European Journal of Applied Physiology
https://doi.org/10.1007/s00421-021-04641-4

INVITED REVIEW

Regulation of satellite cells by exercise in hypoxic conditions: a narrative review

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Received: 10 November 2020 / Accepted: 10 February 2021

Abstract

Purpose To investigate in vivo the adaptations of satellite cell induced by exercise performed in acute or chronic hypoxic conditions and their contribution to muscle remodeling and hypertrophy.

Methods Search terms related to exercise, hypoxia and satellite cells were entered on Embase, PubMed and Scopus. Studies were selected for their relevance in terms of regulation of satellite cells by in vivo exercise and muscle contraction in hypoxic conditions.

Results Satellite cell activation and proliferation seem to be enabled after acute hypoxic exercise via regulations induced by myogenic regulatory factors. Several studies reported also a role of the inflammatory pathway nuclear factor-kappa B and angiogenic factors such as vascular endothelial growth factor, both known to upregulate myogenesis. By stimulating angiogenesis, repeated exercise performed in acute hypoxia might contribute to satellite cell activation. Contrary to such exercise conditions, chronic exposure to hypoxia downregulates myogenesis despite the maintenance of physical activity. This impaired myogenesis might be induced by excessive oxidative stress and proteolysis.

Conclusion In vivo studies suggest that, in comparison to exercise or hypoxia alone, exercise performed in a hypoxic environment, may improve or impair muscle remodeling induced by contractile activity depending upon the duration of hypoxia. Satellite cells seem to be major actors in these dichotomous adaptations. Further research on the role of angiogenesis, types of contraction and autophagy is needed for a better understanding of their respective role in hypoxic exercise-induced modulations of satellite cell activity in human.

Keywords Angiogenesis · Autophagy · Hypertrophy · Hypoxia · Inflammation · Satellite cell · Skeletal muscle

Abbreviations

CD	Cluster of differentiation
FGF	Fibroblast growth factor
HGF	Hepatocyte growth factor
HIF	Hypoxia-inducible factor
IGF	Insulin-like growth factor
IL	Interleukin
MHC	Myosin heavy chain
miR	Micro RNA
MRF	Myogenic regulatory factors
Myf5	Myogenic factor 5
MyoD	Myogenic differentiation
NO	Nitric oxide
Pax7	Paired box 7
PCNA	Proliferating cell nuclear antigen
PGC-1α	Peroxisome proliferator activated receptor gamma coactivator 1 alpha
PP2CA	Protein phosphatase 2 catalytic subunit, alpha isoform
PTPN3	Protein tyrosine phosphatase, non-receptor type 3
ROS	Reactive oxygen species
TNF	Tumor necrosis factor
VEGF	Vascular endothelial growth factor

Communicated by Michael Lindinger.

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Published online: 20 March 2021

Introduction

Satellite cells are muscle stem cells located between the basal lamina and the plasma membrane of muscle fibers. Their activation is amongst others induced by mechanical stress, hypoxia, oxidative stress and growth stimuli induced by muscle injury, exercise and aging (Diaz-Ruiz et al. 2015). Activation of satellite cells leads to muscle regeneration and hypertrophy through proliferation and differentiation of these cells into myocytes and fusion with existing myofibers (Beaudry et al. 2016; Chang and Rudnicki 2014). Satellite cell activation, proliferation, differentiation and fusion is a process called myogenesis. Myogenesis is tightly regulated by the sequential expression of paired box 7 (Pax 7) and the myogenic regulatory factors (MRF), i.e. myoblast determination protein (MyoD), myogenic factor 5 (Myf5), myogenic regulatory factor 4 (Mrf4) and myogenin (Chang and Rudnicki 2014). Their expression varies among the different steps of myogenesis. Pax7 and Myf5 are markers of satellite cell quiescence and activation. To maintain the satellite cell pool, each cell undergoes an asymmetric division. One daughter-cell (Pax7+/MyoD−) will replenish the satellite cell pool whereas the second one (Myf5+/MyoD+/Pax7+) will proliferate and become a myoblast. Newly formed Pax7−/MyoD+myoblasts start to differentiate into myocytes which will fuse to myofibers. Finally, maturation into myofibers is characterized by myosin heavy chain (MHC), Mrf4 and myogenin expression (Chang and Rudnicki 2014).

Environmental hypoxia is a condition characterized by low pO_2 levels, either by decreased atmospheric pressure at altitude, or by reduction of O_2 percentage at sea level. Hypoxia can also be induced by pathological conditions, e.g., chronic obstructive pulmonary disease or sleep apnea (Deldicque and Francaux 2013). Lower oxygen availabilty leads to adaptations within many tissues, including skeletal muscles. The interest in physical activity in hypoxic conditions has increased over the past decades, initiated by the work of J.R. Sutton in the years 1970s (Sutton 1977). Skeletal muscle adaptations to hypoxic exercise appear to be different depending on the duration and severity of exposure to hypoxia (D'Hulst and Deldicque 2017). Long-term or severe exposure to hypoxic conditions associated with physical activity or not, e.g., spending several weeks in the mountains while being active or just sojourning at 4000–5000 m altitude, improves oxygen transport and vascularization, but also induces muscle atrophy (Deldicque and Francaux 2013). Acute exercise sessions in hypoxia, e.g., in hypoxic rooms with recovery at sea level, is associated with improved VO_2max, muscle hypertrophy and increased one-repetition maximum (Nishimura et al. 2010). Several mechanisms involved in those adaptations have already been uncovered such as the regulation of protein balance, the oxidative and glycolytic metabolism, the hypoxia-inducible factor (HIF)-1α pathway and targeted genes, mitochondrial biogenesis and modifications at the neuromuscular junction (Deldicque and Francaux 2013). In addition to the aforementioned mechanisms, satellite cells may also be regulated by hypoxic conditions. Self-renewal, activation and proliferation of satellite cells were found to be higher in a hypoxic environment, whereas satellite cell differentiation, terminal maturation and myotube formation were impaired in those conditions (Beaudry et al. 2016; Chaillou and Lanner 2016). The myogenic potential of satellite cells may also play a role in the adaptations to hypoxic exercise as suggested by some data reported in the literature (Di Carlo et al. 2004; Liu et al. 2012; Yun et al. 2005). However, no study has specifically focused on the regulation of satellite cells in response to exercise in hypoxic conditions in vivo. Therefore, the purpose of this narrative review is to investigate in vivo satellite cell regulation as well as their contribution to muscle remodeling and hypertrophy following endurance and resistance exercise in acute and chronic hypoxic conditions.

Literature search

The search terms "(exercise [Title/Abstract] OR muscle contraction [Title/Abstract]AND hypoxia [Title/Abstract] AND (satellite cell [Title/Abstract] OR myogenic stem cell [Title/Abstract] OR mesoangioblast [Title/Abstract] OR side population cell [Title/Abstract])" returned 4 articles on PUBMED, 4 on Embase and 25 on Scopus on 10/03/2020. After dropping out the duplicate articles, 19 articles resulted from the search terms on the 3 search engines. A first review was made based on title and abstract relevance. Fifteen articles remained after this first review round. Careful reading of the remaining articles led to the inclusion of eight original articles (Table 1). Studies were selected for their relevance in terms of regulation of satellite cells by in vivo exercise and muscle contraction in hypoxic conditions. Pathological conditions leading to hypoxia and contractile activity under blood flow restriction were excluded due to confounding factors coupled to those conditions in addition to hypoxemia. Blood flow restriction is not fully comparable to systemic hypoxia as the local pressure and local hypoxia induce different adaptations regarding vascular resistance, metabolite accumulation, vasodilation and motor unit recruitment (Scott et al. 2014).

The results are presented in the following section divided according to the exercise conditions, i.e., single vs repeated exercise, and the hypoxic conditions, i.e., acute vs chronic

Table 1 Summary of the selected studies

References	Subjects	Exercise conditions	Hypoxic conditions	Main results	Conclusions
Single exercise–Acute Hypoxia					
Masschelein et al. (2014)	Young men, monozygote twin pairs	20 min cycling at 1.2 W/kg	10.7% FiO_2 for 20 min	Exercise in hypoxia vs normoxia: ↗ PCNA mRNA in skeletal muscle	The regulation of satellite cell activation and/or proliferation by hypoxia alone or in combination with exercise might be promising
Gnimassou et al. (2018)	Young healthy physically active men	Knee extension 8×8 reps at 80% 1RM	14% FiO_2 for 30 min	Exercise in hypoxia vs normoxia: In skeletal muscle: ≈ PCNA, Myf5, cyclin D1 and p21 mRNA trend to ↗ MyoD and Mrf4 mRNA ↗ myogenin mRNA Fos mRNA ↗ directly and ↘ 4 h post-ex	Single hypoxic resistance exercise: ≈ short-term anabolic response after resistance exercise initiation of transcriptional regulations that could translate into long-term satellite cell incorporation and ↗ force production
Britto et al. (2020)	Young healthy physically active men	Knee extension 8×8 reps at 80% 1RM	14% FiO_2 for 30 min	Exercise in hypoxia vs normoxia * In skeletal muscle: ↗ myostatin, IGF-1 and -2 mRNA ↗ TNF-α, IL-6 mRNA and NF-κB, STAT3 protein levels ↗ immune markers CD68 and CD197 mRNA * In SC cultures (1% O_2): ↗ Mrf4, Myf5, MyoD and myogenin mRNA STAT3 siRNA blunted hypoxia-induced increase in MyoD and Mrf4 mRNA	Single hypoxic resistance exercise: ≈ Acute and transient activation of the inflammation pathway in skeletal muscle ≈ Muscle immune cell invasion ≈ Acute potentiation of IL-6/STAT3-dependent myogenesis + immune cells-dependent muscle regeneration
Okabe et al. (2017)	Thoroughbred horses	2 min at 4 m/s, 1 min at 7 m/s and till exhaustion	16% FiO_2 for 5–7 min	Exercise in hypoxia vs normoxia: In skeletal muscle: ↗ number of SC in type IIa muscle fibers 7 days post-ex ↗ HGF, IGF-1 and IL-6 mRNA VEGF and PGC-1α mRNA: ↗ 4 h and ↘ 24 h and 3 days post-ex ↘ angiopoietin 1	Transient hypoxic exposure during exercise: ↗ glycolytic energy supply contribution ↗ satellite cell activation ↘ angiogenesis ↘ mitochondrial biogenesis

Table 1 (continued)

References	Subjects	Exercise conditions	Hypoxic conditions	Main results	Conclusions
Repeated Exercise–Acute Hypoxia					
Nagahisa et al. (2016)	Thoroughbred horses	2 min at 100% VO_2max, 3 days a week for 4 weeks	15% FiO_2	Exercise in hypoxia vs normoxia: ↗ running distance and VO_2max In skeletal muscle: ↗ capillary density and angiogenesis ↗ VEGF and angiopoietin 1 mRNA ≈ Pax7, MyoD and myogenin mRNA	Endothelial cell-derived growth factors activate satellite cells, which in turn stimulate angiogenesis Hypoxic training can increase the duration of the promotion of angiogenesis by satellite cells
Repeated Exercise–Chronic Hypoxia					
Martinelli et al. (1990)	Healthy men, climbers	10-week expedition	> 5000 m (up to 8000 m)	From before to after expedition: In skeletal muscle: - ↗ lipofuscin volume - ↘ mitochondrial volume - ↗ SC volume - ≈ number of myoblasts and myonuclei	↗ SC number following long duration exercise and recovery in hypoxic conditions may promote muscle regeneration
Mancinelli et al. (2011)	Healthy men, climbers	21-day expedition to Nepal: 25 km or 7 h trekking/day at 5000 m + 8-–0 km or 6 h trekking/day at 5900-6400 m	5000–6400 m	From before to after expedition: * In skeletal muscle: ↗ nuclei density ↘ Pax7 + cells ↗ Myf6 (Mrf4), PTPN3, PP2CA and ↘ tetranectin mRNA ↗ genes coding for oxidative metabolism and ↘ glycolytic metabolism * In SC cultures: ↘ myogenicity ↘ fusion index	Exercise at altitude leads to a rearrangement of skeletal muscle fiber type towards oxidative metabolism rather than regeneration

Table 1 (continued)

References	Subjects	Exercise conditions	Hypoxic conditions	Main results	Conclusions
Mancinelli et al. (2016)	Healthy women	14-day trekking expedition	4132 m	From before to after the expedition: * In isolated muscle fibers: ↘ Pax7 + cells * In SC cultures: small ↗ Pax7 in SC with ↗ ROS production post expedition and large ↗ in SC with ≈ ROS production ↘ MyoD and myogenin mRNA and miR-133b and -206 in SC with ↗ ROS production post expedition and ↗ in SC with ≈ ROS production ↘ miR-1 and % fusion in both ↗ and ≈ ROS production ↗ lipid damage in SC with ↗ ROS production only	High-altitude trekking may ↗ ROS production in SC SC modulation following trekking at altitude may be dependent on ROS production and oxidative stress SC with ↗ ROS production following trekking at altitude are the most sensitive to impairment of differentiation and fusion

exposure. Of note, none of the studies investigated the short-term effects of a single bout of exercise during chronic hypoxic exposure. The results are summarized in Table 1 and schematized in Fig. 1.

Regulation of satellite cells by exercise in hypoxic conditions

Single exercise in acute hypoxic conditions

The ultimate goal of the present review is to gather the available sources that highligth the contribution of satellite cells to muscle remodeling and hypertrophy following exercise performed in hypoxic conditions. Although this type of events takes weeks or months, the study of acute responses to one single exercise is valuable to better understand the molecular mechanisms resulting in long-term changes. In total, four in vivo studies, three in healthy young men and one in horses, investigated the effects of one single exercise session in hypoxic conditions on molecular adaptations in skeletal muscle.

In the first study in young men, higher mRNA levels of proliferating cell nuclear antigen (PCNA), a marker of cell proliferation, were found after 20 min of moderate intensity cycling in hypoxia (10.7% FiO_2) in comparison to normoxia in skeletal muscle (Masschelein et al. 2014). Although not having investigated other satellite cell markers, this study uncovered the perspective that satellite cells could be regulated by exercise in hypoxic conditions (Masschelein et al. 2014). In that perspective, in a follow-up study, the mRNA levels of several satellite cell markers were analyzed in young men after a single session of resistance exercise in hypoxia (14% FiO_2) (Gnimassou et al. 2018). In comparison to normoxia, increased myogenin and a tendency towards increased MyoD and Mrf4 mRNA levels were observed in hypoxia. No effect of hypoxia on the cell proliferation markers Cyclin D1, Myf5, p21 and PCNA mRNA was found. While the short-term anabolic response to resistance exercise was not enhanced by hypoxia, the trend to increased expression of several myogenic markers suggests that hypoxic resistance training may result in a greater satellite cell activation and differentiation (Gnimassou et al. 2018). However, to date and to the best of our knowledge, no long-term study has confirmed the latter hypothesis of enhanced satellite cell activation and differentiation after hypoxic resistance training.

In a subsequent study investigating the role of the inflammatory pathway in myogenesis from the same research group, it was suggested that myogenesis may be promoted by the secretion of the inflammation markers interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-α by skeletal muscle and immune cells (Britto et al. 2020). IL-6 and TNF-α, as

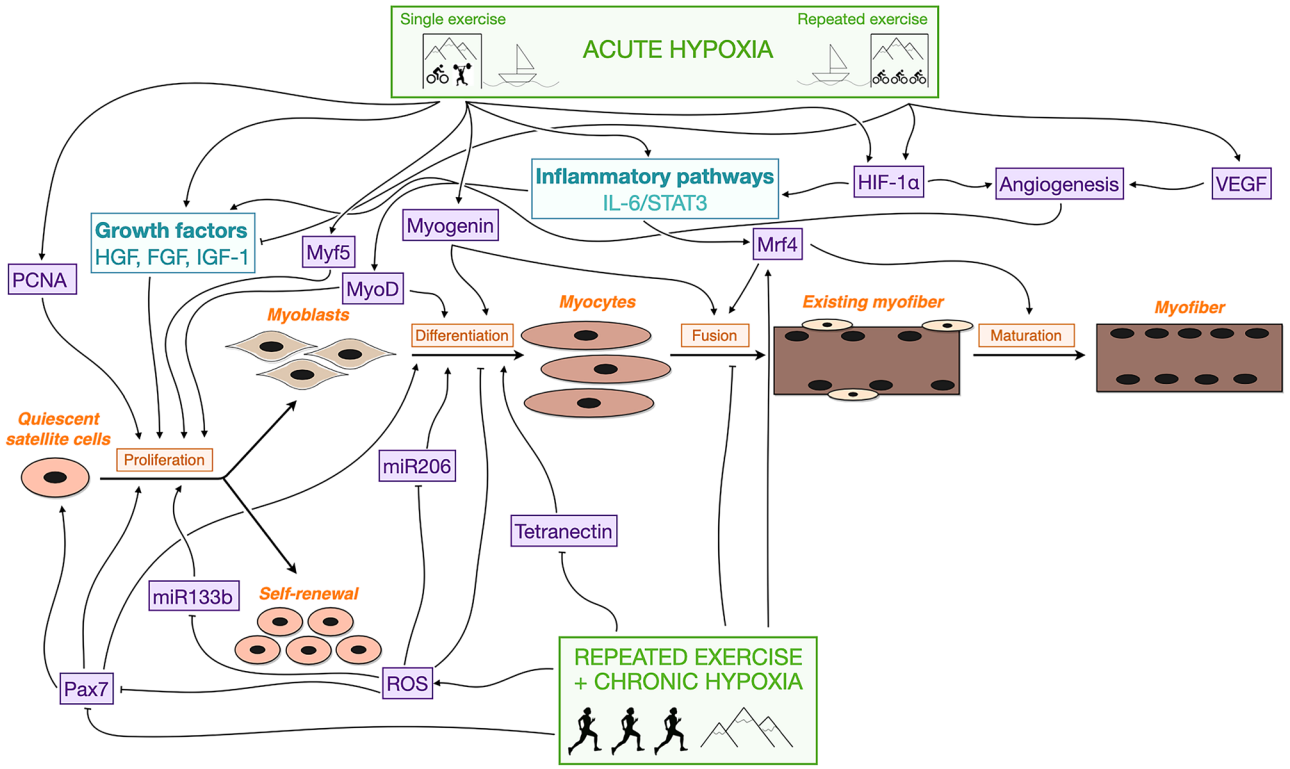

Fig. 1 Schematic overview of the regulation of adult myogenesis by single or repeated exercise in acute or chronic hypoxia, in comparison to normoxia. Myogenesis starts with the activation of quiescent satellite cells. The latter will undergo an asymmetric division and proliferation, which will give other satellite cells for pool self-renewal, while other cells will differentiate into myoblasts and myocytes and finally fuse with existing myofiber. Thin arrows indicate an activation, thin T-arrows indicate an inhibition. FGF: fibroblast growth factor; HGF hepatocyte growth factor; HIF: hypoxia-inducible factor; IGF: insulin-like growth factor; miR: Micro RNA; MRF: myogenic regulatory factors; Myf5: myogenic factor 5; MyoD: myogenic differentiation; Pax7: paired box 7; PCNA: proliferating cell nuclear antigen; ROS: reactive oxygen species

well as cluster of differentiation (CD) 68 and 197 mRNA levels, both macrophage/neutrophil markers, were shown to be higher following hypoxic resistance exercise than after the same exercise performed in normoxia. CD68 and CD197 are also known to regulate skeletal muscle regeneration, which may involve activation of satellite cells (Britto et al. 2020). Inflammation mediated by the activation of the IL-6/STAT3 pathway may lead to the activation, proliferation and differentiation of satellite cells, as measured by concomitant increases in MyoD and Mrf4 mRNA levels (Britto et al. 2020). Furthermore, it was postulated that the IL-6/STAT3 pathway might also contribute to the regeneration of exercise-induced muscle tissue damage through the recruitment of lymphocytes, monocytes and neutrophils, and thereby contribute to the potentiation of myogenesis (Tierney et al. 2014). Finally, HIF-1α stabilization and nuclear translocation in acute hypoxic in vitro conditions was associated with increases in STAT3 protein expression in human primary muscle cells, underlying the importance of this pathway in the adaptations to hypoxic conditions in skeletal muscle (Britto et al. 2020). Practically, those results underline the importance of a moderate and well-controlled inflammatory response to induce myogenic adaptations after hypoxic resistance exercise. They also question the strategy for reducing or even blunting the acute inflammatory response post-exercise, certainly in hypoxia, by taking anti-inflammatory drugs or nutrients.

The last in vivo study looking at hypoxic exercise-induced adaptations in satellite cells was performed in horses. Noteworthy, in opposition to human, horses may experience a large oxygen desaturation of hemoglobin during high intensity aerobic exercise at sea level (Thomas and Fregin 1981). To sustain the intensity and meet oxygen requirements, an increase in erythrocytes, hematocrit and hemoglobin levels, driven by the spleen, is observed (Mukai et al. 2020; Thomas and Fregin 1981). After 5 min of high-intensity cantering at 16% FiO_2, high levels of hepatocyte growth factor (HGF), insulin-like growth factor (IGF)-1 and IL-6 mRNA, all three known as satellite cell activators, were elevated in horses' skeletal muscle (Okabe et al. 2017). In addition, satellite cell number in type IIa muscle fibers was higher at 7 days post-exercise in hypoxia. Those results suggested that a single

hypoxic exercise session may enhance satellite cell number and activation, though, in comparison to normoxic exercise, MyoD, myogenin and Pax7 mRNA levels were not modified. In comparison to normoxia, lower mRNA levels of angiogenesis and mitochondrial biogenesis markers such as vascular endothelial growth factor (VEGF), angiopoietin 1 and peroxisome proliferator activated receptor gamma coactivator 1 alpha (PGC-1α) suggested that these processes may be downregulated following a single exercise session in hypoxic conditions in horses (Okabe et al. 2017).

In summary, specifically looking at the regulation of satellite cells, a single resistance exercise bout performed in hypoxia might induce satellite cell activation through increased expression of myogenic markers, possibly via the inflammatory pathway. Yet, other unidentified signaling pathways to the inflammatory pathway probably contribute to the regulation of the myogenic markers and satellite cells. While usually not directly associated to skeletal muscle hypertrophy, a single hypoxic endurance exercise session seems to regulate satellite cells as well. Whether those acute adaptations in satellite cells translate into changes at the whole muscle level and muscle mass will be analyzed in the two following sections.

Repeated exercise in acute hypoxic conditions

This section deals with repeated exercise sessions performed in acute and intermittent hypoxic conditions, meaning that recovery and the rest of the time is spent in normoxia. This training strategy is quite popular in athletes as it is known to induce intramuscular adaptations related to both aerobic and anaerobic performance (Millet et al. 2010). Much less has been reported concerning the regulation of muscle mass (Manimmanakorn et al. 2013; Nishimura et al. 2010) and even less concerning the regulation of satellite cells. Only one in vivo study was found in thoroughbred horses. In horses trained for 4 weeks at 100% VO_2max three times a week, an increase in VO_2max was observed in the hypoxic (15% FiO_2) but not normoxic conditions after training (Nagahisa et al. 2016). This increase was concomitant to a higher capillary density. The mRNA levels of angiopoietin and VEGF were found to be increased after hypoxic but not normoxic training. No differences in Pax7, MyoD and myogenin mRNA levels were noticed between normoxic and hypoxic exercise training. Three days post-hypoxic training increases in HIF-1α mRNA and decreases in HGF, fibroblast growth factor (FGF)-2 and IGF-1 mRNA were observed, which are all known to regulate the activation of satellite cells (Nagahisa et al. 2016). Despite a higher capillary density post hypoxic training, no change in satellite cell density (number of satellite cells per muscle fiber) was observed in either the normoxic or the hypoxic training group. As they are found close to capillaries, activation and differentiation of satellite cells by endothelial cell-derived growth factors such as FGF-2, HGF, IGF-1 and VEGF could have been expected in the hypoxic training group (Nagahisa et al. 2016), suggesting that angiogenesis plays a major role in the stimulation of satellite cells (Parise et al. 2020). However, as reported above, amongst the latter factors, only VEGF increased in the hypoxic training group. Another option that could explain the increased capillary density in the hypoxic training group is the stabilization of HIF-1α, which is known to activate satellite cells, promote angiogenesis and lead to improvement in capillary density in skeletal muscles following hypoxic training (Favier et al. 2015). However, HIF-1α stabilization was not determined in that study (Nagahisa et al. 2016) and the mRNA levels are not sufficient to reliably conclude on the activation of this pathway. From their side, satellite cells may also release factors that promote angiogenesis like angiopoietin 1, FGF-2, HGF and VEGF. Release of these factors is noticeable in satellite cells expressing myogenin, i.e., during satellite cell differentiation (Nagahisa et al. 2016).

Altogether, the results of this section show that, in horses, high-intensity exercise training in acute hypoxia improves VO_2max and concomitantly increases capillarity and the expression of angiogenic factors. Whether this can also be observed in human and whether hypoxic training-induced angiogenesis favors satellite cell activation and differentiation or inversely satellite cell activation and differentiation contribute to angiogenesis should be further investigated. We cannot exclude that both processes interact reciprocally.

The last results section tackles a condition often encountered by hikers during high-altitude expedition and usually associated with a loss of muscle mass. Though, whether satellite cells are impacted as well and whether their proliferation and differentiation properties are altered after such expedition deserves a close analysis as this could influence the recovery from subsequent hypoxic exposures and the ability to repeat sojourns at altitude in healthy conditions.

Repeated exercise in chronic hypoxic conditions

In total, three studies investigated the effects of high-altitude expedition on the regulation of satellite cells. The first one published in the 90 s was a follow-up investigation of muscle biopsies taken in experienced men climbers to look at skeletal muscle morphological changes after a 10-week expedition above 5000 m (Hoppeler et al. 1990; Martinelli et al. 1990). From before to after the expedition, the cross-section of the vastus lateralis was decreased by 10% and the mitochondrial volume by 25% (Hoppeler et al. 1990). In comparison to pre-expedition, myoblasts and myonuclei number remained unchanged, satellite cell volume density, a marker of muscle regeneration, was increased by 215% and lipofuscin volume density, a marker of muscle degeneration (Roth

et al. 2000) and impaired mitophagy (Konig et al. 2017), increased by 235% (Martinelli et al. 1990). Although this first study deserves the primacy of studying the effects of high-altitude expedition on the regulation of satellite cells, it should be acknowledged that one major limitation is the lack of molecular analyses and the use of indirect markers for determining the role of satellite cells in regenerative events. Whether there is a link between subsarcolemmal lipofuscin accumulation and increased satellite cell volume density needs further investigation.

The two other studies, both from Fulle's research group, having looked at the effects of repeated exercise in chronic hypoxic conditions are more recent, rendering the accessibility to biomolecular techniques and analyses far easier (Mancinelli et al. 2011, 2016). The first published in 2011 found a reduction in satellite cell proliferation, fusion and myogenicity after compared to before an expedition to Nepal (5000–6400 m) (Mancinelli et al. 2011). Those observations were related to lower capacity of skeletal muscle regeneration and dysregulation of several signaling pathways involved in the regulation of myogenesis, oxidative metabolism, proteolysis and protein synthesis (Mancinelli et al. 2011). After the expedition, thigh cross sectional area was increased whereas force development was unchanged (Doria et al. 2011). In addition, compared to pre-expedition, total myonuclei number was increased, whereas number of Pax7-positive cells and satellite cell proliferation rate were reduced. More specifically, the mRNA levels of the myogenic factor 6, coding for Mrf4, were upregulated and the mRNA levels of tetranectin, a marker of myogenic differentiation, downregulated after the expedition (Mancinelli et al. 2011). Together with the reduced myogenicity and satellite cell fusion observed in cell cultures assessed from the muscle biopsies, these results suggest a decrease of satellite cell activity in response to chronic hypoxic exercise (Mancinelli et al. 2011). In addition, the mRNA levels of protein phosphatase 2 catalytic subunit, alpha isoform (PP2CA) and protein tyrosine phosphatase, non-receptor type 3 (PTPN3) were upregulated after the expedition at altitude (Mancinelli et al. 2011). Knowing that PP2CA and PTPN3 inactivate ribosomal protein S6 Kinase 1 (S6K1) and that the mechanistic target of rapamycin (mTOR)-S6K1 pathway regulates satellite cell activation and proliferation (Wei et al. 2019), it is possible that a long-term exposure to hypoxia due to the duration of an expedition slows down satellite cell growth in human skeletal muscle. An upregulation of genes involved in oxidative metabolism, such as AU RNA Binding Methylglutaconyl-CoA Hydratase, ATP synthase and hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase (trifunctional protein), alpha subunit, and genes coding for mitochondrial proteins and fatty-acid oxidation was observed. Concomitantly, a series of genes involved in the glycolytic metabolism was downregulated. Altogether, those results suggest an increase in the oxidative capacity and a switch towards a slow-oxidative phenotype (Mancinelli et al. 2011). Enhanced oxidative metabolism is known to favor a switch in muscle fiber type towards oxidative fibers. Post-expedition, the proportion of slow muscle fibers increased by 18% together with a 15% increase of MHC-I expression, whereas fast intermediate IIa muscle fiber distribution decreased by 12% and MHC-IIa expression decreased by 8% (Doria et al. 2011). In summary, satellite cell activity was lower and slow fiber phenotype increased following high-altitude expedition. This latter observation may be seen as uncommon, as hypoxic exposure is known to promote glycolytic rather than oxidative metabolism. Strength maintenance and the increase in thigh cross-sectional area observed after repeated exercise in chronic hypoxic conditions might be driven by a switch in muscle fiber type rather than muscle hypertrophy driven by myogenesis, as satellite cell activity was low (Mancinelli et al. 2011). Although this first study from Fulle's research group was quite exhaustive, looking at several molecular mechanisms known to regulate or to be regulated by changes in satellite cells activity, they did not investigate one major mechanism potentially present during a high-altitude expedition, i.e., oxidative stress. They did so in a second study wherein muscle biopsies were taken before and 5 days after a 14-day trekking in the Himalayas in women (Mancinelli et al. 2016). They investigated the production of reactive oxygen species (ROS) and the subsequent oxidative stress as well as their influence of satellite cell proliferation in culture. The main finding was that, after a 14-day trekking, oxidative stress may impair the regenerative capacity of satellite cells. It was suggested that hypoxia-induced ROS accumulation and excessive oxidative stress production might impair mitochondrial activity. In isolated muscle fibers, it was observed that Pax7+ nuclei number and satellite cell fusion were decreased after the high-altitude expedition, suggesting a decrease in satellite cell differentiation (Mancinelli et al. 2016). In cell cultures, differences were found between satellite cells showing increased ROS production after the trekking and satellite cells showing unchanged or even decreased ROS production. Satellite cells showing increased ROS production had a more prominent reduction in Pax7+ nuclei number, in the rate of fusion and in lipid damage. In ROS producing satellite cells, MyoD and myogenin mRNA levels were decreased in comparison with those producing less ROS. Those results suggest that, in contrast to a single hypoxic exercise, myogenic differentiation and myofiber formation may be impaired by long-term trekking at altitude and related ROS accumulation in muscle fibers (Mancinelli et al. 2016). Of note, ROS production in isolated satellite cells after a high-altitude expedition was highly variable from one subject to another. Why such a high inter-subject variability in ROS production was present is not known. In the search to understand how ROS

production could affect regulation of satellite cells, potential candidates were highlighted such as microRNAs (miR)-133b, that regulates satellite cell proliferation, and miR-206, that regulates satellite cell differentiation. In comparison to miRNA expression pre-expedition, miR-133b and miR-206 were downregulated in ROS producing cells and upregulated in the other cells. Based on their respective role and the context of the study, it is possible that downregulation of miR-133b induced apoptosis in ROS producing satellite cells and downregulation of miR-206 impaired satellite cell differentiation (Mancinelli et al. 2016). Post-transcriptional regulation of satellite cell proliferation and differentiation may thereby be impaired by ROS production. More research is needed to understand how ROS production can regulate satellite cells, certainly using direct measurements in vivo. Indeed, one limitation of the latter study is that the production and the role of ROS were investigated in cultured satellite cells isolated from muscle biopsies taken pre- and post-expedition, not directly in muscle biopsies. The question is whether satellite cells maintain their intact physiological potential, more specifically here their ability to produce ROS, once cultured. Globally, this is a critical question as it is not an easy task to study satellite cells and their niche directly in vivo but on the other hand how do we ensure the preservation of the in vivo features when cells are cultured? This issue renders the study of satellite cells very tricky and explains why the number of studies in the field are quite scarce.

In summary of this third and last results section, repeated physical activity in chronic hypoxia, such as trekking, appears to impair satellite cell proliferation, fusion and myogenicity via excessive oxidative stress or proteolysis.

Research perspectives

The data from the previous section indicate that exercise in hypoxic conditions regulates satellite cell activity. Whereas acute exercise in hypoxia appears to induce satellite cell activation but to decrease their differentiation, repeated exercise limits satellite cell proliferation, fusion and myogenicity, which could contribute to the loss of muscle mass observed by some authors after a high-altitude expedition. Based on the aforementioned literature, among the mechanisms linking exercise, hypoxia and satellite cell regulation, autophagy, eccentric contractions and angiogenesis are worth further investigation.

Autophagy

Macroautophagy, referred here as autophagy, is a dynamic degradation process through which cytoplasmic components, such as dysfunctional or damaged proteins, organelles and fraction of cytoplasm, toxic proteic aggregates and intracellular pathogens, are wrapped inside a double-membrane cytoplasmic vesicle called autophagosome. Subsequently, the autophagosome fuses with lysosomes to form an autolysosome which contains hydrolases to degrade its content (Martin-Rincon et al. 2018). Endosome formed by endocytosis can also fuse with autophagosome and be degraded by lysosomal autophagy. Increasing evidence shows that autophagy is necessary for the maintenance of skeletal muscle mass and function (Francaux and Deldicque 2019). Autophagy can be activated in response to several stress conditions, such as fasting, high intensity exercise or hypoxia, to sustain cell activity despite nutrient deprivation (Martin-Rincon et al. 2018; Tang and Rando 2014). Exercise-induced autophagy relies on the intensity rather than on the type of contraction (Schwalm et al. 2015). Autophagy plays an essential role in the maintenance of satellite cells' quiescence and regenerative capacity by eliminating excessive ROS and damaged proteins and organelles (Wen and Klionsky 2016). Autophagy also eliminates proteins involved in satellite cells' self-renewal and differentiation. Autophagy appears necessary for satellite cell activation, as it enables them to meet energy requirements to sustain transition to a higher metabolic state (Tang and Rando 2014). Expression of autophagic markers was shown to be increased during satellite cell differentiation. Furthermore, fusion of myocytes into myofibers appears to require autophagy activation (Fortini et al. 2016). In the context of the present review, it is interesting to note that exercise may modulate autophagy activation in satellite cells (Park et al. 2019), and that hypoxia was found to modulate autophagy both after endurance (Masschelein et al. 2014) as well as after resistance exercise (Gnimassou et al. 2018), although this was not specifically analyzed in satellite cells. It can be hypothesized that combining exercise and hypoxia could result in a higher induction of autophagy than each of the stimuli taken separately, which could in turn result in an increased activation of satellite cells due to higher energy requirements. In contrast, satellite cell activation could be delayed or suppressed to protect the stem cell pool from excessive energetic stress. Anyway, whether hypoxic exercise regulates satellite cell activity through a modulation of autophagy remains to be tested.

Eccentric contractions

Eccentric contractions induce larger muscle hypertrophy and strength gains compared to concentric contractions, which are mainly due to enhanced responses from the neuromuscular system (Douglas et al. 2017) and satellite cells (Hyldahl et al. 2014; Imaoka et al. 2015). Several mechanisms are involved in this enhanced response of satellite cells to eccentric vs concentric contractions, which include a larger expression of the MRF and HGF, associated with satellite

cell activation and proliferation, as well as with activation of transient receptor potential canonical 1, a stretch-activated cation channel that can induce satellite cell activation through membrane depolarization (Imaoka et al. 2015). In addition, increased satellite cells activation and proliferation after eccentric exercise may be due to higher muscle damage and inflammatory cytokine levels (Hyldahl et al. 2014). Inflammatory cytokines, such as monocyte chemotactic protein-1 or interferon-gamma-induced-protein-10, can enhance satellite cell activation through the recruitment of T lymphocytes (Hyldahl et al. 2014). Inflammation-mediated satellite cell activation has been observed after hypoxic vs normoxic resistance exercise, that could be initiated by the IL-6/STAT3 pathway in skeletal muscle (Britto et al. 2020). Based on these observations, further research should investigate if hypoxia can potentiate satellite cell response to eccentric exercise through activation of the inflammatory pathway.

Satellite cells and angiogenesis crosstalk

Muscle regeneration depends on activation of myogenesis and angiogenesis (Rhoads et al. 2009). Thus, a certain coordination probably exists between the factors inducing myogenesis and those inducing angiogenesis. Satellite cells are localized close to capillaries, under the basal lamina, and their number seems to depend on the amount of blood vessels, regardless of muscle fiber type and stage of activation (Christov et al. 2007). Illustrating the latter, an increase in satellite cell number was observed around vessels following exercise-induced angiogenesis and muscle regeneration (Christov et al. 2007). In addition, endothelial cells were found to release growth factors promoting satellite cell activation, such as FGF, HGF, HIF-1, IGF-1, platelet derived growth factor and VEGF (Christov et al. 2007). As they upregulate VEGF and HIF-1 expression, hypoxic conditions could enhance satellite cell activation as well (Rhoads et al. 2009). Based on the above, it may be suggested that angiogenesis might control satellite cell activation after exercise in hypoxic conditions through the regulation of growth factor secretion (Parise et al. 2020).

In turn, satellite cells may also stimulate angiogenesis, especially during proliferation, differentiation and fusion, probably to sustain energy requirement for growth, differentiation and maturation (Christov et al. 2007). For example, VEGF expression in satellite cells was shown to be low in resting conditions but increased in regenerating muscle fibers (Christov et al. 2007). Myogenin-positive, not Myf5-positive, satellite cells were associated with markers of neoangiogenesis (Christov et al. 2007). To note, expression of angiogenic factors is also increased in response to endurance exercise, especially after endurance training in hypoxia (Bloor 2005). Altogether, these observations suggest that exercise in hypoxia may enhance satellite cell-induced angiogenesis and in turn angiogenesis induced by hypoxic exercise can activate satellite cells through the secretion of growth factors. Stimulation of nitric oxide (NO) production by hypoxia, exercise or a combination of both may also play a role in the regulation of angiogenesis by satellite cells (Nagahisa and Miyata 2018; Nagahisa et al. 2016). NO activates satellite cells, which in turn release angiogenic factors such as VEGF and FGF (Nagahisa and Miyata 2018). In addition to the aforementioned mechanisms, increased ROS production during hypoxic exercise contributes to angiogenesis and satellite cell activation (Nagahisa and Miyata 2018). While interesting, interactions between satellite cells and angiogenesis in hypoxic exercise conditions has only been studied in animals up to now. Further investigation is warranted to confirm this observation in human.

Limitations

Satellite cells activation following a single bout of exercise seems to peak 48–72 h post-exercise (Hyldahl et al. 2014). Biopsies from acute in vivo studies were taken at different time points post-exercise: directly (Masschelein et al. 2014), 4 h (Britto et al. 2020; Gnimassou et al. 2018), or 24 h, 3 and 7 days (Okabe et al. 2017) after the end of exercise sessions. Making conclusions regarding activation, proliferation and differentiation of satellite cells following exercise in hypoxic conditions from biopsies taken too early after the end of the exercise may thereby be inaccurate. Further studies investigating satellite cell activity in humans should ideally involve biopsies 48–72 h post-exercise or ideally at different time points to examine the time course of satellite cell activity. Another question is to know if the time course of satellite cell activation is similar if the post-exercise recovery period is performed in hypoxia or in normoxia. It can be postulated that hypoxic recovery might delay or on the contrary accelerate satellite cell activation in comparison to normoxic recovery, which remains to be investigated properly.

Further investigations

Only a few human studies have investigated satellite cell activity in acute hypoxic exercise conditions (Britto et al. 2020; Gnimassou et al. 2018; Masschelein et al. 2014). The purpose of this review article could only be partially answered due to the limited number of studies on this topic, partially due to the technical difficulties to study satellite cells in vivo. In addition, the contribution of satellite cells to macroscopic changes in skeletal muscle, i.e., changes in muscle mass, can only be investigated after a few weeks or even months, which implies time-consuming and expensive studies. This said, we acknowledge that more data should be obtained in humans to get valid and trustable conclusions.

Also, no study attempted to compare the effects of endurance vs resistance exercise in the same hypoxic conditions on the regulation of satellite cells. Finally, to get a whole comprehension of the acute and chronic responses of satellite cell activity to hypoxic conditions and their role in the accretion of muscle mass, repeated muscle samples after a single as well as after repeated sessions of hypoxic exercise should be taken to analyze short- and long-term molecular mechanisms and test their possible association with strength and morphological changes in skeletal muscle after a few weeks/months.

Conclusion

In vivo studies suggest that, in comparison to exercise or hypoxia alone, exercise performed in a hypoxic environment, may improve or impair muscle remodeling induced by contractile activity depending upon the duration of hypoxia. Satellite cells seem to be major actors in these dichotomous adaptations. Satellite cell activation and proliferation seem to be activated after acute hypoxic exercise, whereas differentiation and fusion appears to be downregulated after repeated exercise in chronic hypoxia. Whether the aforementioned regulations of satellite cells after hypoxic exercise will translate into macroscopic changes at the skeletal muscle level and modify muscle mass warrants further investigation. Further research on the role of angiogenesis, types of contraction and autophagy is needed for a better understanding of their respective role in hypoxic exercise-induced modulations of satellite cell activity in human.

Acknowledgements MF is supported by the Sports Ministry of the Brussels-Wallonia Federation and the Sports Performance Assistance Centre (SPAC).

Authors' contributions S.v.D.d.t.R. wrote the first draft, drew the figure and made the summarizing table. L.D. and M.F. corrected the draft and L.D. wrote the final version that was approved by M.F. and S.v.D.d.t.R. All authors have read and agreed to the published version of the manuscript.

Funding This research received no external funding.

Availability of data and materials Not applicable.

Code availability Not applicable.

Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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