



Key concepts in muscle regeneration: muscle “cellular ecology” integrates a gestalt of cellular cross-talk, motility, and activity to remodel structure and restore function

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Abstract

This review identifies some key concepts of muscle regeneration, viewed from perspectives of classical and modern research. Early insights noted the pattern and sequence of regeneration across species was similar, regardless of the type of injury, and differed from epimorphic limb regeneration. While potential benefits of exercise for tissue repair was debated, regeneration was not presumed to deliver functional restoration, especially after ischemia–reperfusion injury; muscle could develop fibrosis and ectopic bone and fat. Standard protocols and tools were identified as necessary for tracking injury and outcomes. Current concepts vastly extend early insights. Myogenic regeneration occurs within the environment of muscle tissue. Intercellular cross-talk generates an interactive system of cellular networks that with the extracellular matrix and local, regional, and systemic influences, forms the larger gestalt of the satellite cell niche. Regenerative potential and adaptive plasticity are overlain by epigenetically regionalized responsiveness and contributions by myogenic, endothelial, and fibroadipogenic progenitors and inflammatory and metabolic processes. Muscle architecture is a living portrait of functional regulatory hierarchies, while cellular dynamics, physical activity, and muscle–tendon–bone biomechanics arbitrate regeneration. The scope of ongoing research—from molecules and exosomes to morphology and physiology—reveals compelling new concepts in muscle regeneration that will guide future discoveries for use in application to fitness, rehabilitation, and disease prevention and treatment.

Keywords Satellite cell · Myogenesis · Fibro-adipogenic precursors · Inflammation · Extracellular matrix · Migration · Exercise

Abbreviations

cGMP	Cyclic guanosine monophosphate	MRF	Muscular regulatory factor
ECM	Extracellular matrix	NAMPT	Nicotinamide phosphoribosyl transferase
FAP	Fibro-adipogenic progenitor	NMJ	Neuromuscular junction
HGF	Hepatocyte growth factor	NO	Nitric oxide
Hh	Hedgehog	NOS-I μ	Neuronal nitric oxide synthase
ICU	Intensive care unit	Sema3A	Semaphorin3A
IGF-1	Insulin-like growth factor 1	siRNA	Short interference RNA
IL	Interleukin	TSC	Terminal Schwann cell
mRNA	Messenger RNA	VEGF	Vascular endothelial growth factor
miRNA	MicroRNA		

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Foundational literature

The basis of any scientific exploration lies in the richness of observation and experimentation conveyed by researchers, including their respectful discussion of previous and concurrent work. Generations of emerging scientists, finding a research niche, contributing new concepts, and augmenting earlier ideas as their experience and resources grow, further decorate

the process of providing this review. The field of research on muscle regeneration is remarkably broad in its diversity of approaches and prospects, though nowhere near as remarkable as the myriad processes that are integrated to restore function and enable adaptation. So, a toast to skeletal muscle and all its fascinatingly interactive components, and to the ingeniously creative use of tools and concepts to push the frontiers of understanding muscle regeneration and how it can shape life.

Muscle and physical activity

Early observations, including potential influences of weather (barometric pressure, temperature) on strength (manual grip strength) by Fischer (1947), and the sociopolitical context of rehabilitation after World Wars I and II described by Boynton (1947), illustrate the broad scope of many early ideas about recovery and tissue repair. Few reports are specific to what we now understand as muscle-tissue regeneration, although the perspectives illustrate the way concepts can shape understanding and either extend or squelch curiosity-driven research.

In 1900, for instance, a pathologist (and assistant medical officer for the Royal Exchange Assurance Company) noted that exercise should not be abused (i.e., over-indulged), or undertaken over the level of normal daily activity, as it led to many negative consequences. Lister (1900) cautioned against “violent efforts” on summer holidays and offered now- quaint commentary on the consequence of over-exertion in the non-athletic. He also described that incidence of such injury is likely to increase with the “growing demands made on energies, knowledge, and intelligence in the working months by the increasingly-rapid inter-communications and severe competition of advancing civilization.” The comment that over-exertion was much less frequent among women as they did household chores gives the paper a historical context.

In 1922, Rowlands (1922) suggested for the first time, that activity might accelerate wound healing. While not specific to muscle regeneration per se, Rowlands questioned the prescription of prolonged bedrest after surgery—typical accompaniment to hospitalization after many procedures well into the 1980s. Rowlands was “not aware of any delay in wound healing due to getting up early and taking gentle exercise...[since] gentle movements of wounded soft parts do not hinder but help the process of healing.” In concluding his conference paper, Rowlands called for a more thorough assessment of the influence of activity in post-operative recovery, to prevent adhesions and muscle shortening that appear after prolonged inactivity. He politely recommended that “taking gradually increasing exercise, just short of fatigue” would be useful and provide interesting “mental diversion” during recovery.

Assessing muscle function

By 1949, Newman (1949) recognized “the importance of an accurate evaluation of a disability”, since “muscle strength, to a great extent, governs the amount of function of a part.” While this might seem obvious now, many early measurement devices were not standardized and their use was not subject to guidelines for positioning a patient or calibration that could be reproduced over time. Use of the tools was not standardized across investigators or clinical staff, to assure consistent application, and thus jeopardized assessment of function. In 1949, Woodard (1949) noted that muscle injury in athletes differed from that incurred by non-athletes, and thus required particular therapy including gentle muscle activity rather than rest, for optimal repair.

Brewerton and Darcus (1956) prefaced a 1956 review paper on methods of increasing muscle strength by stating that there little new information on muscle function had accrued since 1900. He cited Siebert (writing in German in *Z. Klin. Med.*, 1928) for recognizing that an increase in muscle size is not achieved by increasing the number of muscle fibers. (This is the current understanding of growth by fiber hypertrophy rather than a hyperplasia of fibers that occurs in indeterminate growers such as sturgeon (Hiebert and Anderson 2020). Darcus noted that “one of the few well-established facts is that the performance of muscles can be improved by systematic voluntary exercise.” He then discussed the lack of consensus on how that could happen or the changes in muscle structure and function that happen during strengthening, despite “the determination of the workers in this field” in developing training routines and equipment. He also noted that researchers were still looking for evidence that the muscle capillary network increases with training and adaptation.

The neuromuscular system and adaptation

Studying the neuromuscular system, Darcus distinguished changes to muscle (from force generation) from those to the nervous system (related to making best use of available force generation). By 1923, it was already established that reinnervating axons could regenerate through nerve stumps from early parabiotic-pair experiments (Morpugo 1923). However, Darcus was not sure that the normal process of muscle hypertrophy was different from that in muscle atrophied by denervation or inactivity. Further, it was not established how much fiber hypertrophy actually contributed to increases in human muscle strength, since findings from animal experimentation were not directly applicable to rehabilitation in people. Darcus recognized that training-induced increases in strength implied the existence of important neuromuscular adaptations in skill, recruitment of motor neurons and motor

units, and sensory (afferent) inflow to the central nervous system from muscle spindle contractions and from other tissues. However, he did not know whether the exercise by patients recovering from injury should be allowed to induce muscle fatigue, and cautioned against inducing “subjectively unpleasant” sensations that produced residual stiffness or soreness. In short, Darcus considered neuromuscular adaptations to be more important in the outcome of training than structural and biochemical changes in muscle. Neuromuscular adaptation, later termed muscle plasticity, was reviewed more recently (Pette 2001).

By 1949, Denny-Brown had published some of his classical work on electromyography and motor unit recruitment (Denny-Brown 1949); others had reported the importance of afferent information from muscle, tendons, and muscle spindles in regulating contractile force. Darcus noted that neuromuscular impulses facilitated synaptic transmission at nerve–muscle junctions (NMJs) and all along the reflex arc, and with sufficient repetition, might reduce resistance to signal transmission from stimulus to contraction.

Writing in the context of a raging polio epidemic, Darcus and his contemporaries would have had many daily reminders that **compensatory movements during rehabilitation were critical to restoring overall function**. Relevant to the current review, Darcus cited a 1943 paper by Griffiths (1943) that “the ultimate recovery of function may be delayed by inhibiting the normal habit” of a muscle. This further emphasized that exercise or at least muscle activity is important to functional recovery. Griffiths distinguished passive movement and anti-gravity assistance from active movement during recovery to restore muscle power after injury or surgery, and noted effective venous return was dependent on muscle contraction, without discussing myogenic repair itself.

The following year, Eccles (1944) concluded from animal physiology experiments that disuse atrophy is best countered by exercise in which muscle shortens during contraction; he noted that strong isometric contractions can maintain muscle condition reasonably well. Eccles also determined that the effectiveness of muscle stimulation to maintain muscle mass depended on more than changes in muscle length since the outcome of stimulation differed between extensor and flexor muscles. A 1957 address to the British Medical Society (Anonymous 1957) referenced Darcus’ work on neuromuscular adaptation, and noted a lack of consensus on how best to tailor resistance-exercise protocols to specifically build endurance, speed, strength, or coordination.

Modeling muscle

The cultivation of chopped muscle in a medium of embryo extract, Tyrode’s solution, and plasma, using a “lying drop” technique was described by Popogeff and Murray in 1956 (1956). Use of that culturing method quickly revealed that

precursor **cell dormancy (muscle satellite cells) was longer in normal than in dystrophic human muscle, and demonstrated myotube growth or hypertrophy in culture** (Geiger and Garvin 1957). The advent of tissue-culture methodologies opened the door to many research questions.

Studying muscle regeneration

As early as 1947, Diaz-Guerrero and Thomson reported (Diaz-Guerrero et al. 1947b) that the restoration of function after denervating gastrocnemius muscle (using a crush injury of the tibial nerve) was slower in hypothyroid than hyperthyroid rats. As well, they reported that **denervation atrophy occurred more quickly in hyper- than hypothyroid animals**. These findings were based on initial studies of muscle strength without denervation. The force of muscle contraction produced after indirect stimulation (i.e., stimulation to an innervating nerve) was lower, and fatigue greater in hyperthyroid than normal animals; hypothyroid animals showed no change in strength and had only a slightly increased fatigue of muscles tested with the nerve-stimulation protocol (Diaz-Guerrero et al. 1947a). In that exercise and activity provide voluntary (nerve-dependent) generation of muscle contractile force, these early studies established the important impact of the metabolic state on nerve–muscle interactions, atrophy, and neuromuscular repair.

Studitsky conducted early experiments focussed on muscle regeneration from 1952 to 1964. He compared regeneration in young and old animals (often rats), and transplanted crushed or minced muscle into an emptied muscle bed. He also documented the progressive return of function during muscle recovery from damage. Unfortunately, the intriguing titles in Russian are not accompanied by translations (Carlson 1968). His book chapter in English in 1963 (Studitsky 1963) describes the fascinating process of myogenesis in cultures of muscle explants. Fortunately, Carlson visited and worked in Studitsky’s lab, and was able to bring to broad attention to those experiments in later reports in English. By 1968, Carlson confirmed that use of minced-muscle in modeling cellular processes provides major opportunities for observing the chronology of a synchronized process of muscle regeneration (Carlson 1968).

Notably, by 1945, the surgical literature had identified the features of muscle regeneration induced by loss of vascular supply, including the “myotube stage” discussed by Le Gros Clark and Blomfield (1945) and took note of previous studies of contractures after traumatic wartime injuries or vascular occlusion (Brooks 1922). Brooks confirmed findings of an earlier paper by Rowlands (1905) that identified the serious sequelae of muscle damage from ischemia–reperfusion injury. Church cited even earlier work by Waldeyer (1865) and Volkman (1893) that described regeneration processes that involved “continuous sprouting from viable fibres...

and discontinuous budding from surviving fibres of single cells... that ultimately give rise to new fibers” (Church et al. 1966). These were early observations that identified the role of activated satellite cells in myogenic repair, although the cells were not named as such, or identified in their quiescent state, for years to come.

Carlson’s impressive monograph in 1973, *The Regeneration of Minced Muscles* (Carlson 1972), detailed the histological progression of muscle tissue repair. In the epilogue, Carlson notes seven “potentially... most profitable directions for future research,” including how damaged muscle survives, the source of muscle progenitor cells, muscle interactions (with vessels, nerves, and endocrine signals), the functional outcome of muscle regenerates, and the possibility that transplanting muscle minces or cells could be used to treat muscle damage or disease. Carlson identified problems in repairing muscle damage that involved excessive deposition of connective tissue and skeletal nodules; those sequelae were often related to poor vascularization at a particular stage of myogenic regeneration.

Muscle histology

Our current knowledge of the muscle regeneration process was founded on the rich descriptions of histological features of normal or pathological muscle repair under various conditions reported by many investigators, typically using mammalian models (e.g., Le Gros Clark and Blomfield 1945; Murray and Kodicek 1949). The often-voluminous descriptive text in these reports would never be accepted for publication in current journals, it clearly provides important details. Early histologists thoroughly explored the chemistry of tissue staining and learned about muscle metabolism. This was followed within a few decades by enzyme histochemistry (Snow 1973) and an early method of staining muscle satellite cells in a particular state (Ontell 1974). Sometimes descriptions were “persuaded” by presumptions about the process under investigation. For example, a description of fiber fragmentation (Murray and Kodicek 1949) refers in error, to two structures shown in figures that are actually muscle spindle fibers and “cuffs” of myoblasts and myotubes within endomysial sheaths of fiber remnants. Since such observations, confounded by interpretation or assumption, can linger in the literature and our brains, their influence on understanding may persist longer than new evidence. There is real merit to digging back with a skeptical lens, through classical reports to explore the basis of our current etymologies and insights. Often, though, early descriptions are valuable, and serve as a caution when we consider an observation is “the first report” on a topic.

Muscle satellite cells

Histology studies were quickly augmented by major advances in development of electron microscopy techniques in the 1950s. Techniques for ultrathin sections and electron-dense stains led to Mauro’s report (1961) of a presumptive muscle precursor cell, termed the satellite cell due to the position of those cells on muscle fibers. The same cells were the subject of speculation by Church et al. (1966), Shafiq et al. (1967), and Carlson (1968) who suggested they may become activated into myoblast precursors for muscle formation. By 1966 (Church et al. 1966), satellite cells were known to survive muscle damage and serve as reserve cells that transform into myoblasts that proliferate and form new fibers.

The 1969 monograph on *Regeneration of Striated muscle, and Myogenesis* (Mauro et al. 1970) illustrates the intense discussions during an international conference at the Institute for Muscle Disease in New York on the time-course of regeneration in amphibians and rodent muscle. Attendees at the conference also discussed the myoblast cell cycle, myoblast fusion into myotubes in vivo and in vitro, and the ultrastructural morphology of the satellite cell. In 1968, Carlson showed that muscle fibers regenerate with guidance from the internal structure of connective tissue in a muscle, such that new fibers are aligned to the direction of tension in the muscle regenerated from minced fragments, and that early muscle regeneration occurs independent of nerve supply (Carlson 1968).

In 1975, Bischoff (1975) reported use of a method of culturing single muscle fibers to examine the population of inactive satellite cells in residence on isolated fibers. In addition, he used a direct method, autoradiography to track the entry of satellite cells into the cell cycle, by their uptake of tritiated-thymidine into new strands of DNA during mitosis. Although immune detection methods are much faster, autoradiography is still a valuable technique, especially in combination with other methods of tracking gene expression and the histology of regenerative processes (Anderson et al. 1996, 1998a; McIntosh et al. 1998). By the 1980s, research had identified differences between muscle development in the embryo and muscle regeneration in adults (e.g., Hansen-Smith and Carlson 1979; Carlson and Faulkner 1983) and many details of the time-course of muscle regeneration (e.g., Aloisi 1970; Reznik 1970; Shafiq 1970; Hall-Craggs 1980; Maxwell et al. 1984; Schultz and Jaryszak 1985; Ontell 1986; Grounds 1987; Grounds and McGeachie 1987; McGeachie and Grounds 1987; Brooks and Faulkner 1988; Carlson and Faulkner 1989).

Muscle fiber types

In 1968, McComas and Thomas (1968) reported electrophysiology studies that implicated the existence of slow and fast muscles in humans. In 1976, Khan confirmed the likelihood that slow-twitch muscle had the same histochemical pH-dependent staining pattern as type-I oxidative fibers (Khan 1976b) and had identified fast-oxidative-glycolytic fibers (type-IIA) (Khan 1976a). By the end of the 1980s, there was a burgeoning literature describing fiber-typing studies that compared different muscles in a huge range of species, and during development, adaptation, aging, regeneration, reinnervation, metabolic shifts, and disease (McComas and Thomas 1968; Tomonaga 1977; Hagglmark et al. 1981; Hagglmark et al. 1986; Staron and Pette 1986, 1987a, b; Anderson et al. 1988; Coulton et al. 1988; Jakobsson et al. 1988; Termin et al. 1989; Dusterhoft et al. 1990; Klitgaard et al. 1990; LaFramboise et al. 1990; Parry and Wilkinson 1990; Goldspink, 1991; Coggan et al. 1992; Welle et al. 1993).

The basics of myogenic regeneration

Myogenic regeneration begins with damage to fibers that degenerate and are removed by phagocytosis. Damage also activates satellite cells which proliferate as spindle-shaped myoblasts that cycle, fuse and form new syncytial fibers, initially with central nuclei. Myotubes subsequently elongate toward attachment sites at tendons and on bone. Bone also responds to the presence or loss of pull from muscle (Anderson et al. 1993). Tissue repair in a muscle belly can be highly successful, comprising restoration of many types of tissue: myogenic, vascular (initially capillaries), nervous (initially Wallerian degeneration of axons and then elongation of growth cones through any surviving nerve stumps, or toward NMJs on remnant tubes of endomysial basal lamina tubes (previously surrounding fibers), and connective tissues (extracellular matrix (ECM) including endomysium, perimysium, epimysium, and tendon connections to fibers). Regenerated muscle fibers are typically aligned to the original orientation of fibers.

Given the architecture of skeletal muscle tissue and the wide range of injuries and diseases that provoke muscle to regenerate, it is important to remember that a reproducible approach to sampling the regeneration time-course requires attention to the location and type of injury in the tissue and the time elapsed since injury. Regeneration is typically localized around an area of injury, with some extension into the surrounding undamaged tissue due to the migration of myoblasts along fiber and endomysial remnants in the ECM (McIntosh et al. 1994). Injury can be very focal, more broadly segmental across a short portion of the fiber length as in muscular dystrophy, or widespread as in avascular

necrosis modelled by denervation–devascularization injury (Anderson 1991; Mechaliuk and Bressler 1992; Lefaucheur and Sébille 1995). Thus, the extent and location of initial tissue damage, whether it is synchronous or sporadic and recurrent, and its homogeneity in a muscle belly should determine the timing and location of any approach to investigating the time-course or outcome of regeneration. It is useful to remember that delayed regeneration is not necessarily defective.

Early concepts

- i. Myogenic regeneration follows a similar pattern and sequence, albeit with different timing, across species and many types of damage; the pattern differs from the epimorphic regeneration of limbs in urodele amphibians.
- ii. Muscle tissue regeneration can be very successful but does not always restore function.
- iii. Large areas of damage often leave a deep fibrotic scar.
- iv. Cells in skeletal muscle can form bone, adipose, and fibrous connective tissues.
- v. Regeneration from ischemia–reperfusion injury has a less functional outcome than after anoxia.
- vi. Assessing muscle function to track regeneration requires standardized protocols and tools.

The current context

Myogenic regeneration is the subject of many excellent reports and reviews (Charge and Rudnicki 2004; Ciciliot and Schiaffino 2010; Carosio et al. 2011; Tidball 2011; Musaro 2014; Dumont et al. 2015a; Domingues-Faria et al. 2016; Qaisar et al. 2016; Joannis et al. 2017; Le Moal et al. 2017; Zammit 2017; Cornelison 2018; Li et al. 2018; Wosczyzna and Rando 2018; Chen and Shan 2019; Chazaud 2020; Forcina et al. 2020), and there are many more related to the benefit of activity or exercise, the impact of aging, differential injury-dependent regenerative responses, roles of micro-RNAs in regulating the stem cell niche, and the responsiveness of satellite cells. Although selected topics in the overall process will be highlighted, this review is primarily focussed on a high-level synthesis rather than a comprehensive overview of the wealth of important or essential factors involved in orchestrating effective myogenic regeneration and muscle tissue repair.

Injury

A diverse range of injuries leads to muscle regeneration, and some damage to fibers is needed to prompt the onset of the

muscle regeneration cascade; this is a truly beautiful example of tissue homeostasis in action (Musaro 2014; Musarò 2020). The impact of trauma changes the environment of all types of proximate and surrounding cells and the acellular matrix, and cells respond in marvelously coordinated fashion toward resolving an injury and restoring muscle function. However, the extent to which muscle-tissue damage is followed by regeneration and functionality is highly dependent on many variables. There are considerations about the initial insult, such as whether it is an acute or chronic injury or a single or repetitive injury; the volume of tissue injury and its distribution (widespread or focal) are also important. The age of the individual or animal are notable features as well, since age affects the number of satellite cells, the state of satellite cells (activation, senescence, stemness and self-renewal capacity, and exhaustion), and their responsiveness to muscle injury. Age also affects the composition and character of the ECM, the vascular supply, innervation, insertion points on bone, and any accrual of prior injury, scarring or disease conditions. The nature and configuration of the ECM (fibrotic or not) are additional determinants to the ultimate recovery of function, as is the possible involvement of denervation that may accompany the injury to fibers.

The timing by which inflammation is resolved has a major impact on functional recovery, as is the timing of vascular regeneration to ensure blood supply for debris removal and support regenerating tissue. Adiposity within muscle fascicles and the level of physical activity prior to an injury also play into the timing and extent of recovery, along with stresses of metabolic disease, transient systemic conditions, and/or the secondary impact of genetic, biochemical, developmental or epigenetic modifications to cells or molecules that mediate the outcome of regeneration, as reviewed elsewhere (Urso 2013; Mok et al. 2017; Robinson and Dilworth 2018; Mitchell et al. 2019; Long et al. 2021; Machado et al. 2021; Vechetti et al. 2021; Wen et al. 2021).

The discovery of muscle regulatory factor genes (MRFs) was a remarkable turning point in our understanding of the embryological development of muscle (Esteves de Lima and Relaix 2021); the four MRFs are re-expressed during the post-natal myogenic process of muscle regeneration. Expression of the first two MRF genes, MyoD and Myf5 by satellite cells increases after satellite cell activation. MyoD and Myf5 regulate the commitment of daughter myoblasts into the muscle lineage and myoblast proliferation, and induce expression of myogenin. Myogenin and MRF4 are expressed soon after under appropriate conditions, and induce differentiation (Bentzinger et al. 2012; Knappe et al. 2015; Zammit 2017). Pax7 and Pax3 function in advance of MRFs in postnatal myogenesis (Buckingham and Rigby 2014; Buckingham and Relaix 2015).

Satellite cell activation, stemness, and motility

Initial damage induces degeneration of fibers and at the same time, activates muscle satellite cells, the stem cells that possess the all-important dual capability of self-renewing the stem cell compartment and producing committed myogenic cells. Satellite cells activation and cell cycle entry are regulated through Notch Wnt-signaling pathways (Conboy and Rando 2002; Conboy et al. 2003; Dhawan and Rando 2005; Luo et al. 2005; Le Grand and Rudnicki 2007; Srivastava et al. 2010; von Maltzahn et al. 2012; Subramaniam et al. 2013). It is well established that muscle satellite cells are a heterogeneous population (Tierney and Sacco 2016) that is regulated to maintain quiescence (Subramaniam et al. 2013; Arora et al. 2017; van Velthoven et al. 2017; Purohit and Dhawan 2019; Puri et al. 2021). Satellite cells are rapidly activated in response to damage, mechanical stretching and nitric oxide release, exercise and physical activity (Anderson 2000; Anderson and Pilipowicz 2002; Wozniak et al. 2003; Wozniak and Anderson 2007, 2009; Wang et al. 2009). Such regulation is affected by aging (Brack et al. 2005, 2007; Brack and Rando 2007; Collins et al. 2007; Joannis et al. 2017; Snijders and Parise 2017; Hwang and Brack 2018; Tierney et al. 2018, 2019; Kimmel et al. 2020).

Recent study of the capacity for stem-cell renewal—by way of CD34 expression modulated through insulin-like growth factor-1 (IGF1)-mediated Akt activation that reduces CD34 expression by inhibiting FoxO—introduced even further complexity in satellite cell heterogeneity. Experiments identified a state of “primed stemness” (cells with myogenic commitment) and more prevalent “genuine stemness” in muscle of younger animals (García-Prat et al. 2020), expanding on earlier studies of CD34-mediated satellite cell motility (Alfaro et al. 2011).

Although the proportion of the satellite-cell population with genuine-stem capability declines with age (Day et al. 2010; García-Prat et al. 2020) and satellite cells become increasingly refractory to stretch-induced activation with age (Leiter and Anderson 2010), those cells retain the capability of responding to damage and producing effective repair in old animals (Smythe et al. 2008; Shavlakadze et al. 2010; Lee et al. 2013; Domingues-Faria et al. 2016; Snijders and Parise 2017; Franco et al. 2019; García-Prat et al. 2020; Kimmel et al. 2020; Yamakawa et al. 2020; Delsmann et al. 2021). Thus, satellite cells clearly respond to mechanical stimulation through exercise (Wozniak et al. 2003; Gomes et al. 2004; Tidball 2005; Tatsumi and Allen 2008; Wozniak and Anderson 2009; Leiter and Anderson 2010; Tatsumi 2010; Hara et al. 2012; Zhang and Anderson 2014; Li et al. 2018; Eliazer et al. 2019); that and the regenerative response to injury are muscle-specific and

age-dependent (Leiter and Anderson 2010; Gigliotti et al. 2015, 2016).

The timing of satellite cell activation is important in muscle tissue regeneration. Premature activation before injury, established using treatment with a nitric oxide donor, can accelerate myogenesis following a myotoxic or crush injury, whereas the restoration of NMJs on newly formed myotubes is disrupted (Daneshvar et al. 2020). This reminds us that the desired outcome of regeneration, strength and voluntary control, results from coordinated nerve–muscle interactions, and that myogenesis is only one, albeit an important aspect of muscle-tissue regeneration. Interestingly, experiments with nitric oxide-donor treatments in mice also improve regeneration and reduce exercise-induced damage in dystrophic mice (Archer et al. 2006; Wang et al. 2009; Mizunoya et al. 2011), attenuate disuse atrophy after hindlimb suspension (Anderson et al. 2017b), enable exercise-induced hypertrophy in atrophic muscle of old mice (Leiter et al. 2012). While many mouse studies highlight the exciting potential for treating human Duchenne dystrophy via nitric oxide donors (Sciorati et al. 2006, 2010, 2011, 2013; Brunelli et al. 2007; De Palma and Clementi 2012), simply increasing its bioavailability by inhibiting phosphodiesterase can be detrimental (Timpani et al. 2020). Further investigations of applications to safely deliver nitric oxide to replace the normal functional release during muscle activity and mechanical stretch (Wozniak and Anderson 2007, 2009) in a dosing regimen that avoids excessive oxidative stress could promote muscle growth and regeneration, and benefit people with dystrophy, disuse atrophy, and sarcopenia (Alrushaid et al. 2018). Satellite cells are essential for myogenesis, hypertrophy during maturation, and regeneration. By contrast, muscle hypertrophy in adults can occur without satellite cell contributions to myofibers. However, that hypertrophy ultimately restricts growth, vascular arborization, strength, and remodelling of collagen, which affect longer term plasticity and adaptability (McCarthy et al. 2011; Jackson et al. 2012; Fry et al. 2014, 2015; Englund et al. 2020, 2021). The elegant experimentation demonstrated that the satellite cell population affects expression by myonuclei *inside* fibers, possibly through their production of extracellular vesicles. To quote a perspective on the paper, “in essence, satellite cells are more than just myonuclei in waiting, capable of affecting muscle health in a fusion-independent fashion” (Hawke 2020).

Migratory movements by myoblasts and others cells are implicated as determinants of the success of muscle regeneration (Siegel et al. 2009, 2011; Alfaro et al. 2011; Stark et al. 2011; Kowalski et al. 2017). Myoblast movement is itself, mediated from the supporting substrate containing fibronectin, which regulates Wnt7a signaling and myoblast proliferation (Bentzinger et al. 2013, 2014). The research platform of microfluidics technology with applications to tissue engineering, is a powerful tool in studying migration.

Microfluidics experiments provide major advances over earlier approaches to the real-time visualization of cellular physiology under exquisitely controlled conditions (Roveimiab et al. 2019) and disease modeling (Wang et al. 2021). For example, our recent microfluidics study explored the mechanisms by which the niche substrate has significant impact on responses by myoblasts (Roveimiab et al. 2020). Myoblast interactions with the substrate composition (collagens, fibronectin, laminin, etc.) as well as the extent and nature of connective tissue elements in the substrate, affect myoblast migration by the complex process of haptotaxis. Very recent experiments with inhibitors (Roveimiab, Lin and Anderson, *unpublished*) suggest a hierarchy of disruptions to different aspects of adhesion, speed and direction of movement, and cell–cell fusion result from interference in the fibronectin-integrin signaling pathway, affect the alignment of one myoblast and its juxtaposition toward the nucleus of a differentiated myotube. The movements of individual cells play a significant role in the outcome of myogenesis during muscle-tissue regeneration.

In addition, soluble elements in the niche also provide input to guide myoblast movements including the speed and direction of migration along isolated fibers (Siegel et al. 2009, 2011) or within a microfluidic device (Roveimiab et al. 2020). In particular, hepatocyte growth factor (HGF), also called scatter factor, binds to the “motogenic” c-met receptor expressed by both activated and quiescent satellite cells (Hartmann et al. 1992; Sonnenberg et al. 1993; Cornelison and Wold 1997; Dietrich et al. 1999; Webster and Fan 2013). HGF delivers a potent signal for positive chemotaxis and mobilizes populations of myoblasts (Roveimiab et al. 2020). Traction enabled by a haptotaxis substrate interacts with the configuration of the chemokine signal provided by the concentration or a directional gradient of HGF (Roveimiab et al. 2020). Even more complex is the signaling among different cell types including leukocytes (Panci and Chazaud 2021) and other inflammatory cells (Sakaguchi et al. 2014; Chen et al. 2015; Ferreira et al. 2015; Saini et al. 2016) in the environment of muscle precursors that are mobilized by injury.

Recently Hox10 expression and epigenetic methylation events at the Hox-A locus were found to mediate the topographical distribution of differential responsiveness by adult muscle stem cells (Yoshioka et al. 2021). This paper recalled earlier reports on cranial muscles that present continuous “remodeling” through satellite cell turnover and fusion into undamaged muscle fibers above levels seen in limb muscle fibers (e.g., McLoon and Wirtschafter 2002, 2003; McLoon et al. 2004). In these cases, there was higher Hox-A hypermethylation and Hox-A and Hox-C cluster gene expression, both robustly sustained after transplantation and regeneration by engrafted satellite cells. Loss of *Hoxa10* expression by postnatal muscle reduced the capacity for regeneration, indicating that satellite cells display a fascinating “positional

memory” based on developmental topography (including distinction between limb muscles and those innervated by cranial nerves). This memory-of-source feature of regeneration did not affect Pax7 or MyoD expression, the size of the satellite cell population or its ability to become activated. However, with *Hoxa10* inactivation, satellite cells resident on fibers cultured ex vivo, were not as good at migration—an essential process in myogenic repair; they also had impaired proliferation without displaying apoptosis. Rather, satellite cell-specific disruption of *Hoxa10* affected genes important in chromosomal segregation and spindle formation during mitosis, and in limb muscle, induced changes that led to the formation of micronuclei and chromosomal bridges without affecting myogenic differentiation or self-renewal capacity. Human satellite cells in culture mirrored the position-dependent distinctions in cell-cycling, gene expression, and the impact of HOXA10 knockdown by short interference RNA (siRNA) found in the transgenic mouse experiments. This report opens a new avenue toward understanding regional and muscle-specific differences in regeneration capacity and plasticity of limb muscles toward adaptation.

Two ideas: that the potential of muscle for regeneration and plasticity is regionalized, and that stem-cell function is influenced by epigenetic acetylation of Pax7 (Sincennes et al. 2021), together bring new implications to considering epigenetic modifications in responses to exercise, training, aging, hormones. Such ideas also raise to mind the regional patterning of genetic neuromuscular diseases such as the family of muscular dystrophies involving disruptions of the dystrophin-associated cytoskeleton (Sunada and Campbell 1995; Cohn and Campbell 2000; Durbeej and Campbell 2002). Epigenetic modifications to post-mitotic muscle fibers, recently identified to involve long non-coding RNA molecules, also affect adaptive responses to stress (El Said et al. 2021). The full-length influences of RNA sequences will likely be revealed to have further impact on skeletal muscle adaptation and repair.

Inflammation

Inflammatory cells are resident (as macrophages) in muscle tissue and attracted to the site of injury. They promote sarcolemmal repair, fiber growth, and regeneration (Cheung and Tidball 2003; Tidball and Wehling-Henricks 2007) in addition to removing damaged tissue following muscle injury. Macrophages resident within muscle tissue are highly plastic in establishing the stem cell niche and interact with satellite and other cells (Ratnayake et al. 2021). Experiments using a beautifully designed system to follow individual macrophages in real time in living zebrafish (Montandon et al. 2021) revealed that there are early interactions of muscle-resident macrophages with satellite cells through a macrophage-secreted compound, nicotinamide phosphoribosyl

transferase (NAMPT). NAMPT in turn, acts via the CCR5 chemokine receptor and establishes a short-lived niche that activates satellite cells; the same signaling contributes to regulate the pace and timing of myogenic regeneration (Ratnayake et al. 2021).

Muscle stem cell interactions with pro-inflammatory macrophages are thus very broad, and as macrophages rapidly shift to become anti-inflammatory, clues for both myogenic and non-myogenic processes are compiled over time through interactions of immune cells including macrophages with muscle stem cells (Chazaud 2020). Recent literature highlights the notion that macrophage activity determines whether repair is regenerative or fibrotic (Moyer and Wagner 2011; Muñoz-Cánoves and Serrano 2015; Juban et al. 2018; Yang and Hu 2018) through considerable cross-talk with muscle cells (Mann et al. 2011; Muñoz-Cánoves et al. 2013; Yang and Hu 2018). Thus, there is a balance between inflammation and myogenic repair in regenerating muscle: the inflammatory response to damage will ideally maximize the prospects for an effective regenerative response while avoiding a large catabolic response (Urso 2013).

The timing of macrophage transition from pro- to anti-inflammatory—required to trigger the resolution of inflammation during muscle regeneration—is critical, since early and late transition are both detrimental for recovery (Chazaud 2020). Signals that resolve inflammation begin when prostaglandins and other proinflammatory signals are inactivated or blocked; inflammatory cells are then removed from the damaged tissue by reverse migration, drainage and cell apoptosis, and apoptotic neutrophils (to minimize secondary necrosis) are cleared from the tissue. The transition to an anti-inflammatory state is facilitated by macrophage plasticity (Sugimoto et al. 2019).

Notably, muscle regeneration is impaired in autoimmune myopathies that result from inflammatory cell activation by antibodies against signal-recognition protein or HMG-CoA reductase; the impairment, a defect in myoblast fusion and fiber formation, was associated with deficient levels of IL-4 and IL-13 (Arouche-Delaperche et al. 2017). Thus, inflammation, its resolution and its etiology including direct muscle infection by viruses such as Zika, arboviruses, and SARS-CoV-2 (COVID-19) (Disser et al. 2020; Filipponi et al. 2020; Legros et al. 2020; Paliwal et al. 2020), are important during regeneration.

Fibro-adipogenic precursors

Fibro-adipogenic precursors (FAPs) in muscle are derived from neural crest; since the first report in 2010, FAPs are now understood to play key roles in configuring lineage determination and the outcome of proliferation by mesenchymal cells—both essential in regeneration of muscle (Joe

et al. 2010; Uezumi et al. 2010; Theret et al. 2021) and other tissues (Natarajan et al. 2010; Lemos et al. 2012; Paylor et al. 2014; Giuliani et al. 2021). FAPs are non-myogenic and give rise to fibroblasts and adipocytes, depending on signals such as from the innate immune system that regulates eosinophil and anti-inflammatory macrophage activity soon after tissue damage. Interleukin signaling, specifically IL-4 from eosinophils, promotes FAP proliferation and restricts the progression of FAPs to adipocytes. Notably, FAPs also mediate the removal of damaged, necrotic tissues after injury or in culture, and stimulate myogenic differentiation and MRF-gene expression by muscle precursors (Heredia et al. 2013).

Recently, a subset of FAPs that express Gli1 and Hh (hedgehog) proliferates rapidly after muscle injury and was identified as being responsible for restricting the development of adipose tissue during muscle regeneration. The role of Gli1-positive FAPs was emphasized by genetic ablation of Gli1-expressing cells, which impaired muscle regeneration through a transient expansion that produces paracrine signaling factors such as IL-6 and IGF-1 that act on satellite cells (Yao et al. 2021). That fibrosis—another essential aspect of muscle regeneration—reduces satellite cell proliferation and delays fiber growth during the regenerative response when FAP proliferation is inhibited (Fiore et al. 2016). Essentially, although the influences of FAPs during muscle repair may be short-lived, they make major contributions to the overall “tuning” of different molecular players regulating myogenic and other stem cells (Biferali et al. 2019; Forcina et al. 2020). Interactions of FAPs with fibroblast growth factor 2 (FGF2) through via miRNA-29a signaling promotes formation of adipose tissue in muscle during aging (Mathes et al. 2021).

Fascinatingly, fibroblasts were recently shown to fuse to skeletal muscle, a feature that enables the transfer of fibroblast-specific mRNAs that facilitate the transition of the fiber toward its tendinous attachment sites (Yaseen et al. 2021). That report solved a puzzle from earlier electron microscopy observations of muscle regeneration (Anderson 1991).

Very recently, direct isolation of FAPs, muscle stem cells and macrophages from human skeletal muscle biopsies, using a combination of fluorescence-activated cell sorting and mRNA sequencing at the single-cell level, was found to preserve the phenotypic behavior and expression of those cells (Jensen et al. 2021). The transcriptomics approach should prove exceedingly useful in translating discoveries of FAP contributions to muscle regeneration, and age-related changes in muscle tissue.

Extracellular matrix

The ECM plays a major role in muscle health, development, disease, and regeneration (Goetsch et al. 2003; Csapo et al.

2020; Forcina et al. 2020). Dynamic ECM interactions with every type of cell in the tissue (Cisternas et al. 2014; Dunn et al. 2018, 2019; Marcinczyk et al. 2019; Patel et al. 2019) occur through enzymatic degradation and remodelling by proteinases, including matrix metalloproteinases (Chen and Li 2009; Lu et al. 2011). The ECM also serves as a reservoir for growth factors, including HGF and IGF-1, with which matrix metalloproteinases can interact to promote regeneration (Kok and Barton 2021). ECM actually promotes muscle regeneration (Kuraitis et al. 2012), in part by haptotaxis-induced myoblast migration (Roveimab et al. 2020). And, ECM proteins mediate adhesion or attachment of muscle stem cells, meaning the ECM mediates satellite cell responses to mechanical activity and tissue perturbation (Li et al. 2018; Moyle et al. 2020).

The ECM forms a complex three-dimensional meshwork of proteins that surrounds myogenic and vascular cells, fibroblasts, and nerves within muscle tissue; that meshwork is synthesized and then modified by epigenetic and post-translational modifications with important implications in disease pathophysiology (Theocharis et al. 2016) and stem cell function (Sincennes et al. 2021). Proteins such as proteoglycan, integrin, collagen, fibronectin, hyaluronan, elastin, tenascin, and others, form a vast reference “library” that participates in any aspect of cell physiology, including regeneration. Realignment, damage, and remodelling of the ECM during regeneration also affect function and the outcome of regeneration, partly through cell attachments to the ECM through growth factor and other ligands it displays for binding with receptor-expressing cells. Such binding thus enables the internal actin cytoskeleton of those cells to be polarized according to their residency and migration within the interstitial space (Li and Gundersen 2008).

Our understanding of the signaling interplay between myogenic cells (and other cells) with components of the ECM and basement membrane adherent to cells (Pozzi et al. 2017) through receptors, proteolysis, and unmasking of cryptic sites in ECM proteins (Clause and Barker 2013; Brown et al. 2015; Barker and Engler 2017; Yeh et al. 2021) has shown major recent advances. These new ideas have brought biomechanics, tissue engineering, and nano-scale three-dimensional scaffold production into the realm of therapeutics for muscle regeneration (Turner and Badylak 2012; Choi et al. 2018; Dunn et al. 2019; Marcinczyk et al. 2019; Patel et al. 2019; Baiguera et al. 2020; Gilbert-Honick and Grayson 2020; Mihaly et al. 2021), promising prospects for implantable volumes of muscle tissue that will promote the ingrowth of vessels and nerves (Laumonier and Menetrey 2016; Gilbert-Honick and Grayson 2020). Interstitial fibroblasts between muscle fibers, produce many components of the extracellular matrix (ECM) and wrap around collagen cables (Gillies and Lieber 2011; Gillies et al. 2017).

Excessive deposits of connective tissue are detrimental to muscle function in muscular dystrophy, as suggested over 40 years ago (Duance et al. 1980); that impact is now well established in physiological experiments, computational modeling (Mann et al. 2011; Martin et al. 2016; Virgilio et al. 2021), and the clinical literature (Best et al. 2013; Lieber and Ward 2013; Teixeira and Duarte 2016). For example, the negative functional impact of extensive fibrosis and collagen deposition in skeletal and cardiac muscle of dystrophic *mdx* mice was demonstrated by functional gains after an anti-fibrosis treatment that reduced expression of collagens I and III. Treatment attenuated dystrophic damage due to the tissue stiffness that affects myofibers (Huebner et al. 2008), the satellite cell niche (Moyle et al. 2020), satellite cell proliferation, and myogenesis (Teixeira and Duarte 2016).

Vascular tissue

The supply and configuration of blood vessels around, along, and sometimes within muscle fibers is critical to regeneration and maintenance of muscle. Plasma carries potent systemic factors, and proteins including hormones, and cytokines (some anabolic and/or catabolic) (Conboy et al. 2005; Brack et al. 2007; Cornish et al. 2020a) while perfusion removes waste products and conveys red blood cells. Vascular architecture itself regenerates differently among various models of injury by freezing or toxicity (Hardy et al. 2016). Muscle satellite cells in particular, survive the loss of vascular supply and local ischemia, and will actively recruit endothelial cells to their niche during muscle regeneration (Collins and Kardon 2018). Notably, the impact of many circulating factors including metabolic regulators and signaling ligands conveyed via vascular supply, will depend on revascularization in regeneration.

Cell–cell cross-talk

Clearly there is cross-talk—a “social network”—among cells and between cells and the abiotic environment of degenerating and regenerating muscle tissue (Wosczyzna and Rando 2018; Biferali et al. 2019; Scognamiglio et al. 2020). Drawing a parallel between populations of organisms and populations of cells in muscle tissue [similar to cancerous cells (Somarelli 2021)], such a network could be considered a “cellular ecosystem,” since both populations are influenced by their environment (as in ecology, the interactions of organisms to each other and their surroundings), during adaptation and regeneration. There is very keen interest in what drives the outcome, which cell or combination of cells coordinates the many possible responses by other cells, and a strong push to identify the signaling networks

that integrate cellular, tissue, and systemic processes. For example, research on the dystrophin cytoskeleton connected to ideas of mechanically induced satellite cell activation by transients of nitric oxide (NO) gas (Wozniak et al. 2003, 2005; Wozniak and Anderson 2005, 2007, 2009). Other research on activity-induced angiogenesis (McAllister et al. 2008; Alfaro et al. 2011) and changes in NO concentration during muscle disuse, aging or dystrophin deficiency (Anderson 2000; Anderson and Pilipowicz 2002; Tatsumi et al. 2002; Anderson and Wozniak 2004; Wozniak and Anderson 2005; Leiter et al. 2012; Janke et al. 2013; Allen et al. 2016; Anderson et al. 2017b; Rogers et al. 2017) are related. The important structural role of dystrophin in the dystroglycan complex, and its anchorage of neuronal NO synthase are considered to “orchestrate” the epigenetic profile of muscle cells and affect adipogenesis through miRNA regulatory pathways during differentiation and regeneration (Marrone and Shcherbata 2011).

Redox control mechanisms also contribute to the process and outcome of muscle regeneration (Le Moal et al. 2017) through NO mediation of initial inflammation, myogenic repair, and the FAP-mediated processes of fibrosis and adipogenesis (Filippin et al. 2009, 2011a, b). Potential therapeutics to manipulate NO concentration or the NO-cGMP signaling pathway that could promote muscle regeneration or growth, attenuate muscular dystrophy, or prevent muscle-disuse atrophy were broadly explored (Archer et al. 2006; Pisconti et al. 2006; Tatsumi et al. 2006, 2009b; Betters et al. 2008a, b; Yamada et al. 2008; Heydemann and McNally 2009; Song et al. 2009; Wang et al. 2009, 2018; Wozniak and Anderson 2009; Li et al. 2010; Tatsumi 2010; Villanueva and Giulivi 2010; Filippin et al. 2011a, b; Mizunoya et al. 2011; Janke et al. 2013; Bonafè et al. 2015; Gigliotti et al. 2015; Aguiar et al. 2017; Anderson et al. 2017b). Mechanically mediated cellular interactions and the potency of NO signaling to satellite cells and surrounding blood vessels must be placed in context with the overarching genetic regulation of satellite cell activation and quiescence by Wnts, Notch, quiescence-specific gene-signaling networks, and epigenetics.

Satellite cells recruit endothelial cells and also promote angiogenesis by secreting vascular endothelial growth factor (VEGF); in turn, endothelial cells promote satellite cell expansion (Latroche et al. 2015). Satellite cells also pattern the architecture of nearby capillaries through VEGF-A signaling, and endothelial cells produce the Notch ligand Dll4 that helps sustain the stemness of satellite cells close to vessels by maintaining their quiescence (Verma et al. 2018). The proximate, even intimate, juxtaposition of two cell types, in this case endothelial and muscle satellite cells, has potent meaning for interpretation of regenerative signaling, just as the proximity of satellite cells on the fiber sarcolemma has for mechanical signal transduction

in satellite cell activation (Anderson 2000; Wozniak et al. 2003; Wozniak and Anderson 2009) and satellite cell influences on myonuclei and fibroblasts (Englund et al. 2021). Satellite cell interactions with macrophages include receiving macrophage-derived HGF which mediates secretion of semaphorin3A (Sema3A) by myoblasts (Yamada et al. 2010; Do et al. 2011; Sato et al. 2013; Sakaguchi et al. 2014). In turn, this influences many cells involved in muscle regeneration (Anderson et al. 2017a), and the development of slow fibers through neuropilinA–plexinA3, myogenin, and Mef2D signaling to slow myosin expression (Tatsumi et al. 2017). Importantly, Sema3A is implicated in synchronizing motor neurite elongation during the re-establishment of NMJs (Tatsumi et al. 2009a; Sato et al. 2013).

It is interesting to consider that while FAPs contribute to regulating satellite cell activity, satellite cells also configure the responsiveness of fibroblasts in the niche around fibers during hypertrophy (Fry et al. 2014). This cross-talk among cells during muscle regeneration thus has a systemic context (Pillon et al. 2013; Xie et al. 2013; Ferreira et al. 2015; Anderson et al. 2017a; Argiles et al. 2016; Belizário et al. 2016; Domingues-Faria et al. 2016; Gorski and Price 2016; Collins and Kardon 2018; Yang and Hu 2018; Chazaud 2020; Daneshvar et al. 2020), and that context means that cell-level responses at the local area niche (Mashinchian et al. 2018) integrate all the interactions among satellite cells, fibers, macrophages, terminal Schwann cells (possibly via Sema3A), the ECM (Huijbregts et al. 2001), and circulating factors such as cytokines, growth factors, and many other molecules.

Nerve–muscle interaction

The fascinating intricacies of nerve–muscle interaction, reviewed elsewhere (Delbono 2011; Shi et al. 2012; Blaauw et al. 2013; Witzemann et al. 2013; English et al. 2014; Tintignac et al. 2015; Gordon and English 2016; Gordon and Borschel 2017; Cornish et al. 2018; Macefield and Knellwolf 2018; Lepore et al. 2019; Rudolf et al. 2019; Swenarchuk 2019; Gordon 2020), underlie the essence of voluntary muscle function after regeneration, and depend on the extent and location of initial and secondary damage to fibers. Terminal Schwann cells (TSCs) bridge the synaptic cleft between axon terminals and the specialized sarcolemma at the NMJ (Barik et al. 2016), help maintain synaptic structure (Reddy et al. 2003; Feng et al. 2005; Feng and Ko 2008), and also contribute to the satellite cell niche. Recent experiments from our lab further implicate satellite-cell derived Sema3A secretion in mediating interactions of satellite cells with terminal Schwann cells during muscle regeneration and reinnervation processes (Daneshvar et al. 2020) (and *Daneshvar, Matsuyoshi, Tatsumi, and Anderson*, unpublished).

Physical activity and exercise

Physical activity and exercise induce muscle plasticity and adaptive responses in the absence of injury. During activity, fibers release myokines (cytokines) that exert autocrine, paracrine and systemic effects on muscle fibers (anabolic and catabolic) and satellite cells (Bugera et al. 2018; Cornish et al. 2018, 2020a, b). Those actions are integrated into the network of signals released from inflammatory and other cells (Febbraio and Pedersen 2005, 2020; Pedersen and Febbraio 2008, 2012) including bone and adipose tissues (Kirk et al. 2020). Regeneration of muscle after injury is significantly enhanced by exercise especially in synergy with injection of muscle stem cells (Contreras-Muñoz et al. 2021). Physical activity also modulates the immune response, releasing growth factors that promote angiogenesis (Gregory et al. 1995; Brutsaert et al. 2002; Faria et al. 2008; Aurora et al. 2014), and muscle contractile activity induced by electrical stimulation promotes nerve repair by upregulating neurotrophins and brain-derived neurotrophic factor (Gordon and English 2016).

Interestingly, optimal fiber hypertrophy requires satellite cell proliferation and accrued contributions of their daughter cells toward fusion, fiber hypertrophy is possible through myonuclear domain expansion without satellite cell contributions, and satellite cells are not essential for fiber-type adaptations to life-long physical activity (Egan and Zierath 2013; Qaisar et al. 2016; Englund et al. 2020). One form of severe muscle atrophy in humans is associated with admission to an intensive care unit (ICU) and is exceedingly resistant to treatment; it is attributed to the critical illness behind admission. A recent review distinguished ICU-acquired weakness by the predominant loss of myosin that affects both type-I (slow-twitch) and type-II (fast-twitch) fibers, and suggested resistance exercise during restricted blood flow (BFR) as a potential treatment (Lad et al. 2020). Metformin, a drug compound used to increase glucose transport into muscle and reduce blood glucose, reduces hypertrophy and transcriptional responses of skeletal muscle to resistance exercise training (Walton et al. 2019; Kulkarni et al. 2020). Interestingly, recent findings on a trial of BFR resistance-exercise training suggested that changes in systemic concentrations of a subset of myokines show differential responses based on age and resistance training, in association with increases in muscle strength and quality (*Cordingly, Anderson, and Cornish*, submitted).

A very recent paper demonstrated that exercise training in adult mice has differential impact on DNA methylation in muscle and non-muscle interstitial cells; detraining and also retraining demonstrated further differential responses, implicating “epigenetic memory” of prior adaptation that may help account for well-established differential response to exercise among muscles (Lavin et al. 2021; Sharples

2021; Wen et al. 2021). Of note, that even non-muscle cells respond to exercise training highlights the system-wide impact of physical activity.

Metabolism

Systemic and muscle-tissue metabolism, including variations due to nutritional status, metabolic diseases (e.g., cachexia), and non-neuromuscular conditions such as diabetes and non-alcoholic fatty liver, affect the outcome of muscle regeneration—so many features of muscle growth, power, strength, endurance, and plasticity are reliant on anabolic processes. Anything that impacts protein synthesis, turnover, and remodelling—including responses to systemic stress—will reduce the capacity for timely regeneration (i.e., the speed of tissue repair) if not its effectiveness. The issue of protein turnover is especially important in interpreting results, given that use of transgenic technologies to conditionally alter the expression of particular genes in a cell or tissue of interest at a particular age, are typically validated by testing the level of mRNA or protein expression from tissue, without identifying the half-life of the targeted protein or synthetic rate after tamoxifen administration ends.

A recently reported atlas of single cells and nuclei in damaged muscle and liver revealed a common stress–response profile or signature is shared by many types of cells in both tissues, and other tissues as found in published datasets. In both liver and muscle stem cells, quiescent prior to tissue damage, ERK1/2 expression was essential prior to the onset of Notch-regulated myogenesis (Machado et al. 2021). With parallel stress-response expression patterns in muscle and liver, it is not surprising to find that muscle is receptive to systemic physiological stressors (or that cell isolation itself is a stressor). The observation that metabolism itself makes system-wide interconnections across many types of cells including muscle stem cells. Each cell type has its own internal metabolic character, responsiveness and regulatory patterns mediated in its own distinctive niche; that idea forms a window into understanding tissue physiology (Chen et al. 2019; Purohit and Dhawan 2019).

A recent exciting report demonstrated systemic signaling through release of exosomal vesicles from myoblasts. Those vesicles are now known to mediate muscle growth (Murach et al. 2021; Vechetti et al. 2021) in the absence of satellite cell cycling. The notion of non-cellular, circulating and/or local influences on growth, cell–cell signaling, and likely regeneration in muscle, extend findings of systemic influences on regenerative capacity between old and younger animals in earlier parabiosis experiments (Conboy et al. 2005; Brack et al. 2007).

Myogenesis vs. muscle-tissue regeneration

Muscle regeneration is a “team effort”; an individual cell lineage acting on its own, cannot establish a fully functional muscle. The effective outcome of muscle regeneration therefore, depends on all the cellular players, the timing of damage and inflammation, muscle-specific architecture, and the physical use and activity of a muscle. The exquisite genetic, biochemical, physiological, and epigenetic regulation of the timing of satellite cell activation and changes in satellite cell transitions to and from quiescence with aging (Addicks et al. 2019; Kimmel et al. 2020; Sincennes et al. 2021) have major implications for muscle regeneration capacity. As well, the distribution of fibrosis, vascular compromise and oxygenation, inflammation, and muscle anatomy *before* injury will affect the whole gamut of myogenic processes that ensue, from a particular mode of injury in each muscle to the outcome of satellite cell cycling and myotube maturation (Csete et al. 2001). Again, fiber type plays a role, since shear forces on the sarcolemma are higher in rapidly contracting type-II fibers and make them more susceptible to exercise-related damage. Different species and taxa also present fascinating distinctions across many features of muscle development, satellite cell distribution and regulation, muscle use, and evolutionary modifications based on life-history that may affect regeneration capacity, as recently explored in a variety of fish species (Zhang and Anderson 2014; Knappe et al. 2015; Gurevich et al. 2016; Ratnayake and Currie 2017; Anderson et al. 2019; Pourghadamyari et al. 2019; Tingle et al. 2019; Christian and Benian 2020; Hiebert and Anderson 2020; Montandon et al. 2021). Although autophagy may decrease with aging, inducing an increase in autophagy can rescue the effectiveness of regeneration by muscles in old animals (Park et al. 2019; You and Chen 2021; You et al. 2021).

The balance between stem capability and myogenic commitment by proliferating myoblasts is highly dependent on the cytoskeleton of the underlying muscle fiber. The dystrophin-associated protein complex (DAPC) distributes neuronal NO synthase (NOS-I μ) within the dividing cell; that distribution, in turn, shapes the polarity of asymmetric division by muscle stem cells and normally ensures stem cell renewal (Dumont et al. 2015a, b; Chang et al. 2018; Feige et al. 2018; Addicks et al. 2019). Loss of dystrophin from the cytoskeletal complex has serious impact in dystrophic muscle, and leads to exhaustion of the stem cells (and self-renewal capacity) during the ongoing regenerative response to dystrophic damage. The mechanistic fine-tuning that retains or restores and sustains the viability of stem cell pool (Wang et al. 2019) is an essential concept for

undertaking future research; that viability encapsulates what otherwise may appear as a stochastic or randomized process that determines the fate of daughter cells—that was the basis of a fascinating discussion at conferences in the late 1990s, and the puzzle took decades of focussed research to resolve. The process by which epidermal growth factor rescues the function of dystrophic satellite cells and builds the stem-cell potential of their progeny (Wang et al. 2019) is only one of many details that now guides the search for therapies to promote regeneration.

The regulation of regenerative-muscle-cell lineages follows the pattern of networks mediated by muscle regulatory genes during development (Hernández-Hernández et al. 2017). The discovery of MyoD and other MRF genes in the mid-1980s (Zammit 2017) and the impact of their deficient expression (Megeney et al. 1996; Anderson et al. 1998b; McIntosh et al. 1998; Huijbregts et al. 2001) have since revealed many key aspects of muscle regeneration (Lassar 2017). The identification of non-coding micro RNAs that help regulate development (Mok et al. 2017) and regeneration (Drummond et al. 2008; Safdar et al. 2009; Aoi et al. 2010; Guller and Russell 2010; Nielsen et al. 2010; Wessner et al. 2010; Cheung et al. 2012; Sharma et al. 2014; Diniz and Wang 2016) adds additional layers of complexity to muscle responses to injury and disease. Further, the notion that exosomal vesicles convey important intercellular signals vociferously demands new approaches for testing hypotheses, including those used to characterize exocrine regulation (Mitchell et al. 2019).

A systems-biology approach incorporates the complexities of stem cell function (Wosczyzna and Rando 2018) and myogenic regeneration that proceeds in synchrony with inflammation and its resolution (Csete and Doyle 2002; Vodovotz et al. 2008), exosome signaling, re-innervation processes (Daneshvar et al. 2020), vascular perfusion, metabolism, and exercise (Henriksen et al. 2012; Bugera et al. 2018; Cornish et al. 2020a). Future research will reveal key intersections of the different processes that regulate muscle regeneration.

Notably, the mechanisms and actions of at least 25 gene products considered essential for myoblast fusion into the multinucleated syncytium known as a muscle fiber are not known (Deng et al. 2017). There is so much more to learn about myoblast interaction with, and migration through the ECM, and many physical properties of the cellular and acellular components of the niche around myoblasts as they fuse (Roveimab et al. 2020). Figure 1 provides an overview of local influences, muscle-specific environment, regional adaptive plasticity, and systemic influences on muscle regeneration from a generic injury.

Current key concepts of muscle regeneration

1. Myogenic regeneration occurs within the cellular ecosystem of muscle tissue. The ecosystem includes signals and responses by satellite cells, inflammatory and vascular cells, fibro-adipogenic precursors and derivatives, the ECM, and nervous tissue. Cells and their interactions within muscle tissue during myogenesis are further embedded in systemic physiology, physical activity, and aging. Evaluating the integrative physiology of this “ecosystem” with an open-ended systems-biology approach will become an increasingly essential, counterpart to the exciting and more focussed research that targets the single-cell behavior or molecular interactions.
2. Regenerative potential and the adaptive plasticity of skeletal muscle are overlain by regionalized epigenetic modifications implicated in responses to exercise, aging, hormones, circulating factors, and disease. The extent and timing of regeneration are muscle-specific and inter-related with the vascular architecture and the use of that muscle.
3. Cells “talk” and socialize amongst themselves and with the ECM while they respond to systemic influences. Precisely how this happens is exquisitely complex, as tantalizingly illustrated by ongoing discovery of processes influenced via nanotubes, exosomal vesicles, gaseous transmission, and systemic factors. New hypotheses now must account for the hierarchy by which responses of one cell induce and direct subsequent responses by other cells, including fibers. This systemic, intercellular cross-talk during muscle regeneration forms the gestalt at the satellite cell niche, the focal point of muscle regeneration. However, we should not forget that satellite cells also influence the postmitotic nuclei inside fibers, and can optimize long-term adaptation and muscle responses to exercise.
4. Cells move; all types of cells in muscle, will move, and their migration processes are essential to regeneration. Migration behavior is highly dynamic, both biomechanically and in time. Myoblasts build and change their own operational niche and leave exosome and nano-scale “clues” to other cells along their trajectory, with major implications to fiber formation and health, as well as regeneration. Anticipating cell movement necessitates innovative experiments to visualize and track functional molecular cascades – these methods are real-time “lenses” to help interpret observations by accounting for motility.
5. Physical activity and concomitant signaling are high-impact arbiters of the outcome of regeneration. As in

muscle hypertrophy, such signals to and from satellite (and other) cells in muscle, are mediated by integrated influences of metabolism, myokines, angiogenesis, innervation, and the configuration and composition of the ECM.

6. The intricate architecture of skeletal muscle, from the level of gross morphology in classical anatomy to its structure at ultrastructural, spectroscopic, and nanoscale resolutions, displays the functional hierarchy of a highly evolved muscle physiology. The complexity of muscle regeneration in three dimensions over time cannot be fully modeled by deconstructing the tissue processes in culture.

Research tools

Astute experimental design is critical to the clarity of research findings. The variables we measure, the research tools we use, the independent animal controls or human participants, and the specificity of our hypotheses—the questions we ask—are all part of anticipating research outcomes.

The tools for tracking the outcome of muscle regeneration have evolved tremendously since the early development of standardized instrumentation. Even a new, simple way to isolating primary satellite cells using ice-cold incubation, can advance research on regeneration (Benedetti et al. 2021). Recent discovery of MYC-dependent satellite cell function, revealed through CRISPR/Cas9 editing of the *MyoD* locus in young growing muscle, opened new potential for understanding how genome topology mediates activation of satellite cells (He et al. 2021). Exciting new avenues for conditional, cell-specific genetic manipulation will provide highly refined, wonderful insights into processes that change with gain- or loss-of-function by particular cells at particular junctures in regeneration, disease, and activity [e.g., (Wen et al. 2021)].

Multivariate readouts of muscle and single-cell transcriptomics, physiology and metabolism; systemic metabolism and biochemical interactions; and muscle structure coupled with functional genomics, cell-lineage tracing, and single-cell real-time tracking are all powerful tools, often accessible through collaboration. In effect, data readouts from studies on single fibers, dispersed cell cultures and co-cultures, and in vivo muscle tissue, coupled with diagnostics and treatment outcomes in a clinical setting can now be re-integrated by systems approaches (Owens et al. 2015). My lab ventured a short distance in that direction in our investigations of potential denervation and preserved satellite-cell responsiveness in muscle after rotator-cuff injury (Gigliotti et al. 2015, 2016, 2017), aiming toward eventual clinical trials to promote regeneration (Gigliotti et al. 2016).

Gaps

There are still major gaps in our knowledge of muscle regeneration related to the impact and type of physical activity, with all the local and systemic mediators released by exercise (Bugera et al. 2018; Cornish et al. 2018, 2020a, b). Physical activity likely influences the resolution of inflammation, where the timing is critical; myotube alignment during regeneration; and the role of the ECM and ECM-bound ligands in guiding cells during movement. Myoblast migration (Roveimab et al. 2020) and the mechanisms of axonal targeting to neuromuscular junctions through synchronized myogenesis and nerve–muscle connectivity during regeneration (Daneshvar et al. 2020) can be closely scrutinized by microfluidics applications, now used for high-throughput screening for mutations (Markin et al. 2021) and biological assays (Grant et al. 2018).

Newly formed fibers will continue to grow by hypertrophy and nuclear accretion as part of adaptations to activity or compensation for disease, but the epigenetic “finesse” on the outcome of regeneration (Giordani and Puri 2013) remains to be mapped. As well, the mitotic clock that shortens telomere length with repetitive cell cycling of precursor cells during regeneration from disease (Decary et al. 2000; Renault et al. 2000; Cooper et al. 2003) plays a role that is still contentious. We have yet to understand observations that in athletes, minimum terminal restriction fragment length is reduced only in proportion to the degree of stress during distance running and power lifting (Mouly et al. 2005; Kadi and Ponsot 2010).

Conclusions

Overall, the philosophy of research on muscle regeneration, if it could be characterized as a philosophy, is ultimately directed toward improving the outcome, however, remotely feasible. Indeed, functional recovery is the primary hallmark of muscle regeneration (Forcina et al. 2020). In considering how key concepts in this field of muscle regeneration have changed in the past 100 years (Table 1) and how methodologies and technologies have advanced, we find that even classical ideas, misinterpretations and assumptions (revealed by our current knowledge), and speculation and discussion by experts, all contribute to re-imagining the horizons of possibility.

The stepwise pattern of tissue changes during muscle regeneration is well established, involving inflammatory cells (M1 and M2), vasculature, satellite cells, fibers, FAPs, extracellular matrix, nerves, and myelinating and terminal Schwann cells. Each of type of cell both produces and

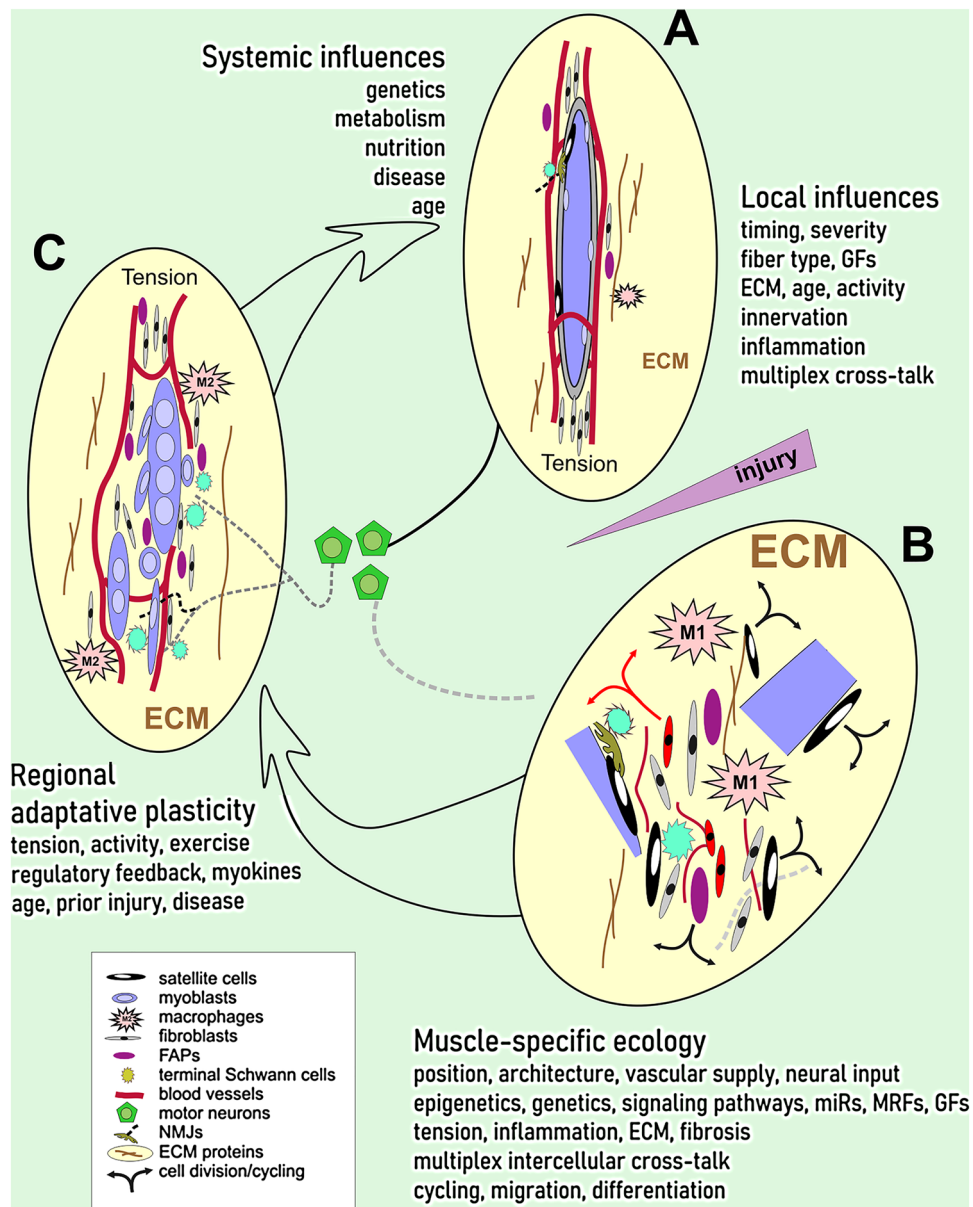


Fig. 1 Skeletal muscle regeneration in context of local, regional, and systemic influences. **A** Under normal conditions (top right), muscle fibers with adjacent muscle satellite cells are innervated at neuromuscular junctions (NMJs) and situated in an active environment of multiplex cross-talk with components of the extracellular matrix (ECM), fibro-adipogenic precursors (FAPs), resident macrophages, fibroblasts, terminal Schwann cells, and endothelial cells lining blood vessels. The tissue complex is under tension from muscle insertions. **B** Soon after a disruptive injury (pointed wedge at the right), cells and fiber fragments (bottom right) are dispersed in the ECM, inflammatory (M1) macrophages infiltrate, satellite cells are activated, and many types of cells proliferate. Axons from spinal cord motor neurons (centre) begin to undergo Wallerian degeneration. Cellular cross-talk is fully engaged at cellular and molecular levels. Muscle-specific ecology related to 3-dimensional position and architecture (formed through development), the vascular and nerve supplies, and

influences of genetics and epigenetics, engages signaling pathways through microRNAs, muscle regulatory genes, growth factors, exosomal vesicles, and their interplay with tension, inflammatory processes, ECM composition and fibrosis, with impact on cell cycling, migration, and differentiation behavior. **C** Regional adaptive plasticity shapes the regenerating muscle tissue (left) through a balance of tension, activity, and exercise with metabolic regulatory feedback loops (through endocrine, exocrine, and myokine pathways), age, prior injury, and extant disease. These influences act on myoblasts, fibroblasts, FAPs, endothelial and anti-inflammatory (M2) macrophages, as neurites begin to reconnect with elongating myotubes at nascent NMJs. Systemic influences of other tissues on the regenerating muscle, including genetics, metabolism, nutrition, disease and age, all contribute to the maturation of muscle 3-dimensional structure, stiffness, function, and adaptive responsiveness. Legend to symbols appears in the box (bottom left)

Table 1 Side by side compilation of early and current concepts of muscle regeneration, as presented in the review

Early concepts	Current concepts
Cells in skeletal muscle can form bone, adipose, and connective tissues	Contributions by muscle satellite-stem cells, fibroadipogenic precursors, immune cells, endothelial precursors, and innervation occur within an “ecosystem” of systemic physiology, physical activity, and aging
Regeneration of muscle does not always restore function	Muscle-specific overlay of regionalized epigenetic influences and vascular architecture
large Injuries often leave a scar	Cell–cell cross-talk via exosomal vesicles, nanotube connectivity, gaseous transmission, systemic and local secretions, including satellite cell influences on myonuclei
Similar pattern across types of injury with variable timing	Cells are dynamic in time and through biomechanical influences on molecular signaling pathways
often Less successful after ischemia–reperfusion injury than after anoxia	Physical activity arbitrates the outcome, mediated by metabolism, myokines, angiogenesis, innervation, and the extracellular matrix
Tracking functional repair requires standardized protocols and tools	3-Dimensional skeletal muscle architecture over a broad range of resolutions, is an important readout of a highly evolved hierarchy of function

receives multiple signals within their occupied niche at any given time. While the niche locations of satellite cells and terminal Schwann are particularly identifiable, *every* cell occupies *and tailors* its niche—a niche that presents signaling ligands and receptors, and stores signaling molecules produced elsewhere. And every cell responds or very likely will respond to metabolic and mechanical or activity-based signals, from local to systemic.

All those signals change in a time-dependent manner during regeneration; each type of cell and structure “recognizes” the signals and compiles or integrates them in a way that directs a particular response or action. That integration parallels the way in which the electrical output of a neuron is compiled from excitatory and inhibitory input at dendritic spines, soma, and axon in a complex summative and time-dependent mechanism. In muscle, systemic and localized signaling combine to impact the manner of such responses. That understanding enhances our ability to dissect and describe the behaviour of a given cell population in a region of regenerating muscle tissue.

Notably, the population-level behaviour of any type of cell will be displayed as an average response that accounts for the level of population heterogeneity. Single-cell approaches are astute in displaying responses based on gene and protein expression, morphological interactions, and extant physiology at a single time point; vital and video-capture imaging help capture those responses. We use many models of muscle regeneration, imposing particular injuries or metabolic and disease conditions to test new ideas, and have found great success in revealing how those cells interact. Over the decades of inquiry, those many models of muscle damage were explored with increasing ability to resolve patterns. Technologies have developed through application of highly specific molecular, cellular, and imaging tools that can observe and manipulate individual cells or a cell population. And objective observations and data can be analyzed

with powerful computational and statistical approaches of genomics, genetics, computational biology, and time-lapse imaging. Ongoing research will probe ever-further into the mechanisms regulating cell behaviour and interactions.

While science rapidly embraces new methods, classical methods are still valuable, as is a review of historical literature. Understanding the trends in thinking can give insights that refine an experiment or modify an approach. Reading old monographs is also fascinating as it helps us feel the energy of previous scientists as they reached toward their own technological limits to pose questions and open doors, ever hopeful they too, might advance the concepts of muscle regeneration.

The goal of this review was not to characterize the burgeoning literature on molecular genetics, epigenetics, and cell signaling by all types of cells involved in muscle regeneration. Nor was it to review the exquisite combinations of modern technology such as CRISPR in intraosseous chimeric cell therapy to promote systemic muscle regeneration and prevent disease progression, now supporting huge strides in systemic treatment of diseases such as Duchenne muscular dystrophy (Siemionow et al. 2019, 2021). Rather, the review aimed to identify distinctions between current concepts in muscle regeneration and earlier historical ideas, and trace the general timeline of research advances (Table 2). Our conceptualization of a process shapes the way we approach its exploration, just as the model of injury we select for an experiment will shape the nature of findings and variables that are available in studying the outcome of a perturbation or potential therapy we might superimpose (Hardy et al. 2016; Tatsumi et al. 2017).

It is the accessible scope of activities or responses made by a single cell, a cell population, or a mixed collection of all the cells within a tissue, that provides the basis of our clinical and research practices. Concepts—how we think

Table 2 Rough timeline of topical themes and approaches in research on muscle regeneration

Themes in muscle regeneration research	up to 1920	1921-1940	1941-1960	1961-1980	1981-2000	2001-2020	2021
life history, whole body physiology, trauma surgery, scarring							
exercise (exerc) speeds healing, physical activity, training, over-use and disuse, atrophy, athletic injury		1922 exerc					
perfusion, vascular architecture, ischemia-reperfusion, anoxia							
nerve regeneration, neuro- and myotrophic factors, influence of metabolism							
functional recovery, rehabilitation toward occupation, mobility, activities of daily living							
measurement tools, EMG, contractile physiology in clinic (Cx), autoradiography, PCR, immune detection, “omics,” high-throughput screens			1956 Cx				
in vitro culture of muscle cells, explants, fibers to model phenotypes of health, disease, injury			1956				
genetic modeling of disease (spontaneous, induced) with up- or down-regulation							
structure & chemistry observed with increasing resolution, variable frequency/modality							
precursor mitosis (in vivo, on fibers, and in vitro), mitotic clock, myostatin (mstn), timing				1968 mitosis	1997 mstn		
genetic modeling of disease (spontaneous, induced) with up- or down-regulation							
ECM and fibrosis, transcriptomics regulating local balance of muscle and fibrotic tissue							
fiber typing, fiber growth, innervation, nerve-muscle interactions, adaptive changes							
features by age, sex, strain, and anatomical muscle; plasticity and responsiveness to injury							
dystrophin (dyst), cytoskeleton, nitric oxide synthase-1, stem cell polarity, asymmetric mitosis				1984 dyst			
satellite cell activation, quiescence, and responsiveness; Notch, Wnt, HGF, nitric oxide (NO) release; latency with age, stretch, cell mobilization, migration, fibronectin				1998 HGF/SF 2000 NO			
inflammation, macrophages, cross-talk with muscle, coordinated stem-cell responses (coord)						2018 coord	
genetic markers for muscle satellite-stem cells: MyoD and other muscle regulatory factors					1987		
cmet					1997		
Pax7 as essential for myogenic specification					2000		
fibroadipogenic precursors (FAPs), Gli1+ FAPs, adipogenesis, oxygenation, fibrogenesis					2010 FAPs		2021 Gli1+
myokine release from stretch/exercise (myok), interleukins, muscle as endocrine, anabolic effect of resistance training/flow-restricted exercise					2008 myok		
topological and hierarchical regulation of muscle-immune cells (m-im), muscle satellite-stem cells (SCs), stem-cell positional memory (Hox10)					2008 m-im		SCs Hox10
semaphorin3A and motor neuritogenesis (sema), nerve-muscle interplay in muscle regeneration					2009 sema		
microRNAs (miRs) and skeletal muscle, epigenetics and memory of previous adaptation, nanotubes, exosomal vesicles (EVs)						2006 miRs	2021 EVs
satellite cells essential for sustained long-term muscle growth							2021

about each level of organization—form the foundational map of our understanding. Alas, our concepts also form the basis of our assumptions, since we use that map to speculate on the unknown, choose a direction, and anticipate the next horizon. It's exciting to learn new concepts in our own and other fields, since those ideas bring, even force, a paradigm shift in perspectives and redirect our attention. Our focus shifts to the next question, whether new or refreshed from classical literature by modern technologies, insights, and skepticism.

The impact of intricate molecular-genetic signaling networks—a critical foundation in understanding cell behaviour in muscle regeneration and therapeutics—must be interpreted in context of the bigger picture of structure–function relationships and systemic influences (Swaggart and McNally 2014). Ongoing discoveries highlight that every part of the muscle structure is important in some fashion. That notion provides important clues to us as researchers, about the functional context and functionality of muscle during regeneration. The beautiful three-dimensional architecture of skeletal muscle has evolved to optimize the functions of all cells in normal muscle; recognizing how that architecture integrates with physiology is critical to advancing our understanding of muscle regeneration. Deciphering the interplay of layered mechanisms of damage in traumatic muscle injury, for example, by high-energy ballistic damage from firearms (Moriscot et al. 2021), will advance our thinking about rehabilitation approaches that promote regeneration and function.

Research on muscle regeneration intersects at many levels, with ideas gleaned from other research domains. Even apparently simple concepts can spark creativity and drive new hypotheses directed to pose the *why?* and *how?* and *what happens then?* questions at the core of research. Skeletal muscle, the engine of our voluntary activity, is critical to health, both physical and mental; one can only hope that the remarkable capability of muscle tissue to regenerate through myriad dynamic inter-cellular interactions and signaling processes, continues to capture the imagination of future generations of researchers. Key concepts in skeletal muscle regeneration will evolve as does our understanding of the processes influencing cellular and molecular interactions.

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