle fibers (1). Targeting NF-κB may have a more general applicability, since chronic activation of this pathway by IKKβ overexpression in muscle leads to severe muscle atrophy (17).

In summary, mechanical defects in muscle integrity, inherent in a number of myopathies, elicit chronic inflammation of the tissue with a complex interplay of proinflammatory and anti-inflammatory mechanisms associated with the outcomes of muscle wasting versus muscle fibrosis. Modulating the immune cell infiltration of muscle in myopathies may hold promise in lessening the severity of disease.

High-Fat Feeding, Obesity, and Diabetes

Obesity, high-fat diet, or short-term lipid infusion in vivo causes insulin resistance in mice and humans, characterized by a drop in insulin-stimulated glucose uptake into muscle tissues and reduced ability of insulin to suppress liver glucose output (61, 134, 146). This is due to interference with insulin signaling, activation of stress signals (e.g., JNK, ER stress), and activation of inflammatory pathways (e.g., NF-κB) within adipose, liver, and muscle tissues (127).

The first indication of an inflammatory component in the pathogenesis of insulin resistance was the release of TNFα from adipose tissue of genetically or diet-induced obese mice (48). However, it was the discovery that most of the TNFα and other proinflammatory cytokines were produced by infiltrating macrophages within the adipose tissue that revealed that com-

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ponents of the innate immune system play a pivotal role in obesity-associated inflammation (163, 168). Subsequently, it was observed that pattern recognition proteins of the TLR and NLR families in mouse adipose tissue macrophages initiate inflammatory programs in response to saturated fatty acids (132, 164). Moreover, interfering with such innate immune receptors resolved obesity-induced insulin resistance (87, 124, 132, 164). Consequently, it was considered that the cellular inflammation of adipose tissue is a key factor in the development of insulin resistance, which may in turn impact on the muscle and liver (92).

The pathological conditions that lead to insulin resistance, such as high glucose (glucotoxicity), excess fatty acids and ectopic lipid deposition (lipotoxicity), oxidative stress, and ER stress are worsened and/or induced by inflammation (33). Indeed, cytokines and chemokines are elevated in the circulation of obese and diabetic individuals, and some (IL-1β, IL-6 and C-reactive protein) are predictive of diabetes (7, 33, 89, 163, 168). It has been proposed that these cytokines contribute to muscle insulin resistance in vivo (42, 60, 138). Supporting, but not proving this possibility, a number of cytokines elicit insulin resistance in tissues ex vivo and in cell culture (128). Thus, elevated saturated fatty acids and cytokines can each render muscle cells resistant to insulin. This has generated a view of muscle as a target of direct lipotoxicity and a "long-distance" receiver of macrophage output from the infiltrated adipose tissue, temporarily putting aside the possibility that a muscle-macrophage cross-talk may be a part of the insulin resistance phenotype.

Increase in innate immune cells within skeletal muscle. Strikingly, although skeletal muscle is the tissue responsible for the majority of postprandial glucose utilization, the possibility that immune cells within it might contribute to insulin resistance was initially barely considered. This may be because of the dismissal of this eventuality in some early reports that failed to detect macrophages within muscle tissue from obese humans (13), but also of a more recent study (143). On the other hand, a number of more in-depth studies have repeatedly observed increased macrophage numbers in skeletal muscle in association with obesity (34, 46, 89, 99, 154, 163). Specifically, an increase in macrophages was observed in skeletal muscle from obese nondiabetic subjects compared with lean controls, which correlated positively with body mass index and negatively with insulin sensitivity (154). Moreover, C57BL/6 mice fed a high-fat diet for 3 wk had a twofold increase in muscle $CD11b^+F4/80^+$ macrophages compared with mice fed regular chow (47). Another study found only rare F4/80-expressing cells between myofibrils, but showed that the percentage of $F4/80^+$ cells markedly rose in muscular adipose depots surrounding the muscle in obese mice (99, 163). These macrophages may not necessarily have been inflammatory, but interestingly their increase within muscle was averted in transgenic mice with muscle-specific overexpression of the anti-inflammatory cytokine IL-10 (47). IL-10 may have a protective anti-inflammatory role in muscle tissue. However, bone-marrow transplantation from IL-10-null mice into irradiated mice did not worsen inflammation in adipose and liver tissues or insulin resistance of the latter upon high-fat feeding (64). Of note, however, this was confounded by augmented IL-10 expression in adipose and liver tissues but normal circulating IL-10. Thus, tissue production of IL-10 may still have anti-inflammatory actions on infiltrating immune cells.

The above results clearly document a diet-induced gain in macrophages within muscle and indicate that cytokines produced within the muscle tissue affect immune cell infiltration. They also raise the possibility that studies that interfered with macrophage accumulation in adipose tissue by genetic manipulation of the macrophage lineage might have also affected the muscle infiltration. Likewise, it is difficult to link the appearance of macrophages selectively within muscle to insulin resistance, given the concomitant infiltration of adipose tissue.

Building on those findings, we and others have shown that the population of muscle immune cells that increases with high-fat feeding includes *inflammatory* macrophages, denoted by gene expression of the proinflammatory macrophage marker $CD11c^+$ (34, 89). Furthermore, upon collagenase treatment of muscle and dislodgement of single cells, a population of $F4/80^+CD11c^+$ cells was detected by flow cytometry, which was augmented in mice fed high-fat diet (34). Although there were fewer inflammatory cells per gram of muscle than of adipose tissue, the gain was significant and the immune populations were distinct in each tissue. Moreover, in muscle from insulin-resistant type 2 diabetic humans, we found elevated inflammation markers (CD11c and L-selectin) and a rise in macrophage number (CD68) compared with insulin-sensitive controls (34). Collectively, these results suggest that a muscle-immune cell cross-talk arises during obesity and correlates with insulin resistance in rodents and humans.

The gain in macrophages may result from infiltration driven by saturated fatty acid-dependent, muscle-derived cues and/or by adipose cells within skeletal muscle at vascularization sites (157, 163). Additionally, resident macrophages in interstitial spaces of the epi- and perimysium, which typically respond to muscle damage (10), might undergo inflammatory polarization. These findings open a new way of looking at the inflammation that accompanies insulin resistance, revealing that, early on during high-fat diet, muscle gains inflammatory macrophages. Thus, lipotoxicity and inflammation may synergistically contribute to insulin resistance. Based on the time course of gene expression in the course of high-fat feeding, it has been proposed that lipotoxicity may initiate muscle insulin resistance, and chronic muscle inflammation would take a more prominent role once obesity is established (70).

Fatty acid-promoted cross-talk between macrophages and muscle cells. In an attempt to understand the possible consequences of the macrophage and muscle cross-talk, we and others utilized cellular systems of isolated myoblasts and macrophages and exposed one or the other cell type to fatty acids. In particular, the saturated fatty acid palmitate primed macrophages to release inflammatory cytokines such as IL-6 and the chemokine CCL2 (154). Conditioned medium from palmitate-treated macrophages sufficed to confer insulin resistance to L6 myoblasts in culture (60, 120, 154), suggesting the possibility that this cross-talk may also occur within skeletal muscle in vivo between populating macrophages and muscle fibers in the context of excess saturated fat. The insulin resistance was ascribed to the activation of novel PKCθ and -ε within the myoblasts, which caused phosphorylation on Ser^{1011} of the insulin receptor substrate-1 (IRS-1) and phosphorylation of JNK that in turn phosphorylated Ser^{307} of IRS-1. This dual regulation of IRS-1 caused insulin resistance in downstream

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signals (Akt, AS160) ultimately reducing translocation of GLUT4 glucose transporter to the membrane and thus lowering insulin-stimulated glucose uptake (60).

The macrophage-myoblast cross-talk also occurs in the opposite direction. Exposing L6 or C_2C_{12} muscle cells or excised soleus muscle to palmitate promotes IL-6, TNFα, and CCL2 expression (27, 41, 55, 106). These collective observations suggest the possibility that, in vivo, muscle fibers may produce cytokines in response to a lipid challenge during obesity. Indeed, type 2 diabetes is associated with NF-κB activation in skeletal muscle that is preserved upon isolation of primary myocytes, confirming the muscle cell origin of the response, at least in part (41). In exciting new findings, we observed that conditioned medium from palmitate-treated L6 muscle cells rendered macrophages inflammatory, evinced by elevated expression of IL-6, CCL2, and other inflammatory products (106). Together, these results suggest that factors released from muscle fibers and muscle macrophages may act synergistically to worsen the inflammatory environment within the tissue in the course of high-fat exposure (59, 154).

These emerging studies raise important questions. *1*) What are the specific products from muscle cells affecting macrophage phenotype, and what are the specific products from macrophages that render muscle cells insulin resistant? *2*) How are such products first detected by the recipient cell? While these questions are largely unanswered at the moment, there is growing evidence that pattern recognition receptors on muscle cells participate in the insulin resistance response to high-fat diet. TLRs and NLRs are expressed in both myoblasts and mature myotubes, and evidence suggests they play key roles in muscle growth and metabolism (37, 144). Stimulation of TLRs induces muscle cell autonomous inflammation and expression of cytokines and chemokines (9, 57). Although the effect of whole body ablation of TLR4 on insulin resistance is debated (95, 113, 132), LPS, presumably acting via TLR4, lowers muscle protein synthesis (69), elevates glucose utilization, decreases fatty acid oxidation (36), and induces oxidative stress and insulin resistance in muscle cells in culture and muscle tissue in vivo (19, 30, 94, 107, 152). However, TLRs are unlikely to be the only receptors involved, as stimulation of Nod2 (NLRC2) also elicits muscle cell-autonomous innate immune responses and insulin resistance (144). Consequently, it has been suggested that NLRs are innate immune components involved in diet-induced inflammation and its metabolic complications (3, 124). In contrast, during the course of high-fat feeding, activation of the NLRP3 inflammasome in skeletal muscle has yet to be reported, although it arises in adipose tissue (139).

In summary, emerging reports show that macrophage numbers, and in particular inflammatory ones, are elevated in muscle during obesity and that muscle cells can mount autonomous inflammatory responses under metabolic challenge. The consequence of muscle inflammation and the cytokines and receptors involved in the possible cross-talk between immune cells and muscle in vivo are beginning to unravel. Defining precisely the inflammatory signatures of muscle tissue, its

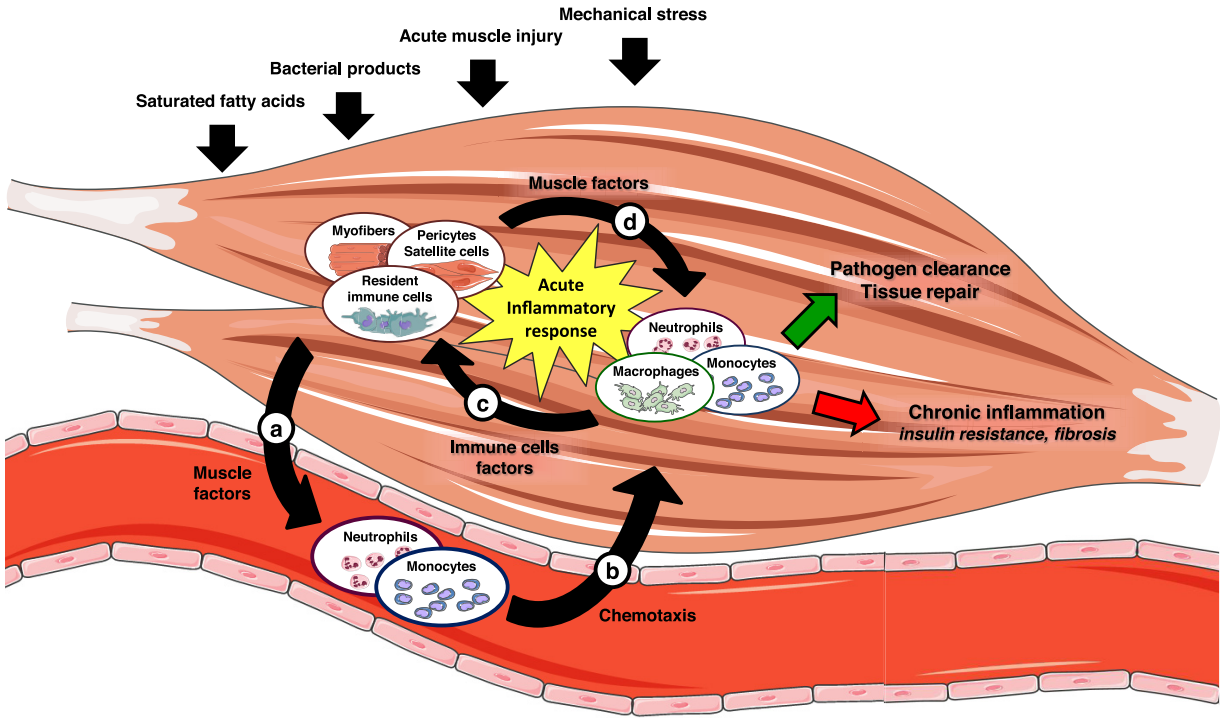

Fig. 1. Muscle inflammatory responses and macrophage cross-talk in response to diverse insults. *A* and *D*: acute muscle injury, mechanical stress (e.g., exercise, muscular dystrophies), endotoxins, and saturated fat signal through different pathways, activating the transcription factors NF-κB and/or c-Jun/AP-1, leading to expression and secretion of muscle factors (e.g., chemokines and nonprotein mediators; see Table 1). *B*: these compounds are responsible for the recruitment of immune cells from the circulation (neutrophils, monocytes) into the muscle. *C*: once in the tissue, the infiltrating and resident immune cells produce additional factors that reciprocally affect the muscle. This leads to the acute inflammatory response necessary for pathogen clearance and tissue repair (green arrow). If this cross-talk is deregulated, chronic inflammation ensues (red arrow) and leads to pathological complications such as fibrosis and possibly impaired insulin action (insulin resistance). This figure was created using Servier Medical Art (http://www.servier.com).

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causes, and how skeletal muscle interacts with immune cells and other metabolic tissues will be important to fully understand the pathology of obesity and type 2 diabetes.

Concluding Remarks

We have presented an overview of physiological and pathological conditions that reveal a close association between innate immune cells, particularly macrophages, and muscle cells. These are briefly outlined in Fig. 1. In particular, the muscle repair that occurs naturally in the course of eccentric muscle contraction may require the participation of recruited and tissue anti-inflammatory macrophages, depending on the severity of muscle damage. During significant muscle damage, cycles of macrophage infiltration with inflammatory and anti-inflammatory properties determine the balance of muscle repair and fibrotic outcomes. A number of myopathies, most likely because of their muscle-damaging consequences, also involve an innate immune cellular inflammatory response, which may exacerbate the disease symptomatology. Finally, early on in the course of high-fat diet in rodents and in the development of obesity and diabetes in humans, muscle beds gain inflammatory macrophages. Based on observations garnered from cellular coculture of media transfer, it appears that saturated fats can unleash a cycle of macrophage inflammatory polarization and muscle cell resistance to insulin. An in-depth analysis of the similarities and differences in the activation of macrophages in these distinct physiological and disease situations should be beneficial to the development of strategies to improve muscle repair, taper myopathic damage in disease, and restore insulin sensitivity. Given the epidemic proportions reached by obesity and type 2 diabetes and the prominent role of skeletal muscle to whole body glucose homeostasis, the cross-talk between muscle and macrophages should be studied in greater depth. The muscle-macrophage cross-talk that occurs in obesity/diabetes should be carefully compared and contrasted with the distinct events that take place during muscle injury, repair, exercise, and myopathies, in order to explore new ways to improve insulin action.

GRANTS

Work toward the realization of this review was supported by Grant MT12601 from the Canadian Institutes of Health Research and a grant from the Canadian Diabetes Association (to A. Klip). N. J. Pillon was supported by a fellowship from the Banting and Best Diabetes Centre of the University of Toronto. L. N.Fink was supported by a fellowship from Novo Nordisk A/S, Denmark.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: N.J.P., P.J.B., L.N.F., and A.K. conception and design of research; N.J.P. prepared figures; N.J.P. and P.J.B. drafted manuscript; N.J.P., P.J.B., L.N.F., and A.K. edited and revised manuscript; N.J.P., P.J.B., L.N.F., and A.K. approved final version of manuscript.

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