



## REVIEW

# SATELLITE CELL REGULATION FOLLOWING MYOTRAUMA CAUSED BY RESISTANCE EXERCISE

JANET VIERCK<sup>1</sup>, BECKY O'REILLY<sup>1</sup>, KIM HOSSNER<sup>2</sup>, JOSE ANTONIO<sup>3</sup>, KATHERINE BYRNE<sup>1,4</sup>, LUKE BUCCI<sup>5</sup> and MICHAEL DODSON<sup>1\*</sup>

<sup>1</sup>Muscle Biology Laboratory, Department of Animal Sciences, Washington State University, Pullman, WA 99164-6351, <sup>2</sup>Department of Animal Sciences, Colorado State University, Fort Collins, CO 80523,

<sup>3</sup>Department of HPERLS – Human Performance Laboratory, University of Nebraska, Kearney, NE 68849,

<sup>4</sup>Molecular Immunology Laboratory, Department of Animal Science, Washington State University, Pullman, WA 99164-6351, <sup>5</sup>Vice President of Research, Weider Nutrition International, 2002 South 5070 West, Salt Lake City, UT 84104-4726, U.S.A.

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It is generally accepted that the primary mechanisms governing skeletal muscle hypertrophy are satellite cell activation, proliferation, and differentiation. Specific growth factors and hormones modulate satellite cell activity during normal muscle growth, but as a consequence of resistance exercise additional regulators may stimulate satellite cells to contribute to gains in myofiber size and number. Present knowledge of the regulation of the cellular, biochemical and molecular events accompanying skeletal muscle hypertrophy after resistance exercise is incomplete. We propose that resistance exercise may induce satellite cells to become responsive to cytokines from the immune system and to circulating hormones and growth factors. The purpose of this paper is to review the role of satellite cells and growth factors in skeletal muscle hypertrophy that follows resistance exercise.

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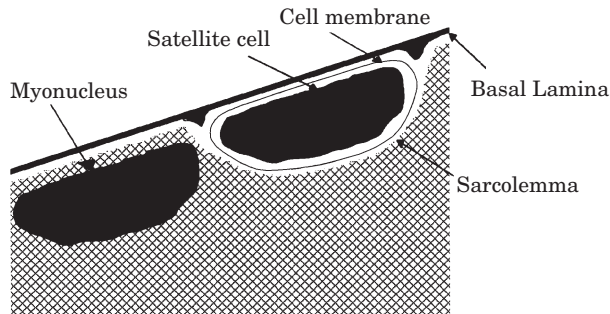
KEYWORDS: satellite cells; hormones; growth factors; steroids; cytokines; resistance exercise.

## INTRODUCTION

Located between the basal lamina and the sarcolemma of myofibers is a population of postnatal myogenic stem cells called satellite cells (Fig. 1; Mauro, 1961). During normal muscle growth, satellite cells contribute nuclei (Moss and Leblond, 1970; Cardiasis and Cooper, 1975a) by proliferating, differentiating and fusing to existing myofibers (Moss and Leblond, 1970). Satellite cell-derived myonuclei are no longer capable of dividing but begin to produce muscle-specific proteins that increase myofiber size (Allen *et al.*, 1979; Giddings *et al.*, 1985; Bourke *et al.*, 1995) in a process known as hypertrophy.

\*To whom correspondence should be addressed: M. V. Dodson, Ph.D., 139 Clark Hall, Muscle Biology Laboratory, Department of Animal Sciences, Washington State University, Pullman, WA 99164-6310, U.S.A. E-mail: [dodson@wsu.edu](mailto:dodson@wsu.edu)

Resistance exercise may functionally be defined as the progressive overload of a skeletal muscle resulting in muscle growth. More specifically, resistance exercise results in an increased myofiber cross-sectional area and myofiber number, significant myofiber hypertrophy (MacDougall *et al.*, 1984; Alway *et al.*, 1992; Crill *et al.*, 1998) and a change in myofiber constituents (Pette and Staron, 1997). Resistance training initially may cause muscle damage ranging from a few macromolecules (Staron *et al.*, 1990; Staron *et al.*, 1994) to large tears in the sarcolemma, basal lamina, and supportive connective tissue, as well as damage within the contractile and cytoskeletal proteins of the myofiber. This myotrauma initiates the release of growth factors that influence satellite cells in a cascade of regenerative events which ultimately lead to myofiber hypertrophy (Allen *et al.*, 1979;

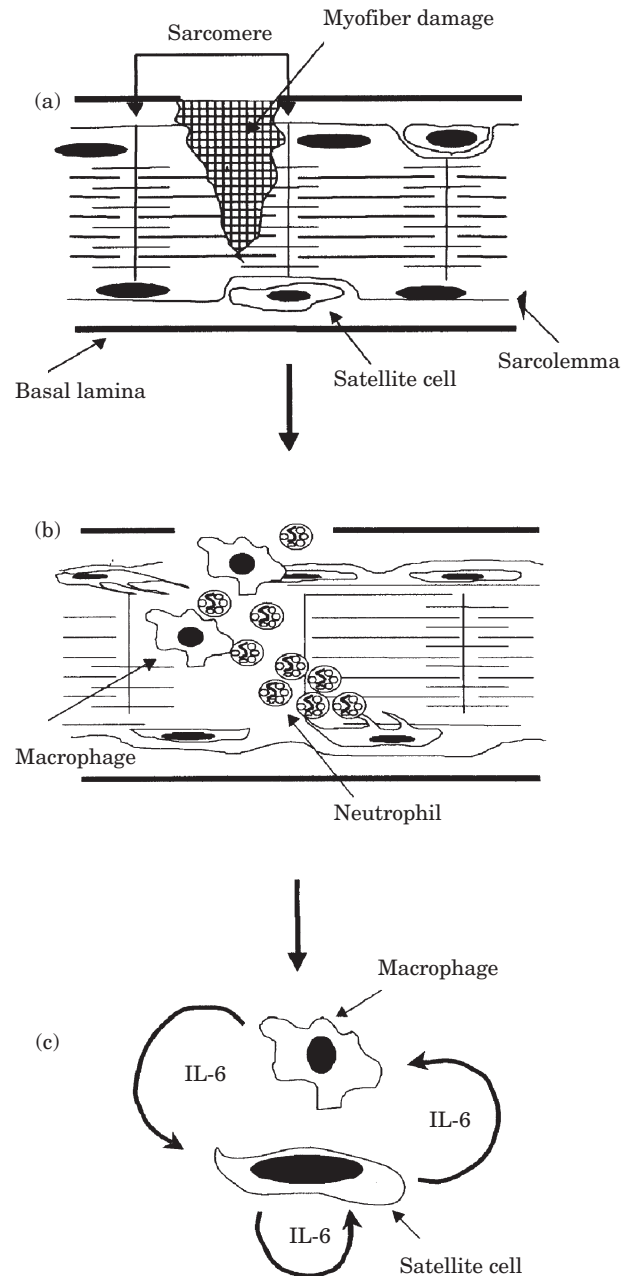


**Fig. 1.** Schematic drawing of a satellite cell surrounded by the basal lamina and the sarcolemma of the juxtaposed myofiber. In this pocket, the satellite cell remains inactivated until stimulated to proliferate and differentiate. During differentiation, satellite cells fuse with the myofiber and become myonuclei. Myonuclei are responsible for protein synthesis for both myofiber maintenance and growth.

Grounds, 1998). In this paper we discuss the relationship between satellite cells, the immune system, and various growth factors that may influence the skeletal muscle hypertrophy observed following resistance exercise.

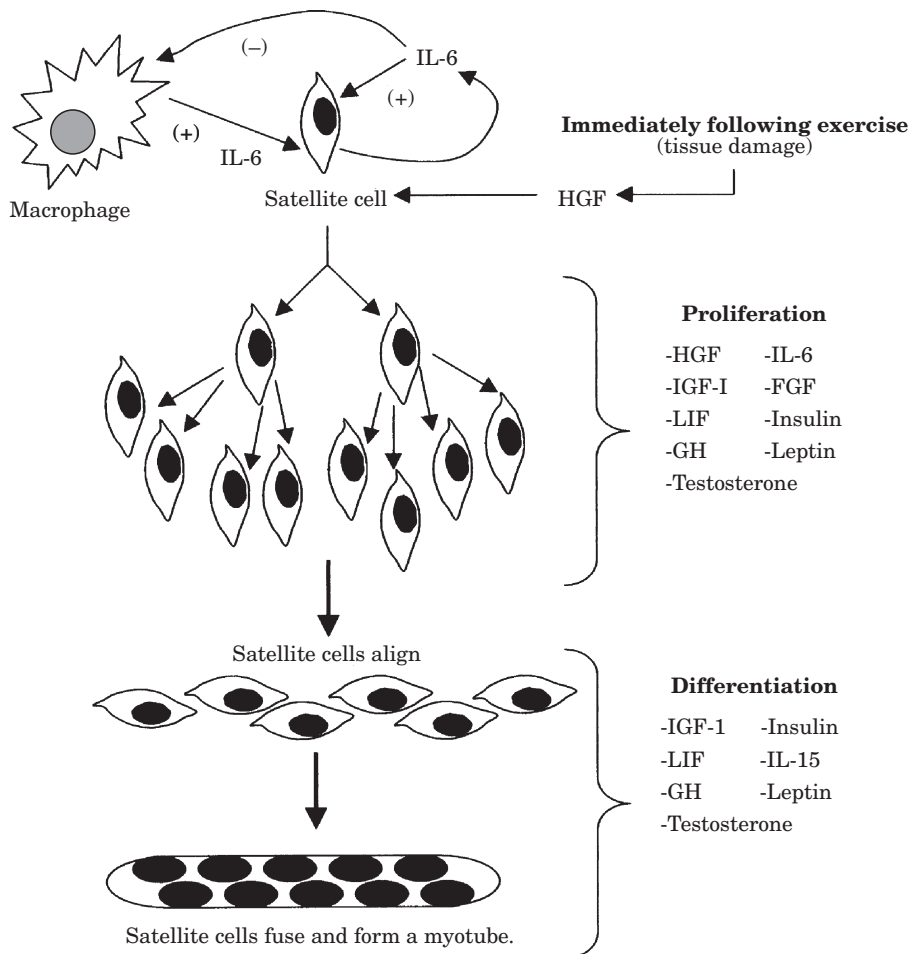
### THE IMMUNE SYSTEM, CYTOKINES AND GROWTH FACTORS

Similarities exist between the acute inflammatory response to infection and the immune response to muscle damage induced by resistance exercise (Sharp and Koutedakis, 1992). Following resistance exercise, neutrophils from the blood increase in number in the area of the myotrauma (Smith *et al.*, 1994). Damaged myofibers release agents that stimulate and attract macrophages and lymphocytes to the injured tissue (Figs 2 and 3; Allen *et al.*, 1995; Kimura *et al.*, 1996). The macrophages remove cellular debris, an important step for maintaining the structure of muscle during repair (Robertson *et al.*, 1993; Grounds, 1998), and also produce cytokines which activate myoblasts, macrophages and lymphocytes (Nathan, 1987; Cantini *et al.*, 1994; Cantini and Carraro, 1996). T-lymphocytes, in particular, are stimulated to move into the damaged area where they bind to adhesion molecules in the regenerating myofiber and release their own library of cytokines (Beauchamp *et al.*, 1992). Other factors released from the damaged myofibers and the surrounding tissue activate the processes of myofiber regeneration. Hepatocyte growth factor (HGF) has been shown to be the active factor in 'crushed' muscle extracts (Allen *et al.*, 1995). In addition, leukemia inhibitory factor (LIF), interleukin-6 (IL-6), and



**Fig. 2.** Satellite cells may mediate muscle repair following a muscle injury. (a) Myofiber damage occurs. (b) Neutrophils and macrophages are attracted to the injury site where they phagocytose cellular debris and chemotactically attract satellite cells. (c) The interaction between the satellite cells and macrophages is mediated by cytokines such as interleukin-6. (Figure adapted from *The Equine ATHLETE* 6: 7-12, 1996, with permission.)

interleukin-15 (IL-15) all appear to be part of a currently emerging model of muscle repair (Austin and Burgess, 1991; Barnard *et al.*, 1994; Cantini *et al.*, 1995; Bischoff, 1997; Jiang and Hiscox, 1997).



**Fig. 3.** Illustration of factors probably involved in the resolution of muscle repair. Extrinsic factors stimulate each stage of muscle repair. FGF: fibroblast growth factor, GH: growth hormone, HGF: hepatocyte growth factor, IGF-I: insulin-like growth factor-I, IL-6: interleukin-6, IL-15: interleukin-15, LIF: leukemia inhibitory factor. (Figure adapted from *The Equine ATHLETE* 6: 7–12, 1996, with permission.)

LIF is a cytokine produced by a number of different cells, including macrophages and myoblasts (Barnard *et al.*, 1994; Grounds and Davies, 1996; Kurek *et al.*, 1996a). Muscle cells have high affinity receptors for LIF (Bower *et al.*, 1995) and respond to LIF by increased proliferation *in vitro* (Barnard *et al.*, 1994). The proliferative effect of LIF lasts 10 days after a 3-day exposure (Austin *et al.*, 1992; Kurek *et al.*, 1996a). LIF also stimulates increased size in newly established myotubes *in vivo* (Barnard *et al.*, 1994; Kurek *et al.*, 1996a). The long-term effect of an initial LIF treatment may be due in part to the stimulation of autocrine secretion of LIF by the muscle cells themselves (Barnard *et al.*, 1994; Kurek *et al.*, 1996b) or to the retention of LIF within the tissue (Barnard *et al.*, 1994).

Originally detected in hepatic tissue (Miyazawa *et al.*, 1989) and referred to as the crushed muscle

mitogen (Allen *et al.*, 1995), HGF was first identified as a mitogen for mature hepatocytes (Michalopoulos, 1992). HGF was also shown to have a direct effect on the proliferation and differentiation of primary cultures of satellite cells (Allen *et al.*, 1995; Bischoff, 1997). Recently, HGF was found in non-injured adult rat skeletal muscle, suggesting that HGF may play an autocrine/paracrine role with satellite cells (Tatsumi *et al.*, 1998). This is supported by the observation that mouse myoblasts secrete HGF and possess HGF receptors (Anastasi *et al.*, 1997). HGF also seems to function as a chemo-attractant for satellite cells (Bischoff, 1997) and is secreted by damaged tissue in amounts corresponding to the severity of the damage (Kimura *et al.*, 1996). Regenerating muscle secretes HGF for the first 3 days after injury (Jennische *et al.*, 1993). HGF may function, in part, to activate satellite cells in the area of myofiber

damage and initiate their proliferation (Cantini and Carraro, 1996).

IL-6 is a cytokine that is often associated with LIF (Kurek *et al.*, 1996b). Macrophages near the damaged myofiber secrete an unknown factor, possibly HGF, which attracts satellite cells and stimulates them to release IL-6 *in vitro* (Cantini *et al.*, 1995). This was also demonstrated with myoblasts and monocytes (Bartoccioni *et al.*, 1994). Once released by satellite cells, IL-6 synchronizes other satellite cells and induces cellular apoptosis of neutrophils and macrophages localized in the trauma site (Cantini and Carraro, 1996). This phase of muscle repair might be a driving factor in resolving the inflammatory reaction (Grounds and Davies, 1996; Haugk *et al.*, 1996). It appears that IL-6 may act as a signal for promoting satellite cell proliferation and fusion and as a regulatory factor for resolving inflammation by inducing apoptosis of infiltrating macrophages and neutrophils in regenerating muscle (Cantini *et al.*, 1995).

IL-15 is secreted by a number of cell types including T-lymphocytes, macrophages, and myofibers (Grabstein *et al.*, 1994). IL-15 functions primarily to induce T-cell proliferation, B-cell maturation, natural killer cell cytotoxicity, and T-cell chemotaxis (Kivisakk *et al.*, 1998). Recently, it has been shown that IL-15 stimulates differentiation of myoblasts into myotubes and their subsequent accumulation of myosin heavy chain (Quinn *et al.*, 1994; Quinn *et al.*, 1995), suggesting that IL-15 assists in satellite cell-mediated myofiber regeneration.

## OTHER ENDOCRINE AND ENVIRONMENTAL FACTORS

The skeletal muscle growth occurring as a result of chronic resistance exercise is regulated by various mechanisms. The immune system (discussed previously), other blood-borne factors, and local/environmental factors must work in concert to facilitate satellite cell involvement in myofiber repair and hypertrophy (Fig. 3). During muscle hypertrophy, fibroblast growth factor (FGF) increases the proliferation of satellite cells (Allen *et al.*, 1984). FGF appears to be synthesized by all cells in the body and possesses high affinity for heparan sulfate proteoglycans (extracellular proteins) (Allen *et al.*, 1986; Bischoff, 1989; Hannon *et al.*, 1996; Brandan and Larrain, 1998). Yamada *et al.* (1988) suggested that FGF might initiate muscle repair following exercise.

A great deal of attention has been focused on the effect of insulin-like growth factors (IGFs) on increased muscle protein formation after exercise (Brameld *et al.*, 1998; Grounds, 1998; Hossner *et al.*, 1997). An increase in IGF-I has been reported in muscle after acute resistance exercise (Yan *et al.*, 1993). *In vitro* studies suggest that IGF-I stimulates satellite cells to proliferate, differentiate and fuse with growing myotubes (Dodson *et al.*, 1985; Florini *et al.*, 1991; Delany *et al.*, 1994; Fryburg *et al.*, 1995; Goldspink *et al.*, 1995).

Insulin stimulates skeletal muscle growth by augmenting protein synthesis (Jefferson, 1980) and facilitating the entry of glucose into cells (Stadel and Lefkowitz, 1989; Kahn and Goldfine, 1993; Koyama *et al.*, 1997; Shearer *et al.*, 1997). Insulin also induces mitosis and differentiation of satellite cells. At physiologic levels, insulin stimulates protein synthesis and glucose uptake in satellite cells (McFarland *et al.*, 1995) and decreases protein degradation in cultured myotubes (Harper *et al.*, 1987; McFarland *et al.*, 1995; Svanberg *et al.*, 1996). Insulin possesses a high affinity for the insulin receptor and a lower affinity for the IGF-I receptor (Zaph *et al.*, 1978; Foley *et al.*, 1982; Kahn and Goldfine, 1993). At greater than physiological levels, insulin stimulates satellite cell proliferation and differentiation, presumably due to interaction with IGF-I receptors (Dodson *et al.*, 1985; Dodson *et al.*, 1988; Doumit and Merkel, 1991).

There is great interest in optimizing growth hormone levels to enhance muscle growth following resistance exercise (Chandler *et al.*, 1994; Hartman *et al.*, 1993). Growth hormone has a short half-life (20–25 min) (Martin, 1978), a large molecular size (21.5 kDa) and is synthesized by and released from the anterior pituitary gland in a pulsatile fashion (Martin, 1978). Resistance exercise stimulates the release of growth hormone, with levels being dependent on the intensity of the exercise (Fry and Kraemer, 1997). Growth hormone acts as a repartitioning agent to induce fat metabolism toward mobilization for use in skeletal muscle tissue growth, resulting in an overall increase in lean body mass. In addition, growth hormone stimulates cellular uptake and incorporation of amino acids into protein in several tissues, including skeletal muscle (Hartman *et al.*, 1993). Recent evidence suggests that growth hormone may act directly on specific populations of satellite cells and not on others (unpublished observation).

Leptin is a polypeptide hormone that is the product of the obese gene and is absent in the genetically obese (ob/ob) mouse. Its absence results

in hyperphagia, hypothermia, and infertility (Zhang *et al.*, 1994). Leptin treatment of ob/ob mice restores fertility, blunts appetite, and selectively reduces body fat (Campfield *et al.*, 1995; Pelleymounter *et al.*, 1995). Plasma levels of leptin are directly proportional to adipose mass, and healthy or fit individuals would be expected to have reduced levels of serum leptin. Studies in exercising humans show that blood leptin levels do not change in response to chronic or acute exercise independent of body fat (Hickey *et al.*, 1996; P'erusse *et al.*, 1997; Racette *et al.*, 1997). However, after 12 weeks of aerobic exercise training, serum leptin concentrations were reduced by 17.5% in women, but were unaffected in men (Hickey *et al.*, 1997). Thus, leptin may be differentially affected by gender in exercising humans.

Many of the effects of leptin on appetite and metabolism are thought to be mediated by the hypothalamus, via a reduction in neuropeptide Y (Stephans *et al.*, 1995; Schwartz *et al.*, 1996). More recently, direct effects of leptin on peripheral tissues have been shown *in vitro*. For example, leptin directly reduces the expression of acetyl-CoA carboxylase, the rate-limiting enzyme for lipid synthesis, in adipocytes (Bai *et al.*, 1996). In addition, leptin has direct effects on skeletal muscle, increasing fatty acid oxidation while reducing triglyceride synthesis in isolated skeletal muscle *in vitro* (Muoi *et al.*, 1997). In a manner similar to the effect of insulin, leptin also stimulates glucose transport and glycogen synthesis in C<sub>2</sub>C<sub>12</sub> myoblasts (Berti *et al.*, 1997), a muscle cell line derived from mouse leg muscle. Collectively, these observations suggest an overall metabolic role for leptin in skeletal muscle. Interestingly, leptin also stimulates proliferation of the pluripotent mouse embryonic stem cell line (Takahashi *et al.*, 1997) that is capable of differentiating into skeletal muscle, adipose or cartilage. This may suggest that an increase in leptin at a specific stage of embryonic growth may enhance skeletal development. By analogy, leptin may also stimulate satellite cells (the postnatal muscle stem cells) to differentiate, contributing to adult myofiber hypertrophy. Thus, leptin appears to have specific effects on the metabolism of tissue types that are directly involved in body composition, with the potential to enhance muscle mass while reducing body fat.

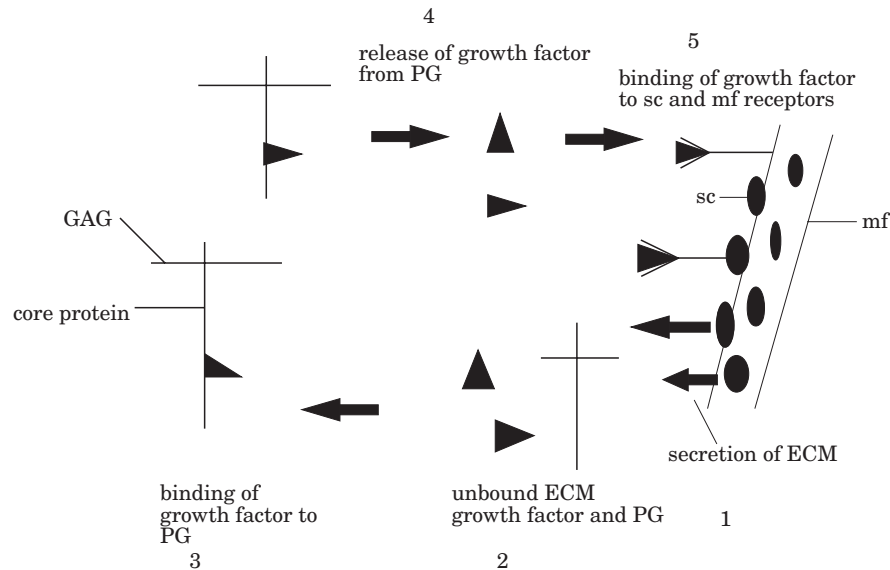
The role of anabolic steroids such as testosterone in enhancing muscle growth has been known for years (Florini, 1987; Celotti and Cesi, 1992). It is generally accepted that anabolic steroids are direct regulators of secondary sexual characteristics like muscling and muscle patterning. Anabolic steroids

also augment muscle growth by stimulating fat catabolism, which enhances muscle definition (Kibble and Ross, 1987). Recently it was suggested that anabolic steroids possess regulatory effects on satellite cells *in vitro* (Joubert and Tobin, 1995; Doumit *et al.*, 1996).

## IMPACT OF RESISTANCE EXERCISE

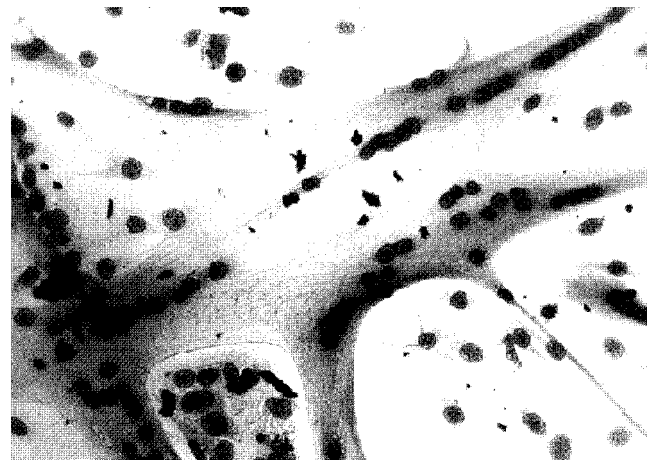
Resistance exercise influences the remodeling of the extracellular matrix that surrounds myofibers (Darr and Schultz, 1987; McCall *et al.*, 1996; Grounds, 1998). The extracellular matrix, sometimes referred to as the endomysium, is composed of numerous molecules including glycoproteins, collagen, laminin, heparin sulfate, and proteoglycans, which play a role in cell growth (Tono *et al.*, 1996; Nishimura *et al.*, 1997; Grounds *et al.*, 1998; Velleman *et al.*, 1998). It is postulated that the extracellular matrix stores and releases growth factors that stimulate satellite cells to proliferate and differentiate (Fig. 4) (Kelso *et al.*, 1989; Timpl, 1993; Hannon *et al.*, 1996; Melo *et al.*, 1996; Tatsumi *et al.*, 1998). Recent work by Velleman *et al.* (1996), suggests that the proteoglycan, decorin, binds to growth factors and controls the flux of growth factors to and from the extracellular matrix. As myofibers undergo hypertrophy in response to resistance exercise, the extracellular matrix also increases to support muscle growth (MacDougall *et al.*, 1982; Bischoff, 1989; McCormick and Schultz, 1994). For skeletal muscle to sustain resistance exercise protocols, it is essential that adequate blood flow is provided (Snyder *et al.*, 1992; Delp and Laughlin, 1998). Therefore, at the onset of exercise an increase in cardiac output is followed by an increase in overall blood flow to the muscle (Snyder *et al.*, 1992). This hyperemia, along with potential tissue damage, initiates the cascade of events resulting in the recruitment of neutrophils and macrophages (Cantini and Carraro, 1995; Stewart *et al.*, 1997). This also initiates the inflammatory process that will eventually remove damaged tissue (Bangsbo *et al.*, 1991; Tidball, 1995; Delp and Laughlin, 1998). Additional systemic as well as local mitogenic factors are supplied to the muscle tissue and are likely to stimulate satellite cells (Fig. 3; Jacobs *et al.*, 1995). In addition, as muscles increase in size, blood flow dynamics adjust to support the hypertrophy (Degens *et al.*, 1992; McCall *et al.*, 1996).

Resistance exercise stimulates motor neurons to release factors that induce satellite cells to



**Fig. 4.** Illustration of satellite cells (sc) of myofiber (mf)-secreted extracellular matrix (ECM), with the proteoglycan (PG) binding free growth factor ( $\blacktriangle$ ) and regulating sc and mf exposure to the growth factor. Following release from the PG, the growth factor may then interact with its cellular receptor, resulting in a cell response. ECM damaged by resistance exercise may release growth factors that stimulate satellite cells. A glycosaminoglycan (GAG), such as heparan sulfate binds to the PC core protein and may protect ECM macromolecules from proteolysis (reprinted from *Domestic Animal Endocrinology* **13**: 107–126, 1996, with permission).

proliferate (Staron *et al.*, 1994; Nikovits and Stockdale, 1996). For example, the area under the motor neuron location/junction on a myofiber contains a higher concentration [ $20 \times$ ] of satellite cells (Wokke *et al.*, 1989). However, the physiological significance of the higher concentration of satellite cells is unknown. Though resistance training usually does not cause neural damage or denervation, it has been suggested that nerves impinging upon a damaged myofiber may stimulate satellite cells (Cardasis and Cooper, 1975b; Barjot *et al.*, 1998). Bischoff (1989) reported that there was an increase in activity of the satellite cells located around the site of a detached motor end plate. However, the level of direct interaction between the nerves and satellite cells varies between muscle bundles within the same individual and even among myofibers in the same muscle (Eberstein and Eberstein, 1996).



**Fig. 5.** Photomicrograph of a satellite cell-derived myotube ( $\times 200$ ; stained with Giemsa). Research with satellite cells from exercised individuals will help elucidate the satellite cell involvement in the muscle hypertrophy that follows resistance exercise (reprinted from *Tissue and Cell* **19**: 159–166, 1987, with permission).

## SUMMARY

Regardless of the type of exercise protocol, resistance exercise may damage the intracellular and/or extracellular tissue of skeletal muscle, which then releases signaling factors that stimulate and attract immune cells to the trauma site. Cytokines from activated immune cells, along with muscle-derived

signaling factors, stimulate satellite cell proliferation. Hyperemia within the damaged muscle supplies satellite cells with anabolic endocrine agents and growth factors, which regulate satellite cell population expansion and subsequent fusion into myotubes. Further research will help define specific regulation mechanisms initiated by resistance exercise, leading to knowledge about satellite

cell mediation of skeletal muscle hypertrophy (Fig. 5).

## ACKNOWLEDGEMENTS

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