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23 **Abstract**

24 Patients with stable chronic obstructive pulmonary disease (COPD) frequently exhibit
25 unintentional accentuated peripheral muscle loss and dysfunction. Skeletal muscle mass in
26 these patients is a strong independent predictor of morbidity and mortality. Factors including
27 protein anabolism/catabolism imbalance, hypoxia, physical inactivity, inflammation, and
28 oxidative stress are involved in the initiation and progression of muscle wasting in these
29 patients.

30 Exercise training remains the most powerful intervention for reversing, in part, muscle
31 wasting in COPD. Independently of the status of systemic or local muscle inflammation,
32 rehabilitative exercise training induces up-regulation of key factors governing skeletal muscle
33 hypertrophy and regeneration. However, COPD patients presenting similar degrees of lung
34 dysfunction do not respond alike to a given rehabilitative exercise stimulus. In addition, a
35 proportion of patients experience limited clinical outcomes, even when exercise training has
36 been adequately performed. Consistently, several reports provide evidence that the muscles
37 of COPD patients present training-induced myogenic activity resistance as exercise training
38 induces a limited number of differentially expressed genes, which are mostly associated with
39 protein degradation.

40 This review summarises the nature of muscle adaptations induced by exercise training,
41 promoted both by changes in the expression of contractile proteins and their function
42 typically controlled by intracellular signalling and transcriptional responses. Rehabilitative
43 exercise training in COPD patients induces skeletal muscle mechanosensitive signalling
44 pathways for protein accretion and its regulation during muscle contraction. Exercise training
45 also induces synthesis of myogenic proteins by which COPD skeletal muscle promotes
46 hypertrophy leading to fusion of myogenic cells to the myofibre. Understanding of the
47 biological mechanisms that regulate exercise training-induced muscle growth and
48 regeneration is necessary for implementing therapeutic strategies specifically targeting
49 myogenesis and hypertrophy in these patients.

50

51

52

53 **Keywords:** COPD, exercise, protein synthesis, anabolism, hypertrophy, myogenesis, muscle
54 wasting

55

56 ***Introduction***

57 COPD is the fourth leading cause of death worldwide and is projected to be the third most
58 common cause of death by 2020 (1). Cigarette smoke constitutes the major preventable risk
59 factor, resulting in a progressive proteolytic, inflammatory and vasoactive response that leads
60 to emphysema, small airway obstruction and pulmonary hypertension. The oxidative stress
61 imposed by cigarette smoking together with systemic inflammation and hypoxia are
62 important contributors to pathogenesis of skeletal muscle wasting and dysfunction and have
63 been previously extensively reviewed (2-4). Skeletal muscle wasting is an important systemic
64 effect of the disease and a strong independent predictor of mortality (5-7). This unintentional
65 accentuated skeletal muscle wasting is frequently associated with altered muscle structure
66 (fiber size, fiber type distribution, capillary density and metabolic capacity) and dysfunction
67 (decreased strength and endurance). While the magnitude of the alterations varies
68 substantially across individuals, some degree of muscle wasting affects all individuals during
69 ageing. Age-related defects in protein metabolism have been proposed to be causally
70 involved in this muscle loss (8). These changes are attributed to both inactivity- and age-
71 related alterations in protein synthesis and degradation, indicating complex
72 pathophysiological phenomena involving both structural changes to the muscle fibres, as well
73 as the enzymatic machinery that controls metabolism. Independently of the factors promoting
74 muscle wasting in COPD, regular physical exercise remains the most potent available
75 treatment option for reversing, in part, locomotor muscle wasting and dysfunction in COPD
76 (9). Indisputably, exercise training promotes a range of beneficial adaptations in the skeletal
77 muscle including increased capillarization, fibre type plasticity, hypertrophy and function.
78 However, exercise training induced muscle benefits are certainly much smaller in COPD
79 patients compared to age matched controls. In addition, not all COPD patients respond
80 adequately to exercise stimulus, even when exercise training is properly performed (10, 11).
81 An improved understanding of molecular mechanisms of exercise induced adaptations in
82 COPD and healthy individuals will be valuable to inform future directions to address the
83 issues on resistance to exercise-induced adaptations in COPD.

84

85 ***Effect of prescribed exercise training to skeletal muscle adaptation in COPD***

86

87 Exercise training is a mechanical stimulus that consists of repeated, episodic bouts of muscle
88 contraction promoting functional adaptation and remodelling not only to the skeletal muscle,

89 but also to various systems in our body (12, 13). Exercise promotes a range of adaptations
90 that is beyond the musculoskeletal system promoting general health(14). Briefly, in parallel
91 with neural signals to the skeletal muscle contraction, powerful neural feed-forward signals to
92 the respiratory, cardiovascular, metabolic and hormonal systems are produced. In response to
93 exercise training, COPD patients demonstrate reduction in dyspnea sensations, improvements
94 in exercise capacity and quality of life (9).

95

96 Skeletal muscle adaptations are dependent on the intensity and duration of the exercise
97 training performed (15). High intensity exercise training ($W_{peak} \geq 80\%$) is generally
98 described to promote improvement in exercise capacity. However, COPD patients with
99 limited ventilatory capacity are usually unable to sustain high intensities for sufficiently long
100 periods. Taking into consideration COPD patients exercise capacity, a number of studies have
101 been performed employing a varied combination of exercise modalities/training, program
102 duration and intensity. Usually, the duration of an exercise training programme is set from 8
103 to 12 weeks and as frequent as 3 times per week. Combination of high intensity aerobic and
104 resistance exercise is described to promote quantifiable muscle hypertrophy in COPD (16, 10,
105 17, 11). Conversely, exercise training of lower intensity ($W_{peak} \leq 60\%$) was found unable to
106 promote quantifiable changes in muscle hypertrophy and fibre type distribution (18, 19).
107 Therefore, programmes incorporating high intensity exercise training are more likely to
108 induce quantifiable skeletal muscle adaptations.

109

110 Different modes of exercise such as endurance- and resistance-based are known to stimulate
111 variable but specific skeletal muscle adaptations, leading to muscle endurance and strength
112 respectively (15). Aerobic/endurance exercise training enhances mitochondrial protein
113 content and oxidative capacity of trained myofibers, improving insulin sensitivity and skeletal
114 muscle metabolic function (20). Whereas, resistance training increases myosin-heavy-chain
115 gene transcripts and synthesis rate of muscle proteins promoting strength (15). When
116 comparing different modalities of exercise prescribed to healthy sedentary people, Robinson
117 et al (21) observed that high intensity interval training (HIIT) enhanced more
118 comprehensively changes such as aerobic capacity, mitochondria respiration and lean body
119 mass (21). HIIT training simultaneously promoted endurance- and resistance-based training
120 skeletal muscle adaptations, that promoted changes in transcription and translation regulation
121 of muscle growth and mitochondrial pathways (21). HIIT reversed age-related proteome,
122 particularly of mitochondrial proteins. But both resistance training and HIIT increase proteins

123 involved in translational machinery. HIIT exercise involves 30s repeated short bouts of
124 activity at near maximal intensity ($W_{peak} \geq 80\%$) interspersed with 30s rest periods, which
125 despite its high intensity, has been successfully applied to COPD patients (10, 17, 22, 11). A
126 representation of basic skeletal muscle adaptation promoted by aerobic/endurance, resistance
127 and HIIT is depicted in Figure 1, originally adopted by Robinson *et al.* (21).

128 Therefore, adaptations seen in COPD skeletal muscle take place in accordance with specific
129 exercise training stimuli, thereby partially explaining the large variability in muscle
130 adaptations seen among studies. The effect of exercise modalities in promoting COPD
131 skeletal muscle adaptations at structural and protein metabolism levels have been recently
132 presented in a systemic review (18).

133
134 Histologically, the skeletal muscle appears uniform, but is composed by a range of
135 heterogeneous myofibres regarding size, metabolism and contractile function. When
136 comparing myosin-heavy-chain isoform expression, myofibres are classified into type I, type
137 IIa, type IIc/x, and type IIb fibres (23). Type I and IIa fibers exhibit high oxidative potential
138 and IIc and IIb are primarily glycolytic. Whether endurance- or resistance-based exercise
139 training can induce myofibre plasticity is still debatable. Certainly, COPD patients present a
140 shift in fibre type displaying fewer type I (oxidative) fibres and greater proportion of type II
141 (glycolytic) fibres in quadriceps muscles (24). This shifting towards glycolytic fibres is
142 associated with increased mortality (7). Exercise training prescribed to COPD patient can
143 only partially reverse this fiber type shifting. Proportion of fiber type I and IIa were increased
144 mainly after HIIT and high intensive aerobic exercise (18, 25) as endurance training confers
145 an increased oxidative profile to trained myofibers (23). Hypertrophy of fibre type I and IIa
146 was more widespread among different modalities of exercise training, (18), Whereas,
147 capillary to fiber ratio adaptations were though observed across various intensities and
148 modalities of exercise training (18).

149

150 ***Contribution of inactivity to COPD muscle wasting***

151

152 Inactivity appears to be an important mechanism in the process of muscle loss in COPD,
153 given that muscles that are active, such as the diaphragm and the adductor pollicis, do not
154 exhibit atrophy in contrast to inactive muscles, such as the quadriceps (26). In experiments
155 comparing different muscle groups in COPD patients, the characteristics exhibited by the

156 deltoid and the diaphragm were different compared to the quadriceps (27). Importantly, the
157 muscles of respiration in COPD exhibit a contrary shift in fiber typing compared to the
158 locomotor muscles, manifested by increased type I fiber distribution (28, 29). Various
159 conditions of reduction in neuromuscular activity promoted by inactivity are known to
160 decrease myonuclear number in atrophying muscle and impact on fibre typing. As reviewed
161 elsewhere (30), detraining experiments in healthy individuals have shown to induce
162 locomotor muscle adaptations that lead to increased number of muscle fibre type Iix
163 phenotype, and attenuation of mitochondrial biogenesis (PPARs and PGC-1 α) as observed in
164 COPD patients. As described above, reassuming activity by exercise training can partially
165 promote changes in fibre type distribution (18). However, inactivity alone does not seem to
166 fully explain the phenomenon of muscle fibre type shifting in COPD.

167

168 *Mechanical stress and mitogen-activated protein kinase signalling*

169

170 The ability of skeletal muscles to respond to physical exercise by executing the appropriate
171 metabolic and transcriptional response is dependent upon the cellular signal transduction
172 through phosphorylation cascades. Multiple kinases, including AMPK, Akt and the mitogen-
173 activated protein kinases (MAPKs) are involved in the regulation of DNA transcription
174 through the phosphorylation of nuclear transcription factors. This either enhances or inhibits
175 the ability of transcription factors to bind DNA, affecting target gene transcription (31, 32).
176 Three main MAPK subfamilies are activated by acute exercise in human skeletal muscle: (1)
177 the extracellular-regulated kinase (ERK1/2), (2) the c-jun N-terminal kinase (JNK), and (3)
178 the p38 MAPK. Activation of MAPKs regulates the transcriptional events by phosphorylation
179 of diverse substrates localised in the cytoplasm or nucleus, including transcription factors,
180 inducing differentiation, hypertrophy, inflammation, and gene expression (33).

181

182 The MAPK p38 is a stress-activated kinase that is transiently activated in response to a
183 strenuous range of stimuli such as physical inactivity and increased intensity of exercise
184 training (34, 35). Activation of p38 in skeletal muscle myoblasts is related to loss a in cell
185 autonomous self-renewal capacity (36). MAPK p38 activation is also observed during
186 skeletal muscle immobilisation in a rat hind limb model of acute muscle wasting (37, 34).
187 COPD are generally more inactive compared to their age-matched healthy counterparts (38).

188 Accordingly, ratios of phosphorylated to total level of p38 MAPK and ERK 1/2 were
189 significantly elevated in patients with COPD compared to controls (39). Whereas, another
190 study have shown no differences in the ratio of phospho-p38 MAPK to total level of p38
191 MAPK protein between COPD patients and healthy age-matched donors. Although patients
192 with COPD present muscle wasting, discrepancies among studies would be expected as it is
193 uncertain whether patients are actively losing muscle mass at the time of experimentation.

194

195 *Major signaling pathways involved in the control of exercise training induced skeletal*
196 *muscle adaptations*

197

198 Endurance- and resistance-based modalities of exercise are controlled by two major signaling
199 pathways regulating mitochondria biogenesis and hypertrophy respectively, as depicted in
200 Figure 2.

201

202 The regulation of mitochondrial biogenesis by endurance-based exercise converge from
203 activation of the cascades AMPK and p38 upregulating PGC-1 α . When compared to healthy
204 controls, mitochondria density is lower in quadriceps muscle of COPD patients, presenting
205 lower expression of peroxisome proliferator-activated receptors (PPARs), PPAR- γ co-
206 activator 1 α (PGC-1 α) and mitochondrial transcription factor (TFAM) in cachectic COPD
207 (40). In patients with COPD, exercise enhances the decrease in mitochondria DNA content of
208 skeletal muscle and the expression of PGC-1 α mRNA seen in healthy subjects, probably due
209 to oxidative stress (41).

210

211 In contrast, resistance training is described to stimulate the signaling pathways responsible
212 for muscle hypertrophy (12, 13). The activation of mTOR and IGF-I appears to be important
213 in this process. To restore muscle mass via regular exercise training, protein synthesis should
214 exceed protein breakdown over an extended period. Hypertrophy of skeletal muscle as result
215 of resistance exercise training is strongly associated with the degree of mTOR activation,
216 ribosomal protein S6K (p70^{S6K}) phosphorylation and downstream targets (42). Contraction-
217 induced p70^{S6K} activation is dependent on mTOR activation, which increases protein
218 translation and inhibits protein degradation via inhibition of both ubiquitin proteasome (43,
219 32, 44) and autophagy-lysosome pathways (45, 46). mTOR activation is critical to load-

220 induced muscle growth, as demonstrated by the attenuation of hypertrophy responses and
221 protein synthesis by the mTOR inhibitor, rapamycin (43).

222

223 We and others have described that Akt/mTOR pathway is downregulated in skeletal muscle
224 of patients with COPD compared to healthy subjects (10). HIIT promotes the activation of
225 the Akt/mTOR pathway in skeletal muscle only in COPD patients with preserved muscle
226 mass compared to aged matched controls. Some studies suggest that hypoxemia
227 characteristically observed in more severe cachectic COPD patients, is associated with
228 resistance of skeletal muscle activation of the Akt/mTOR pathway (16). Exercise training in
229 hypoxemic patients with COPD was not capable to promote muscle fibre hypertrophy and
230 activation of the Akt/mTOR pathway as compared to normoxemic COPD patients (16). Both
231 *in vitro* C2C12 myotubes cultured in normoxic and hypoxic conditions and mice models of
232 hypoxia suggest that the response of the Akt/mTOR pathway to exercise could be
233 compromised in hypoxemic patients (16, 47). Therefore, impairment of skeletal muscle
234 hypertrophy commonly linked to the severity of the disease is associated with the magnitude
235 of muscle wasting, the degree of hypoxia, or both. Interestingly, induced expression of the
236 adaptive response of hypoxia HIF-1 responsive RTP801 (DDIT4) is observed only in trained
237 COPD and not in healthy subjects (48).

238

239 mTOR regulates the mechanisms of protein synthesis at several levels (e.g. translation
240 capacity, translation efficiency) through increases of translation of specific mRNAs, which
241 culminates in skeletal muscle fibre enlargement. mTOR exists as part of two multi-protein
242 complexes: i) mTORC1, which contains raptor and confers rapamycin sensitivity, is required
243 for signalling to p70^{S6K} and 4E-BP1, whereas ii) mTORC2, which contains rictor and is
244 rapamycin insensitive, is required for signalling to Akt-FOXO (49). The effect of mTOR
245 activity on downstream regulators of protein synthesis is principally achieved through a
246 contraction-induced regulation of mTORC1 (50).

247

248 Early work on adaptive hypertrophy has focused on the (transient) post exercise rise in blood-
249 borne anabolic hormones, such as growth hormone and insulin-like growth factor-I (IGF-I),
250 and the consequent activation of the muscle protein synthesis of a signalling cascade
251 (phosphatidylinositol 3-kinase (PI3K)-Akt-mTOR) by IGF-I interaction with insulin and
252 IGF receptors (51). Recently, the muscle growth paradigm has shifted focus to IGF-I-
253 independent mechanisms of mTOR activation and adaptive hypertrophy through mechano-

254 sensory regulation (50). Nutrient-dependent regulation of muscle growth is achieved through
255 insulin- and Akt-dependent activation of the mTOR pathways. These pathways operate
256 synergistically causing muscle growth and can be augmented by appropriate nutritional
257 intake such as post exercise carbohydrate and amino acid ingestion or increased dietary
258 protein (52). Therefore, IGF-I is involved not only in hypertrophy but also in promoting
259 myogenesis and muscle regeneration.

260

261 ***Regulation of skeletal muscle protein synthesis promoting myogenesis and muscle***
262 ***regeneration***

263

264 Skeletal muscle hypertrophy is achieved by both positive protein balance and fusion of
265 satellite cells to myofibres (Figure 1). It is a process that involves (1) accretion of protein in
266 various cellular compartments via mechanosensitive signalling pathways that drive
267 translation, and (2) the activation and recruitment of resident muscle stem cell (satellite cells)
268 that differentiate to fusion-competent myoblasts (53, 54). Regulation of protein translation
269 and synthesis promotes accretion, whereas activation and incorporation of satellite cells
270 facilitates the addition of myofibrils to the muscle.

271

272 Myogenesis and muscle regeneration depend on critical steps for activation of quiescent
273 satellite cell, proliferation, migration, differentiation, fusion and maturation. Fusion of a
274 satellite cell to an existent myofibre results in an increase in the number of myonuclei, and
275 thus the available total amount of genetic machinery for protein production (54). The average
276 number of myonuclei per muscle fibre of non-cachectic COPD is twice as high compared to
277 controls, indicating higher capacity of protein metabolism necessary for maintenance of
278 muscle mass. Quiescent satellite cells are essential to replenishment of myonuclei pool. As
279 satellite cells replicate throughout lifespan, telomeres are shortened. Telomere shortening is a
280 marker of senescence. COPD patients, despite the observation that satellite cells numbers are
281 unaltered in the limb muscle compared to controls, satellite cells present shorter telomeres. A
282 fact suggesting exhausted muscle regenerative capacity, compromising the maintenance of
283 muscle mass (55).

284

285 Satellite cells myogenic regulatory factors (MRF) and myostatin play important roles in
286 myogenesis and muscle regeneration. mRNA and protein expression of the myogenic
287 differentiation factor D (MyoD), involved in the proliferation process, has been shown to

288 increase in the skeletal muscle of non-cachectic COPD patients after HIIT, but no changes
289 were observed in cachectic COPD patients after HIIT (10). MyoD protein expression was
290 also increased after resistance training with or without nutritional supplementation in patients
291 and healthy controls (56). mRNA expression of MRF myogenin, involved in the
292 differentiation process, was not different between a resistance training group and a control
293 group, while addition of testosterone supplementation to resistance training increased
294 myogenin mRNA expression compared to the control group (57). mRNA and protein
295 expression of the myogenic inhibiting factor myostatin, showed no significant change after
296 resistance exercise training neither in patients nor in healthy controls, or after combined
297 aerobic and resistance training (56, 16). After HIIT however, non-cachectic COPD patients
298 showed a significant decrease in mRNA and protein expression of myostatin, while in
299 cachectic COPD patients HIIT did not significantly alter mRNA or protein myostatin
300 expression (10). In addition, mRNA expression of a negative regulator of cell proliferation
301 Kruppel-like factor 10 (KLF11) was increased after aerobic training in patients, but not in
302 healthy controls (48).

303

304 The IGF-I system plays an important role in the regulation of muscle cell growth, muscle cell
305 proliferation and muscle cell survival (58, 59). After HIIT, mRNA expression of both IGF-I
306 and the mechano-growth factor (MGF), an isoform of IGF-I, significantly increases. Both
307 cachectic and non-cachectic COPD patients have shown enhanced MGF mRNA expression
308 post-training (10). However, no significant increase in protein expression of IGF-I and MGF
309 expression was observed in cachectic COPD patients in comparison to non-cachectic. Other
310 exercise protocols such as combined aerobic and resistance training were not capable to
311 increase the expression of the IGF-I variants (16). However, testosterone supplementation
312 was found to increase the levels of IGF-I and MGF protein expression in COPD patients after
313 resistance training (57).

314

315 ***Exercise induced changes in gene expression***

316 Comparing gene transcription among different modalities of exercise in healthy individuals,
317 Robinson et al (21) found that HIIT promotes a stronger increase in gene transcripts than
318 other modalities of exercise tested, particularly in older adults.

319 Skeletal muscle gene expression from COPD after high intensity aerobic exercise training
320 compared to age-matched controls were analysed using Genechip Array (48). High aerobic
321 exercise training induced up-regulation of quantitatively significantly fewer genes in the
322 skeletal muscle of COPD (107 were upregulated and 124 were downregulated) compared
323 with healthy controls (258 were upregulated and 315 were downregulated). Qualitatively,
324 genes associated with protein degradation, such as oxidative stress, ubiquitin proteasome, and
325 COX pathways were distinctly induced only in patients with COPD, potentially reflecting the
326 specific molecular response of the muscle to exercise in COPD, thereby suggesting additional
327 operating mechanisms for exercise limitation in these patients. Whether exercise training can
328 sufficiently enhance muscle hypertrophy to outstrip muscle wasting in COPD patients with
329 substantial muscle loss, remains an unresolved issue.

330

331 ***Regulation of skeletal muscle protein breakdown***

332

333 Muscle tissue homeostasis is maintained by a tight and complex balance between protein
334 synthesis and degradation. Protein metabolism turnover is a dynamic process balancing
335 protein synthesis and breakdown. Muscle wasting due to an increase in protein breakdown is
336 a feature shared among many acute and chronic disease entities as well as healthy ageing.

337

338 Muscle wasting has primarily been attributed to increased protein degradation. Protein
339 degradation in COPD patients peripheral muscles takes place through four proteolytic
340 systems, including the ubiquitin-proteasome (UP) pathway, the calpain pathway, the caspase
341 pathway, and the autophagy-lysosome (AL) pathway as reviewed elsewhere (60).

342

343 Exercise has been found to stimulate mitogen activated protein kinases MAPK-9 and MAPK
344 activated protein kinase 3 (MAPKAPK-3) in COPD compared to healthy controls (48). The
345 MAPK pathway, in turn activates forkhead transcription factors, involved in muscle protein
346 degradation. When inflammatory response to exercise is limited, the muscle recovers in a
347 timely manner; however, persistent systemic inflammation described in COPD, may be
348 associated with muscle wasting and adversely impact on muscle protein metabolism (61).
349 Numerous pathological indicators in COPD, namely systemic inflammation, hypoxia and
350 oxidative stress most likely trigger catabolic processes in skeletal muscle, that are mediated
351 by transcriptional regulators including nuclear factor kappa-light-chain-enhancer of activated
352 B cells (NF-kB) and forkhead box O transcription factors (FOXOs). The activity of NF-kB is

353 increased in COPD compared with healthy age-matched individuals (18, 62, 10, 22) and in
354 particular in patients with muscle wasting compared to those without muscle wasting (63,
355 10). FOXO mRNA and protein expression is increased in patients with COPD (64-67, 62).
356 The expression of FOXO-1 may be associated with physical inactivity as protein expression
357 is increased in lower limbs compared to respiratory muscles in COPD patients, but not in
358 healthy controls (68). Increased catabolic signaling through FOXO and NF-kB activation
359 may induce gene expression of key factors in both ubiquitin proteasome system (UPS) (69,
360 32) and the autophagy lysosome pathways (45).

361

362 *Concluding remarks*

363 Exercise training promotes a range of beneficial adaptations in the skeletal muscle including
364 increased capillarization, fibre type plasticity, hypertrophy and function. All these adaptations
365 are a result of exercise stimuli that challenges muscle homeostasis by activating networks of
366 signalling molecules. Activation of kinases and pre-transcriptional regulation occurs rapidly
367 during exercise and recovery, whereas protein transcription is subsequently regulated.
368 Intensity, duration, and mode of the exercise stimuli collectively contribute to the relative
369 activation and the magnitude of activated pathways and downstream targets (12, 13). All
370 these parameters have to be considered when designing exercise studies, so results are
371 comparable and can advance knowledge in the area. Future studies on the molecular
372 mechanisms of exercise induced satellite cell myogenic capacity in COPD patients are
373 fundamental for designing pharmacological and exercise training interventions aiming to
374 address resistance to exercise-induced adaptations.

375

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378

379

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381 version of the manuscript

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385 **References**

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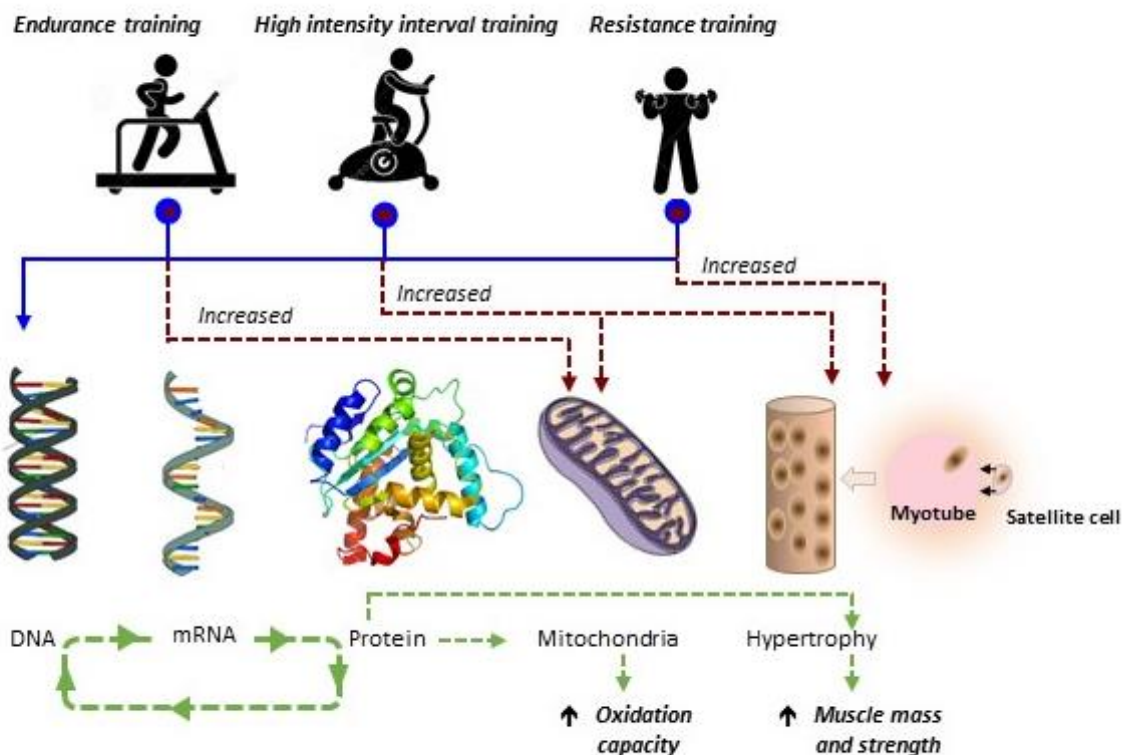
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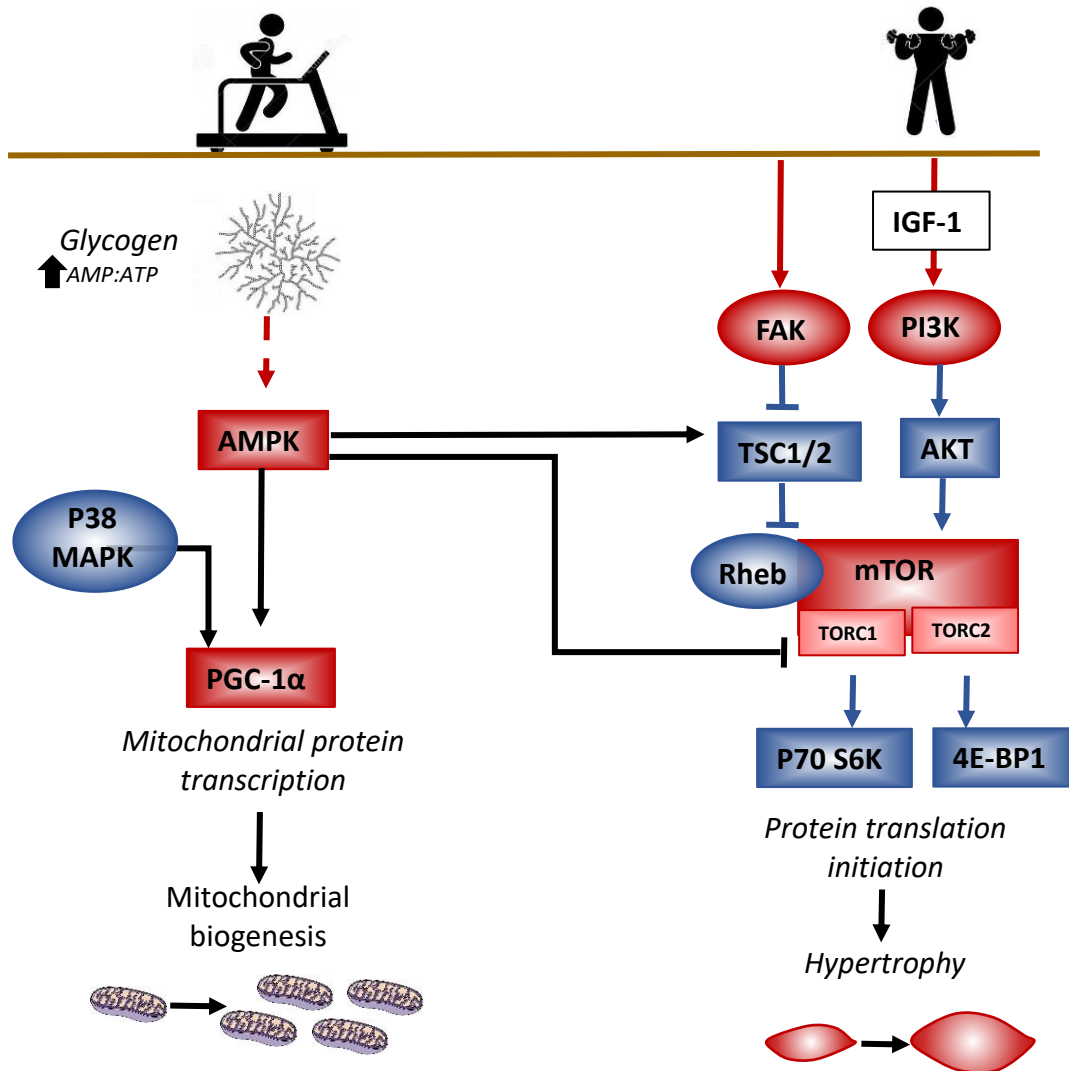
568 Figure 1: COPD skeletal muscle adaptations to various modalities of exercise training.
 569 Exercise training is a powerful stimulus producing hypertrophy and regeneration of muscle
 570 by increased protein metabolism and fusion of satellite cells to existent myofiber. Endurance-
 571 and resistance-based exercise training programmes are characterised as stimuli capable for
 572 increasing oxidative capacity and hypertrophy, respectively. Skeletal muscle adaptations
 573 observed from combined endurance/resistance as well as high intensity interval training
 574 reflect a wider range of stimuli. (The Figure was originally adopted by Robinson *et al.* (21)
 575 and subsequently modified by authors).

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585 Figure 2: Diagram of the major signalling pathways involved in the control of skeletal muscle
586 hypertrophy and mitochondrial biogenesis. Voluntary exercise training activate
587 kinases/phosphatases to mediate a specific exercise-induced signal. The cross talk among the
588 numerous signalling pathways activated and the multiple site regulation produces a high
589 sensitive and complex transduction network.