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REVIEWS

Fusion and beyond: Satellite cell contributions to loading-induced skeletal muscle adaptation

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Abstract

Satellite cells support adult skeletal muscle fiber adaptations to loading in numerous ways. The fusion of satellite cells, driven by cell-autonomous and/or extrinsic factors, contributes new myonuclei to muscle fibers, associates with load-induced hypertrophy, and may support focal membrane damage repair and long-term myonuclear transcriptional output. Recent studies have also revealed that satellite cells communicate within their niche to mediate muscle remodeling in response to resistance exercise, regulating the activity of numerous cell types through various mechanisms such as secretory signaling and cell–cell contact. Muscular adaptation to resistance and endurance activity can be initiated and sustained for a period of time in the absence of satellite cells, but satellite cell participation is ultimately required to achieve full adaptive potential, be it growth, function, or proprioceptive coordination. While significant progress has been made in understanding the roles of satellite cells in adult muscle over the last few decades, many conclusions have been extrapolated from regeneration studies. This review highlights our current understanding of satellite cell behavior and contributions to adaptation outside of regeneration in adult muscle, as well as the roles of satellite cells beyond fusion and myonuclear accretion, which are gaining broader recognition.

Abbreviations: ADAMTS1, A disintegrin and metalloproteinase with thrombospondin motifs 1; CXCL10, C-X-C motif chemokine ligand 10; DTA, diptheria toxin A; ECM, extracellular matrix; FAPs, fibro-adipogenic progenitors; GDF3, growth and differentiation factor 3; HGF, hepatocyte growth factor; IGF-1, insulin-like growth factor 1; IL-4, interleukin 4; IL-6, interleukin 6; MOV, mechanical overload; NAMPT/PBEF, nicotinamide phosphoribosyltransferase/pre-B-cell colony-enhancing factor 1; NO, nitric oxide; Pax7, paired box protein 7; PoWeR, progressive weighted wheel running; SIRT1, silent mating type information regulation 2 homolog.

KEYWORDS
endurance exercise, extracellular vesicles, hypertrophy, muscle stem cells, myonuclei, regeneration, resistance exercise

1 | BACKGROUND

The *bona fide* tissue-specific stem cell in mammalian adult limb skeletal muscle is the satellite cell. Satellite cells owe their namesake to the anatomical position in which they are observed,[1,2] on the periphery of muscle fibers and closely associated with the plasma membrane, as if orbiting the multi-nuclear muscle cell. These satellite cells, originating from the dermomyotome during development,[3–6] usually lay dormant in a quiescent state under resting conditions, and are identified by expression of the transcription factor Pax7.[7] The absence of Pax7+ cells through post-natal development[7] and pre-pubertal life,[8,9] as well as preventing their fusion during this time[10,11] results in smaller limb muscle fibers, implicating a requirement for satellite cells in skeletal muscle fiber growth.[12,13] Satellite cells fuse to radially and longitudinally growing muscle fibers and contribute new muscle cell nuclei (myonuclei),[14,15] which can explain why their absence early in life affects muscle mass throughout life. In mature skeletal muscle of sedentary mice (>4 months of age), satellite cell depletion does not have an appreciable effect on muscle fiber size or myonuclear number throughout the lifespan[16–20]; however, satellite cells are indispensable for regeneration after severe muscle injury.[21–24] In some unique skeletal muscles, such as craniofacial and extraocular muscles, satellite cells are less quiescent, contributing frequently to muscle fibers for homeostatic purposes.[18,25,26] In adult limb skeletal muscles, however, we propose that satellite cells primarily participate during dynamic processes such as growth and adaptation.

With exercise in adults, satellite cells activate, often proliferate, and may fuse to muscle fibers depending on the stimulus.[27–35] Historically, the fusion of satellite cells in response to mechanical stimuli in adult muscle is thought to be for the purposes of: (1) mediating the repair of focal damage to the muscle fiber,[24,36–40] and/or (2) myonuclear addition to maintain the so-called "myonuclear domain"[41–43] (i.e., a given myonucleus in the muscle fiber syncytium can only transcriptionally govern a finite jurisdiction) in response to hypertrophic growth[44,45] (reviewed previously by our laboratory[46]). Maintenance of the myonuclear domain and restoration of muscle fiber membrane integrity via satellite cell fusion are likely important aspects of satellite cell participation in exercise adaptation, but there is recent growing appreciation for the non-fusion roles satellite cells can play in adult muscle.[47,48] Indeed, the ability to specifically deplete satellite cells in an inducible fashion in adult skeletal muscle of mice confirmed their indelible role in myonuclear addition to adult muscle fibers via direct fusion,[21,32] but also revealed effects on ambulatory coordination as well as the behavior of non-satellite cells throughout muscle which has a marked effect on muscle fiber phenotype[23,32,49–53]; this includes secretory communication to muscle fibers, fibrogenic cells, and endothelial cells during adaptation.

The purpose of this review is to discuss the roles of satellite cells in adult skeletal muscle fiber adaptation to resistance- and endurance-type exercise. In addition to fusing to muscle fibers, satellite cells coordinate cellular choreography via secreted factors and potentially cell–cell contact to create a favorable environment for exercise adaptation. Although adult muscle can mount an effective adaptive response to endurance and resistance exercise in the absence of satellite cells, accumulated cellular dissonance within the muscle milieu ultimately results in a compromised long-term phenotype, which is likely driven by dysregulation of multiple cell types, including extra- and intrafusal muscle fibers.

2 | BRIEF HISTORY

2.1 | Satellite cells and adult muscle hypertrophy

Perhaps the first mention of satellite cell involvement in muscle growth outside of an early developmental context was by Reger and Craig, who studied muscle from a young girl diagnosed with neuro-ectodermal dysplasia and "bizarre muscle hypertrophy".[54] In this study, the authors concluded that "... satellite cells may serve as focal points for presumptive filament formation and muscle fiber enlargement by processes similar to those occurring in embryonic myogenesis." Shortly thereafter, using ^{3}H-Thymidine labeling, Schiaffino and coworkers performed functional overload studies in rats that provided compelling evidence for satellite cells as the source of new myonuclei observed during mechanical load-induced skeletal muscle hypertrophy.[44,45] Cheek et al. asserted that the demands on the nucleus are dictated by the protein synthetic requirements of a given cytoplasmic volume,[55] which provided the foundation for the concept of the myonuclear domain during skeletal muscle growth. Following

chronic stimulation, early evidence for a link between myonuclear density and transcriptional demand was provided in vivo,[56,57] although myonuclear number appeared to increase as muscle fiber size remained the same or decreased in these instances. The prevailing view around this time was that satellite cells primarily responded to damage as a consequence of muscle loading.[39,40] Later studies involving mechanically-induced growth posited that maintenance of a constant myonucleus-to-sarcoplasmic volume ratio (i.e., myonuclear domain) was a necessary component for successful hypertrophy, thus requiring satellite cell fusion to the myofiber.[58,59] The ability to directly test this hypothesis emerged almost 20 years later with inducible depletion of satellite cells in mice using a genetic Cre-inducible LoxP approach, the Pax7-CreER; Rosa26 Diptheria Toxin A model (Pax7-DTA).[21] This model, in addition to others where satellite cell fusion can be delayed or prevented during growth,[51,60] combined with very recent non-surgical advances for eliciting exercise in mice,[61–63] has allowed for unprecedented mechanistic insight into how satellite cells contribute to skeletal muscle hypertrophy.[64] Even with these advancements, at the present time, the absolute necessity of satellite cell fusion for hypertrophy is still debated (expanded on below).[65,66]

2.2 | Mechanical loading, physiological muscle damage, and satellite cell fusion to muscle fibers

Once satellite cells were identified as an autonomous cell population and subsequently named,[1,2] their role in non-contraction mediated/pathological muscle regeneration following injury was quickly recognized.[67–71] Unaccustomed activity of any type can be injurious,[72,73] especially if eccentric contractions are involved, but muscle damage is specifically apparent with mechanical loading used to induce hypertrophy in both rodents and humans.[39,74–76] The nature and magnitude of the damage response to muscle contraction is complex, and may involve a degree of muscle fiber degeneration and necrosis that provokes satellite cell activity and regeneration.[39,40] A recent example of extreme muscle damage with exercise in humans was provided by Mackey and Kjaer,[77] where very high volumes of eccentric weightlifting elicited a *bona fide* regenerative response. In this circumstance, the role of satellite cells in muscle repair is intuitive since the reconstruction of large portions of muscle fibers, or the formation of entirely new muscle fibers, necessitates them. Interestingly, it seems that satellite cell expansion with mechanical loading often exceeds what is required to repair muscle damage.[39,40,78] Coordinated regulation of proliferation, differentiation, and apoptosis in satellite cells likely ensures that satellite cell proliferative "overshoot" does not result in excess fusion to muscle fibers,[79,80] while recent evidence provides insight into how satellite cell exhaustion is prevented by exercise.[81] Under less strenuous conditions such as moderate intensity resistance exercise, damage induced by contractions is characterized by disruptions to the internal structure of muscle fibers that involve physical forces and/or excessive calcium release from the sarcoplasmic reticulum,[82–84] as well as localized "focal" damage to the sarcolemma.[36,39,40] In concert with sarcolemmal disruption, factors released from muscle fibers and subsequent immune cell infiltration are the likely main effectors of satellite cell fusion to muscle fibers with traditional resistance exercise (expanded on below).

To study mechanical load-induced adaptations in rodents, the primary approach is the synergist ablation surgical technique.[85–87] This invasive approach involves excision of one or two muscles necessary for ambulation to induce compensatory hypertrophy of a synergist and reliably elicits rapid and robust muscle growth, but is also associated with muscle fiber damage.[88] Even when measures are taken to reduce damage, such as modifying the surgical approach to attenuate the stimulus, signs of muscle damage can still be detected.[89] Satellite cells proliferate markedly and fuse to muscle fibers in response to synergist ablation,[39,90] making it an effective model for studying how satellite cells contribute to muscle fiber repair. Following complete removal of the gastrocnemius and soleus muscle (the most extreme form of synergist ablation) for 14 days in the absence of satellite cells, the plantaris muscle is histologically comparable to satellite cell replete muscle with the exception of less developmental myosin expression and centralized myonuclei, and fewer small de novo myocytes; muscle fiber strength at the single fiber level is also not compromised.[21] Satellite cells could accelerate muscle fiber repair processes given their involvement after muscle membrane re-sealing[37]; however, the findings of McCarthy et al. indicate that muscle fiber damage associated with robust short-term overload-induced hypertrophy is repairable without the explicit need for satellite cells, assuming that the few remaining satellite cells do not compensate in some way or some other cell type does not adopt the damage repair role of satellite cells. Even after 8 weeks of overload without satellite cells, muscle fiber function normalized to fiber size is not compromised.[32] If membrane damage is not catastrophic, cell autonomous membrane repair mechanisms intrinsic to muscle fibers[91–98] seem sufficient under strenuous mechanical load. Conversely, excessively damaging protocols involving forced intense running in the absence of satellite cell fusion results in significant muscle impairments.[24,99] Thus, the degree and cause of damage during load-induced hypertrophy, as well as the specific

hypertrophic stimulus, likely determines the necessity of satellite cells for successful hypertrophic adaptation.

3 | RECENT RESULTS

3.1 | Niche-derived cues for satellite cell proliferation and fusion during load-induced muscle hypertrophy

A challenge to understanding what mediates satellite cell fusion to adult muscle fibers with loading is that it is difficult to parse the effects of external cues from muscle fibers and/or mononuclear cells versus the cell autonomous effects of mechanical loading directly on satellite cells. Muscle fibers can grow appreciably without myonuclear accretion when hypertrophy is induced by genetic or pharmacological means in vivo (i.e., without tension or damage).[99–107] This suggests that mechanical loading is a key stimulus for satellite cell activity during growth. Some studies report that satellite cells on adult muscle fibers can be activated in response to stretch[108] and shear stress,[109] suggesting they are mechanosensitive and can act cell-autonomously with contraction in vivo. Mechanical strain on myogenic progenitors in vitro causes satellite cell proliferation but inhibits differentiation and fusion into myotubes.[110–112] These results suggest that mechanical tension directly on satellite cells in vivo certainly affects their behavior but may not directly stimulate fusion per se. Satellite cells also increase in number in response to in vivo mechanotherapy,[113,114] further pointing to mechanosensitivity of these cells, but this does not result in myonuclear accretion.[113] Collectively, these data suggest that the muscle fiber contraction/tension and/or damaging component of load-induced hypertrophy drives satellite cell fusion, at least in limb muscles.[26,115]

In a series of clever studies, Bischoff illustrated how adult muscle fibers and their associated satellite cells could be studied in vitro, and that the extract from crushed muscle stimulated satellite cell proliferation on adult muscle fibers.[116–118] These early investigations laid a foundation for continued inquiry into understanding paracrine factors that induce satellite cell proliferation and, perhaps ultimately, fusion to adult muscle fibers.[119,120] Recent research provides evidence that factors released in response to mechanical tension on muscle fibers and their associated satellite cells, such as hepatocyte growth factor and nitric oxide (NO),[121–126] may facilitate satellite cell activation and proliferation. NO can be released from differentiated muscle cells in response to stretch[126] and promote satellite cell fusion to muscle fibers in vivo,[127] representing a potential mechanism whereby mature muscle fibers could recruit satellite cells for myonuclear accretion during hypertrophy. Interleukin-4 has been implicated as a factor released from muscle fibers that promotes satellite cell fusion.[128] Serum response factor-mediated release of interleukin-6 (IL-6) from myofibers was also identified as a mechanosensitive cascade that elicits satellite cell-dependent myonuclear accretion[129]; this mechanism is supported by data on muscle fiber-derived IL-6 during development.[130] The exercise-sensitive factor Sirt1, when conditionally over-expressed in skeletal muscle, results in myonuclear accretion, albeit without muscle hypertrophy.[131] Evidence from developmental studies also suggests a YAP/NOTCH/JAG2 axis in muscle fibers during contraction may regulate satellite cell fate.[132] Furthermore, tunneling nanotubes between muscle fibers and satellite cells could transfer signals that promote satellite cell fusion.[133] Other niche factors from the muscle fiber such as Wnt4 are also known to control satellite cell fate progression.[134] Collectively, it is conceivable that when muscle fibers sense tension they communicate via various factors to recruit satellite cells and contribute myonuclei to support hypertrophy and potentially stabilize the "myonuclear domain"; however, further research is required to draw conclusions on when this process is initiated, and to which specific cues muscle fibers are responding to in order to elicit myonuclear addition.

A complex interplay of cellular dynamics ensues in response to mechanical load-induced hypertrophy, but it is becoming evident that exercise-stimulated infiltrating and inflammatory immune cells could be primary drivers of satellite cell activation, proliferation, and possibly fusion.[135,136] Macrophage-derived secreted factors such as ADAMTS1,[135] IGF-1,[137] GDF3,[138] NAMPT/PBEF,[139] CXCL10,[140] and metabolic intermediates[141] among others[142] may facilitate the process of satellite cell-mediated myonuclear accretion to muscle fibers in response to loading. Furthermore, a close physical association between macrophages and satellite cells[135,143–147] could influence satellite cell activity during muscle growth. With few exceptions, however, our understanding of how macrophages affect satellite cells comes from studying regeneration or pathological conditions. It must be emphasized that more work is needed to understand the paracrine and/or physical influence of myeloid cells on satellite cell fusion during growth in healthy adult muscle.

Other cell types in muscle, such as fibro-adipogenic progenitor (FAPs)[148,149] and endothelial cells, may influence satellite cell fusion to muscle fibers during hypertrophy via secreted factors and/or physical contacts. FAPs release a variety of proteins like IL-6 and Follistatin[150] that may promote satellite cell fusion to muscle fibers. Similarly, endothelial cells are known to reside in very close proximity to satellite cells and secrete factors such as Angiopoietin and extracellular vesicles that could ultimately contribute to satellite cell fusion.[151–155] Close anatomical proximity between

satellite cells and endothelial cells with resistance exercise has been well documented,[156–159] but again, little is known mechanistically about these cellular interactions in adult muscle during hypertrophy and whether they can drive satellite cell fusion, so more work is needed in this area.

3.2 | Circulating factors and satellite cell fusion during hypertrophy

In addition to local niche factors, circulating exercise-responsive factors may also facilitate satellite cell proliferation as well as fusion to adult muscle fibers during exercise adaptation. For instance, testosterone promotes satellite cell fusion in adult muscle,[160] but this is not the result of muscle fiber hypertrophy per se (at least initially),[100] and likely a direct cell-autonomous response of the satellite cells themselves.[161] Growth hormone,[162] Follistatin,[127,163] Apelin,[164] Ghrelin,[165] and potentially other factors that are modulated in the circulation by exercise could contribute to satellite cell proliferation and/or fusion to muscle fibers. While circulating factors may trigger satellite cell activity, it likely requires very high levels or continuous exposure to drive a satellite cell to fuse to an adult muscle fiber (as is the case with testosterone). We posit that local niche factors responding to muscle contraction play a larger role in influencing satellite cell behavior than circulating factors that are acutely modified during resistance exercise.

3.3 | Matters of controversy—The necessity of satellite cells for load-induced muscle hypertrophy

Over the last ~2 decades, an engaging discussion has been ongoing in regard to whether satellite cell fusion and maintenance of the myonuclear domain is required for adult muscle fiber growth during mechanical loading.[59,65,66,166–169] The development of the Pax7-DTA model of genetic inducible satellite cell depletion provided a valuable tool for testing the requirement of satellite cells during load-induced hypertrophy in mice,[21] but conflicting results using the Pax7-DTA mouse have left the question unsettled.[21,65,66,170] Although there is myonuclear domain flexibility in developing muscle,[10,11] as well as in myotubes undergoing hypertrophy in vitro,[171] satellite cell depletion in young mice (<4 months) impairs developmental growth.[8] It follows that imposing an additional load-induced hypertrophic stimulus on young growing mice requires satellite cells for adaptation.[89] By contrast, mature mouse muscle fibers have a significant myonuclear transcriptional reserve capacity during hypertrophy[21,89,172] and can activate pro-hypertrophic signaling in the absence of satellite cell fusion,[21] an observation supported by human and rodent studies.[46,173–177] On balance, it has been put forth that the larger the muscle fiber, the smaller the transcriptional reserve.[178] This may be most relevant in the context of early developmental growth since it seems that adult muscle fibers of all myosin types and size can grow during prolonged loading without myonuclear addition,[32,64] so more work is needed to substantiate this concept. Differing ages of mice used for experiments (immature versus adult) could in part explain why some studies report necessity for satellite cell fusion during hypertrophy while others do not. In addition, while human studies suggest satellite cells may be important for hypertrophy in aged skeletal muscle (especially in fast-twitch fibers),[179–182] satellite cell fusion seemingly cannot drive muscle hypertrophy in old age in mice or humans since depleting satellite cells[19] or increasing their number[183] does not alter hypertrophic responsiveness, at least in the short term.

In recent years, alternative models for preventing satellite cell fusion in vivo have emerged. These models disrupt some aspect of satellite cell function via genetic means,[60,88,184–187] and have generally concluded that satellite cell-mediated myonuclear accretion is required for overload-induced hypertrophy. Given dissonance between results from the Pax7-DTA mouse versus other models, we speculate that the presence of dysfunctional satellite cells could be more deleterious to load-induced muscle adaptation than removing satellite cells from the muscle environment altogether; however, the muscle being overloaded (e.g., extensor digitorum longus versus plantaris), post-surgery/stimulus recovery status, genetic background of the mice, diet, or a variety of other factors may also in part explain the discrepancy. Beyond contributing new myonuclei, additional evidence points to satellite cells playing a powerful secretory role in supporting muscle fiber hypertrophic adaptation.[32] Hypertrophy can be initiated and sustained for a time in the absence of satellite cells in adult mice, but long-term hypertrophy (≥8 weeks) across all fiber types is blunted concomitant with excess extracellular matrix (ECM) accumulation.[32,188] Our laboratory reported that satellite cells communicate to fibrogenic cells[53,188] and muscle fibers[51] via delivery of extracellular vesicles containing miRNAs that control ECM deposition, influence inflammatory signaling, and promote muscle hypertrophic adaptation independent from satellite cell fusion. Emerging evidence in humans suggests that satellite cells may indeed control ECM deposition,[189] but more work is needed to confirm this relationship during load-induced

growth. Most recently, non-fusion satellite cell communication was shown to be sufficient to support synergist ablation-induced hypertrophy of the fast-twitch plantaris for 8 weeks, but an upper limit to the myonuclear domain may have been approached in the absence of satellite cell fusion.[53]

While synergist ablation has been the standard for studying muscle hypertrophy in mice, recent advancements in murine exercise models have allowed for more translatable insight into the role of satellite cells during hypertrophic growth.[61] Utilizing a voluntary progressive weighted wheel running approach (PoWeR),[62,63,190] significant muscle hypertrophy occurs when satellite cells are depleted prior to training in glycolytic (plantaris) and oxidative (soleus) muscles of adult mice, but growth is still blunted relative to satellite cell replete muscle.[64] Significant but attenuated hypertrophy with unweighted wheel running in the absence of satellite cells throughout the lifespan has also been reported.[20] Satellite cell fusion, myonuclear accretion, and/or fusion-independent communication alters myonuclear transcription to favor proper adaptation,[64] which emphasizes the necessity of satellite cells for sustained hypertrophic growth. Without satellite cells, a population of transcriptionally dysregulated or "cryptic" myonuclei emerges in response to acute exercise after 4 weeks of PoWeR; this transcriptional stochasticity likely contributes to blunted long-term hypertrophy.[191] Furthermore, once myonuclear accretion stabilizes after 4 weeks of PoWeR in satellite cell replete mice, satellite cells activate but do not fuse in response to a bout of exercise, further pointing to satellite cell contributions to adult muscle adaptation beyond myonuclear donation. Using a different model that prevents satellite cell fusion in vivo (Myomaker depletion)[192] combined with involuntary high-intensity incline treadmill running, a complete lack of hypertrophy was reported.[99] The systemic (frequent shocking) and local stressful nature of this stimulus (evidenced by continuous myonuclear accretion throughout training) and/or disruption to other functions of satellite cells with the deletion of Myomaker may contribute to the absence of hypertrophy observed. Recent evidence suggests that the nature of satellite cell activation and participation during load-induced growth is dependent on the level of muscle damage[88] as well as the stage of adaptation,[191] so there is still much to learn about how satellite cells contribute to hypertrophy.[193] In broad terms, however, resident myonuclei can support an appreciable degree of hypertrophy during exercise/loading in the absence of satellite cells, but the participation of satellite cells via fusion and/or communication maximizes adult muscle growth (Figure 1).

3.4 | Satellite cells and endurance exercise adaptations

Satellite cell contribution to endurance exercise adaptation has been less studied relative to resistance training, likely because satellite cell fusion and myonuclear accretion or replacement is not believed to play a major role with this mode of exercise. Satellite cells are responsive to endurance-type exercise in rodents and humans.[194–199] They can activate, often expand in number, and sometimes fuse independent from hypertrophy[200–203]; however, a degree of muscle damage with unaccustomed endurance exercise may obscure how satellite cells contribute to the adaptive response to endurance training.[63] Satellite cell fusion as a consequence of unaccustomed exercise training in the absence of hypertrophy may be most attributable to damage-mediated satellite cell behavior.[38,72]

In mice, wheel running after satellite cells were deleted in adulthood affects coordination through dysregulation of intrafusal spindle fiber phenotype and function,[20,204] suggesting that satellite cells preferentially contribute to intrafusal fiber homeostasis. The classic fast-to-slower fiber type transition with wheel running is not influenced by the loss of satellite cells in limb[204] or diaphragm muscle.[18] To our knowledge, no study involving satellite cell depletion has reported impaired fiber type transitioning regardless of the stimulus.[20,48,64] Furthermore, there is no loss of myonuclei with wheel running over 8 weeks in the absence of satellite cells in adult mice,[204] nor with wheel running throughout the lifespan.[20] These findings suggest that satellite cell-mediated myonuclear replacement is not a prominent feature of endurance exercise adaptation,[32,64,188] assuming a different non-satellite cell population does not mediate myonuclear replacement. Hypertrophy induced by genetic manipulation may occur independent from satellite cell contribution,[99,102,103] but artificially driving an oxidative phenotype simultaneous with genetically-mediated muscle growth is associated with increased myonuclear number, suggesting a potential causal link between metabolic demands, growth, and the need for myonuclear accretion.[104] In the absence of satellite cells, PoWeR (which involves endurance- and resistance-type stimuli) elicits myonuclear transcriptional disruptions to metabolic pathways, purporting a tradeoff between oxidative and hypertrophic adaptations when satellite cell contribution is abolished. To this point, endurance cycle training in sedentary humans elicits hypertrophy in oxidative and glycolytic fiber types,[33,205] but only oxidative fibers experience an increase in satellite cell abundance and myonuclear accretion.[205] Since there is often a certain degree of hypertrophy that ensues during endurance type-training,[206] it can be difficult to tease out the specific effects of endurance training adaptations

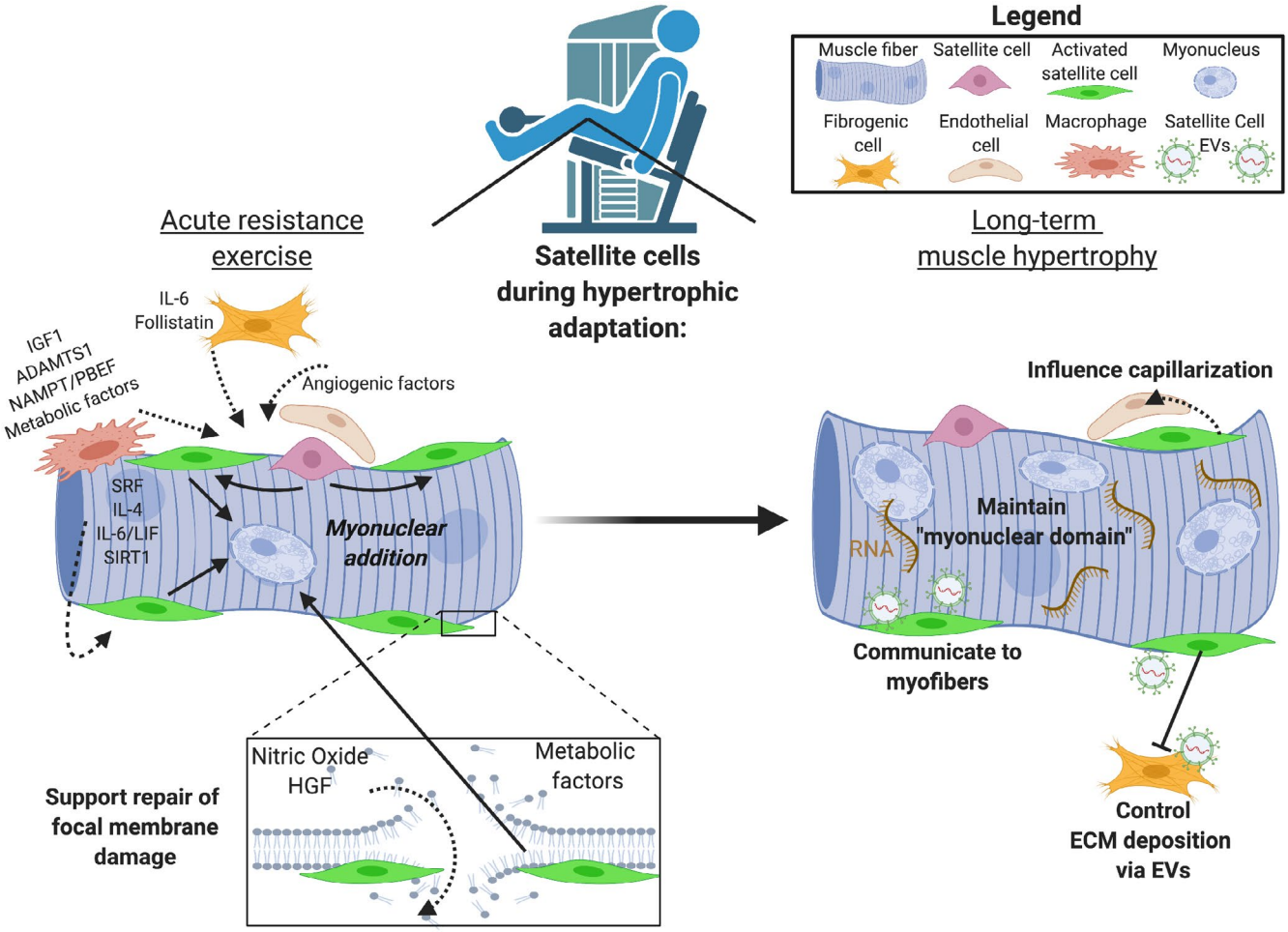

FIGURE 1 Summary of how satellite cells contribute to hypertrophic muscle adaptation in response to loading

versus muscle growth[20,33,205]; more work is warranted in this area.

As mentioned above, there appears to be a relationship between satellite cell activation and proximity to endothelial cells in response to resistance exercise.[159] It stands to reason that satellite cells may affect endothelial cell adaptations to endurance training. During voluntary wheel running in the absence of satellite cells, capillarization was not compromised[204]; worth noting is that satellite cell depleted mice ran less relative to replete mice in this study, likely due to dysregulated ECM deposition around spindle fibers that impaired proprioception and running performance. Conversely, with a hypertrophic component added to high-volume running (PoWeR) and equal running volume, capillary density tended to be reduced in the absence of satellite cells. More demanding exercise may therefore rely on satellite cells for capillary adaptations; this finding was supported by muscle transcriptional profiling data and single nuclear RNA sequencing.[64] Further work is needed to understand how satellite cells influence capillarization, but there is likely an important relationship that is dependent on the mode, volume, and/or intensity of exercise. Endurance exercise training can also improve muscle regeneration in response to a subsequent severe injury in young[207] and old animals,[208,209] and this enhancement could be mediated by increased satellite cell number[196] as well as cell-intrinsic mechanisms.[209] One benefit of endurance training may therefore be improvements in healing potential with severe injury through augmented satellite cell participation. In general, the global contribution of satellite cells to endurance training adaptations seems more nuanced than the contribution to resistance training, but muscle fibers can still adapt to an appreciable extent without satellite cells.

4 | UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Regardless of the duration of satellite cell depletion in limb muscles under resting conditions, resident myonuclei do not appear to be lost, suggesting a low rate of basal myonuclear turnover.[16,20] Some work alternatively

reports a high contribution of satellite cell fusion to adult limb muscle fibers for homeostatic maintenance using genetically-driven cytoplasmic-localized fluorescent reporters,[17,210] and even higher contribution during exercise.[200] Interestingly, these fluorescent reporters can be transferred between myogenic cells in vitro and in vivo via extracellular vesicles,[51,211] thus complicating the interpretation of these findings. Improved genetic tools are required to elucidate the contribution of satellite cells to adult muscle fibers under different conditions. Satellite cells are widely accepted as the primary donors of myonuclei, but various lines of evidence suggest that alternative cell populations may contribute nuclei directly to muscle fibers.[212–217] Collectively, the amount and source of myonuclear turnover in adult skeletal muscle, and whether this is affected by exercise, are open questions that deserve further exploration. While muscle can adapt to an extent without satellite cells, it is currently unclear whether having augmented satellite cell number or function could enhance exercise adaptation through development and/or in adulthood; human resistance training studies point to this possibility in some instances,[35,182,218–221] but correlation does not mean causation. How satellite cells contribute to neuromuscular junction stability, as well as the myotendinous junction, are also provocative areas of inquiry,[50,222–225] especially in the context of exercise adaptation during aging. The precise effects of the process of satellite cell fusion itself during adaptation to exercise, independent from myonuclear addition, is also an open area of inquiry.

It is becoming apparent that stem cells in muscle, and specifically satellite cells, communicate with other cells via a variety of mechanisms. For example, satellite cells are enriched for the microRNA miR-206[188] and deliver it via extracellular vesicles to different cell populations (specifically fibrogenic cells) throughout muscle during loading,[53,188] but recent evidence also suggests miR-206 is expressed cell-autonomously in fibrogenic cells during regeneration and with muscular dystrophy[226,227]; more information on the nature of miR-206 regulation in muscle is therefore warranted. Uncovering all the ways by which satellite cells affect non-satellite cell populations during adult muscle adaptation, and translating these results to human populations, will be an exciting challenge for future investigations. More attention should also be paid to sex differences in satellite cell contributions to muscle adaptation, as this is incompletely understood.[27,220,228,229] Unfortunately, the vast majority of knowledge on satellite cell behavior during adaptation is extrapolated from developmental myogenesis or injury and regeneration experiments. More emphasis should be placed on how satellite cells behave and contribute to adult muscle adaptation outside of catastrophic damage and injury.[88,193] It is likely that the factors influencing satellite cell behavior during exercise differ from those during toxin injections, the study of which could potentially re-shape our understanding of satellite cell dynamics and niche interactions under different conditions.

5 | PERSPECTIVES AND SUMMARY

Although satellite cells were initially named for their anatomical location orbiting the muscle fiber, it is becoming clear that the name "satellite" was fortuitous, since these cells have a major function as communicators throughout muscle. As the principal cells responsible for the complicated multicellular process of tissue reconstitution, it seems intuitive that satellite cells in adult muscle play a central role in coordinating the activity of other cell types during exercise adaptation. In the absence of satellite cells during physiologic stress, fibrotic deposition can ensue, capillarization and coordination may be impaired, and myonuclear transcriptional dysregulation develops. Furthermore, if satellite cells are dysfunctional, it is possible that they may actively inhibit adult muscle adaptation, perhaps via altered communication with muscle fibers and/or mononuclear cells. We have learned much in the preceding decade about how satellite cells orchestrate muscle adaptations: through fusion and myonuclear donation to muscle fibers, secreted factors including extracellular vesicles, and physical contacts with other cell types (see Figure 1). The development of new murine genetic tools for conditionally and temporally controlling gene expression in muscle fibers[230] and satellite cells,[209] as well as novel exercise approaches for studying muscle adaptations in model organisms[61] will facilitate further discoveries that reveal how satellite cells contribute to adult skeletal muscle adaptation throughout the lifespan, and whether having augmented satellite cell number or manipulating their function could enhance exercise responses.

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DISCLOSURES

The authors have no disclosures to declare.

AUTHOR CONTRIBUTIONS

Kevin A. Murach conceived of the work, wrote the manuscript, and generated the figure. Christopher S. Fry, Esther

E. Dupont-Versteegden, John J. McCarthy, and Charlotte A. Peterson provided critical feedback and edited the manuscript. All authors approved the final version of the manuscript.

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