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MYOSTATIN AND ITS ROLE IN THE REGULATION OF MUSCLE MASS AND METABOLISM

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Abstract

Skeletal muscles which constitutes to about 40% of human body despite their role in movement, breathing and heat generation play a central role in whole-body protein, lipid and carbohydrate metabolism. During last years a wealth of studies focused on intracellular signals participating in muscle mass regulation with special attention paid to myostatin (MSTN) also known as growth differentiation factor - 8 (GDF-8). Myostatin mRNA is expressed predominantly in skeletal muscles and to lesser extent in adipose tissue and heart. In addition, relatively high circulating myostatin suggest its systemic action in skeletal muscle where myostatin suppresses cell growth and differentiation by signaling through specific receptors (the activin type IIB receptors - ActRIIB). Myostatin knockout in mice brings about increased myogenesis and muscle hypertrophy, but decreased adipogenesis. Additionally, loss of myostatin in two models of mice obesity (ob/ob, agouti) partially suppressed fat accumulation together with improved glucose disposal and reduced insulin resistance. Both in humans and animals resistance and endurance training brings about decreased mRNA expression in muscles and lower level of circulating myostatin as well as improved insulin resistance. Genetic studies have indicated that myostatin gene mutation or polymorphism at least partially explain the predisposition to exercise demanding strength and/or speed. However, much more studies are needed to eluciadate to which extend myostatin variability contribute to sport performance.

Key words: *myostatin, skeletal muscle growth, adipose tissue, metabolism*

Introduction

Skeletal muscles which constitute up to about 40% of human body despite their role in movement, breathing and heat generation play a central role in whole-body protein, lipid and carbohydrate metabolism [1]. However, during last years most studies concerning effects of body composition on human health focused on adipose tissue stores and its contribution to metabolic disturbances [2, 3]. In consequence, disturbances in skeletal muscle mass in health and disease was markedly underappreciated mostly due to complicated methods of its measurement [4].

On the other hand, U-shaped relationship between all-cause mortality and BMI suggested that both components of body weight (i.e. fat and lean mass) affected disease risk and mortality [5]. Recent data of Heitman et al. [6] have indicated that total mortality is linearly increasing with low lean and high fat mass.

At present there are data indicating that skeletal muscle mass is a better indicator of mortality than BMI in chronic obstructive pulmonary disease and cancer [7, 8]. However, it should be stressed that the relationship between low skeletal muscle mass and all-cause mortality is especially strong in older men [9-11].

In addition, it is well documented that skeletal muscle mass resulting from both nutritional and genetic factors as well as from mode of training plays an important role in sport performance [12].

In consequence, the mechanisms responsible for the regulation of skeletal muscle mass have been the focus much attention with respect to health and sport.

Mechanisms of muscle hypertrophy

Skeletal muscle mass in the mature individuals is primarily dictated by the balance between the rates of protein synthesis and degradation and over last decade, extensive progress has been made to our understanding of the molecular basis of this processes [13, 14]. In consequence, activation of the muscle protein synthesis pathway due to mechanical loading such as in resistance training brings about elevation in muscle mass [15].

For this reason dietary protein intake shortly after training plays an important role in both muscle mass maintenance and hypertrophy [16]. Furthermore, anabolic hormones stimulating protein synthesis, such as insulin, growth hormone, insulin-like growth factor-1 and testosterone has been recognized to positively affect muscle hypertrophy [17].

On the contrary, muscle unloading (e.g. prolonged bed rest) activates protein breakdown and induces muscle wasting and/or atrophy [18].

Significant role of satellite cells (SC) in muscle regeneration following injury is well documented [19]. On the other hand, at present the contribution of SC to muscle mass maintenance and hypertrophy is under

debate. It is well documented that in developing muscle fibers SC undergo intensive proliferation and fusion with myofibers [20] and similar activation of SC and their fusion with myofibers has been observed following resistance training [21]. However, recent data have indicated minor role of SC in muscle hypertrophy in adult mice since they are activated after the onset of hypertrophy and SC ablation exerts only minor effect on hypertrophy due to mechanical load [22, 23].

In sport science is a common belief that muscle hypertrophy in response to resistance exercise is due also to training-induced elevation in anabolic hormones (growth hormone, testosterone, insulin-like-growth factor-1) [24-26]. In contrast, there are data suggesting that anabolic hormones exert their effect on muscle mass during growth and puberty, but in adults exclusively when taken in supraphysiological doses or in subjects with their deficiency [27].

In consequence, exercise-induced muscle mass increase is supposed to be regulated by the activation of local processes in the muscle, but not by external factors [28].

During last years a wealth of studies focused on intracellular signals participating in muscle mass regulation with special attention paid to myostatin – muscle-originated protein with a potent anti-hypertrophic action.

Skeletal muscle and myostatin

For a long time so called "double muscling" phenotype in cattle breeds and in the Texel sheeps was well known among biologists and animal scientists. However molecular basis of this phenomenon was not recognized until identification of myostatin (MSTN) also known as growth differentiation factor - 8 (GDF-8) expressed predominantly in skeletal muscles and to a lesser extent in adipose tissue and heart [29, 30].

The role of myostatin in skeletal muscle hypertrophy was confirmed when its gene mutation was found in "double muscling" cattle and in rare cases in humans [31-33]. Since then a wealth of studies have focused on the contribution of myostatin to the regulation of muscle mass and other metabolic processes.

Myostatin structure and activity

Myostatin is a member of transforming growth factor β superfamily (TGF-β) – multifunctional cytokines affecting a vast array of developmental and homeostatic processes [34, 35]. Like other TGF-β family members myostatin is synthesized as 376 amino acid latent form with N-terminal propeptide domain and C-terminal domain considered as active molecule. Endoprotease action releases mature myostatin and N-terminal propeptide and both unprocessed and mature myostatin form disulphide –linked dimers representing the only form of active protein [36]. (Fig. 1)

In skeletal muscle myostatin suppresses cell growth and differentiation by signaling through specific receptors (the activin type IIB receptors - ActRIIB) [37]. *In vitro* data have suggested that myostatin-induced inhibition of protein synthesis in muscle is due to activation of ubiquitin signaling and inhibition of the insulin-like growth factor-1 pathway and subsequent loss of sarcomeric proteins [38, 39]. Additionally, many

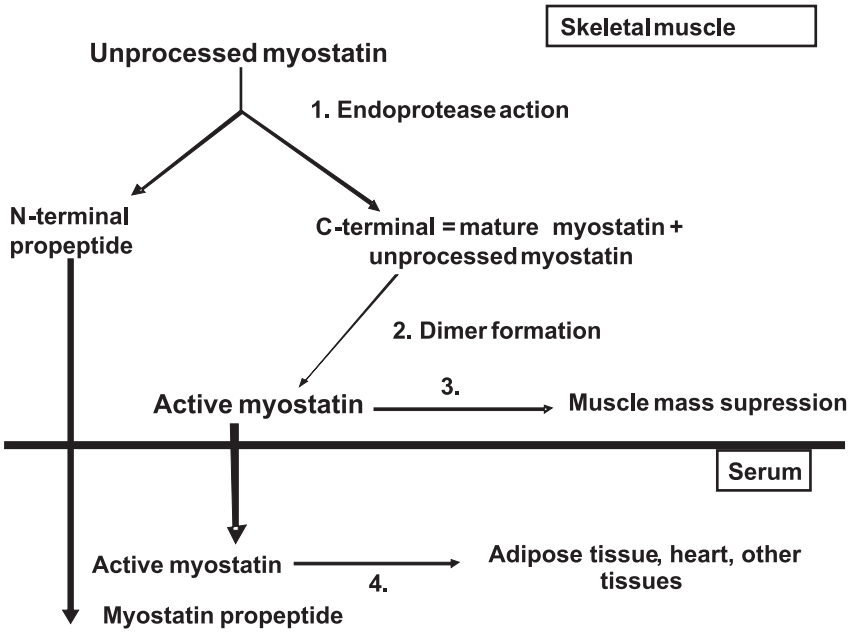

Fig. 1. *Myostatin synthesis in skeletal muscle*
1. Mature myostatin is formed by endoprotease separation of N-terminal propeptide from unprocessed myostatin; 2. Mature myostatin forms SH- bridges with unprocessed myostatin and resultant dimer is the only active myostatin form present in the muscle and blood; 3. Muscle hypertrophy is suppressed by intramuscular myostatin; 4. Circulating myostatin affects other tissue metabolism

data have indicated that myostatin wasting effect is due to negative regulation of stem cells in muscles [40]. It is why myostatin mutation or deletion positively affects muscle growth and mass.

However, it should be stressed that myostatin plays an important and positive role during myoblast growth and differentiation by down-regulation of myogenic factors such as myogenin and Myf5 and contributes to the regulation of fiber-type composition [41-43].

Moreover, relatively high circulating myostatin levels and mentioned above myostatin gene expression in adipose tissue and heart suggest its systemic action. This seems feasible, since blood myostatin activity is precisely regulated by binding to several proteins which modulate its activity (e.g.follistatin, decorin and myostatin pro-peptide) [44-46].

However, it should be pointed out that the mechanism of myostatin action has not been fully elucidated. In skeletal muscle myostatin has been shown to autoregulate its own gene expression [47]. On the other hand, recently it has been speculated that more important for myostatin action is the regulation of extracellular pool, since circulating myostatin is mostly inactive and is activated locally in the muscle and other tissues by specific endoproteases and other unidentified factors [48].

Despite all doubts concerning regulation of myostatin activity its pronounced effect on muscle growth has been well documented by many genetic studies.

Myostatin overexpression or knockout in skeletal muscle

In transgenic male mice with muscle-specific overexpression of myostatin were characterized with lower muscle mass, decreased fiber size and myonuclear number, decreased cardiac muscle, but increase fat mass [49]. Moreover, ectopic expression of myostatin in one limb muscle of adult rats caused decreased muscle mass, muscle fiber cross-sectional area and protein content together with depressed expression of myosin heavy chain IIb in comparison to muscles of contralateral limb [50]. Furthermore, systemic overexpression of myostatin in adult mice brought about significant loss of muscle and fat resembling to that observed in cachexia syndrome [51]. The contribution of myostatin overexpression in cachexia was proved in rats bearing the Yoshida AH-130 hepatoma in which myostatin signaling pathway was markedly enhanced [52].

More studies have been performed with myostatin-null mice providing interesting data concerning a broad spectrum of myostatin action in mammals.

The myostatin knockout in mice was found to cause increased myogenesis and muscle hypertrophy, but decreased adipogenesis [53]. In addition, loss of myostatin in two models of mice obesity (*ob/ob*, agouti) partially suppressed fat accumulation together with improved glucose disposal and reduced insulin resistance [54, 55].

Moreover, loss of myostatin expression affects fiber-type distribution and myosin heavy-chain expression leading to an overall faster and more glycolytic phenotype [56, 57]. The more pronounced effect of myostatin in type II fibers is due to greater density of the myostatin receptor, activin type II, in fast than in slow muscle fibers [58].

Additionally, it has been demonstrated that in response to the lack of myostatin mitochondria number are decreased suggesting loss of muscle oxidative potential and shift to glycolytic metabolism with no changes in fiber capilarization [59]. On the other hand, Ploquin et al. [60] have revealed that lack of myostatin adversely affect mitochondrial function *in vitro* uncoupling the respiration and increasing basal oxygen consumption, but also changing redox status in the muscle - depressing SOD and CAT activity but inducing glutathione system.

Thus, it is clear that myostatin effects in skeletal muscle are not limited to the regulation of muscle mass but cytokine also exerts multidirectional metabolic actions.

Relationship between myostatin, hormones and growth factors in the regulation of skeletal muscle mass

Identification of myostatin gene and myostatin action in skeletal muscle enable to clarify the mechanism of muscle-wasting action of glucocorticoids, which markedly increase myostatin expression in mice *in vivo* [61].

Moreover, it has been found that in growth hormone-deficient humans myostatin is a target of GH anabolic action in skeletal muscles decreasing myostatin expression which is sustained for up to 18 months after treatment [62]. Additionally, it has been shown that GH and its receptors are responsible for decreasing myostatin mRNA expression in the mice [63].

However, it is worth noting that growth hormone contribution to muscle mass development has to be analyzed in concert with insulin-like growth factor-1 (IGF-1) role, since mutual relationship between both factors in muscle hypertrophy and wasting is well documented [64, 65].

Human studies have revealed that age-related deficits in GH and testosterone may lead to increased myostatin expression and to disturbances in IGF-1 effects on muscle protein synthesis [66]. However, precise mechanism of IGF-1 – myostatin interaction is not fully elucidated.

Miyake et al. [67] have demonstrated that in mice myostatin expression is not affected by IGF-1 knockout. On the contrary, it has been found that *in vitro*

myostatin inhibits IGF-induced myotube hypertrophy [68]. Recently, it has been noted that in myostatin-null mice circulating IGF-1 levels are elevated what in turn brings about negative feedback control of GH resulting in decreased gastrocnemius muscle mass [69].

Interestingly, myostatin-deficient mice were also characterized by higher expression of components of IGF-1 and IGF-1-binding protein axis in the liver suggesting that myostatin affects muscle growth directly at the cellular level and by indirectly affecting the IGF axis [70].

It is well documented that androgens positively affects muscle mass and testosterone administration brings about elevation in lean body mass in elderly humans [71]. Animal studies have shown that androgens exert their anabolic action by down-regulation of myostatin mRNA in androgen-sensitive *levator ani* muscle of the rat and reverses sarcopenia in old mice at least partially due to myostatin inhibition [72, 73]. It is worth noting that higher muscle mass in males than in females is due to decreased expression of myostatin in former at least partially due to sex-related differences in testosterone secretion and plasma levels [74].

Data concerning the relationship between estrogens and myostatin action are scarce. However, it has been found that in female rats ovariectomy does not affect soleus muscle fiber size [75]. On the contrary, estrogen replacement reduces soleus muscle fiber size, increases half relaxation time and reduces time to peak tension. More detailed study has revealed that in ovariectomized rats one week estrogen treatment significantly elevates myostatin expression in slow soleus muscle, however these effects are transient and disappear in 5-week replacement study [76]. The effect of ovarian hormones on myostatin expression was at least partially confirmed in postmenopausal women, since myostatin expression in skeletal muscle was lower in subjects on HRT vs. untreated ones [77].

It is worth noting that estrogen contribution to the regulation of muscle mass is far from being elucidated, since this hormone also affects other factors important for muscle mass such as myogenic differentiation factor (MfD), myogenin and insulin-like growth factor (IGF-1) [76, 77].

The above data shed more light on anabolic action of GH, IGF-1 and androgen suggesting that myostatin is a real target of their action inducing muscle hypertrophy (Fig.2).

Myostatin action in non-muscular tissues

It has been demonstrated that its deficiency in mice bring about small, brittle and hypocellular tendons with lower peak strain and increased stiffness due to depressed collagen synthesis possibly contributing to decreased force generation [78, 79].

At present it is well known that myostatin despite its effect on fat mass has a potential to influence adipose tissue metabolic profile.

As was mentioned earlier myostatin knockout in mice causes significant decrease in body fat *in vivo*. Moreover, both *in vivo* and *in vitro* myostatin induces small adipocytes resembling immature cells, characterized by improved insulin sensitivity [80, 81]. However, at present it has been suggested that decreased adiposity in myostatin null mice is a consequence of metabolic changes in skeletal muscle (increased glucose uptake and insulin sensitivity) but not in adipose tissue [82].

Additionally, administration of myostatin antibody and subsequent inhibition of its action markedly affects metabolic profile of obese, insulin-resistant mice decreasing body fat accumulation, increasing the expression of genes of oxidative metabolism, improving glucose homeostasis and leptin sensitivity as well as stimulating energy expenditure [83, 84].

Moreover, in LDL-receptor null mice characterized by dyslipidemia genetic elimination of myostatin im-

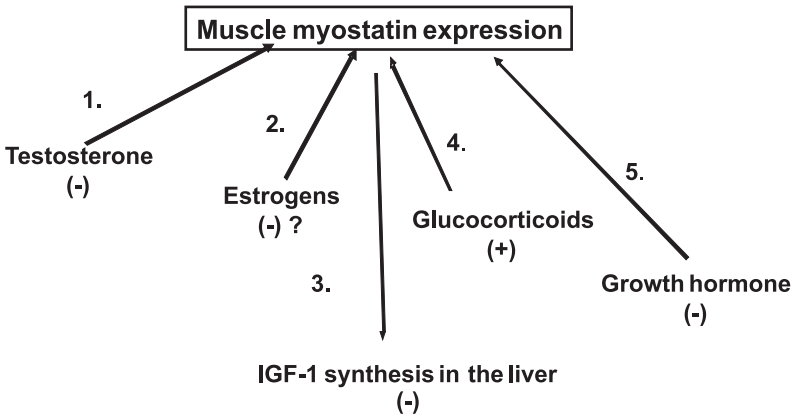

Fig. 2. *Relationships between hormones and growth factors affecting skeletal muscle mass and myostatin expression*
1. Testosterone inhibition of myostatin expression is well established; 2. Data concerning estrogen action are scarce, but in HRT-treated menopausal women myostatin expression is decreased; 3. IGF-1- myostatin association seem to be related to inhibitory effect of myostatin on IGF-synthesis in the liver; 4. Muscle wasting effect of glucocorticoids is due to its stimulatory effect on myostatin expression; 5. Administration of GH to hormone deficient subjects resulted in decreased myostatin expression.

proves insulin sensitivity and protects animals against diet-induced hepatic fat accumulation and liver steatosis due to enhanced free fatty acid oxidation [85-87].

On the other hand, it has been found that high fat feeding induces higher myostatin expression in muscles and spleen of mice susceptible to high-fat diet obesity (C57BL/6) together with increased proinflammatory cytokine production in the spleen vs. animals resistant to adverse effects of high-fat feeding (SWR/J) [88]. The above data indicate that myostatin possibly contributes to obesity development and inflammation.

Human data concerning associations between myostatin expression, body fat and disturbances in insulin sensitivity and glucose disposal are scare. It has been noted that in muscle of healthy first degree relatives of subjects with type II diabetes myostatin is upregulated suggesting its role in muscle wasting observed in many diabetic patients [89]. Additionally, in patients with type II diabetes higher levels of muscle myostatin mRNA has been demonstrated vs. healthy counterparts [90]. However, it healthy subjects muscle myostatin mRNA is significantly and positively correlated with index of insulin resistance –HOMA-IR but not such a relationship is found in diabetic patients. The above data support the idea concerning negative metabolic effects of myostatin and its adverse role in whole body insulin sensitivity.

On the other hand, in extremely obese women (BMI approx. 49) increased expression and secretion of myostatin from the isolated muscle has been noted correlating significantly with BMI values and with index of insulin resistance – HOMA-IR [91]. In contrast to others, the authors of cited study suggested that obesity and insulin resistance induce elevated myostatin synthesis in the muscle.

Myostatin role in obesity and type 2 diabetes is far from being elucidated, especially in the context of contradictory data concerning positive effects of myostatin receptor inhibition on both insulin sensitivity and body fat stores [92-95] (Table 1).

The first study concerning myostatin action in heart muscle was published in 2009 and revealed that *in vitro* myostatin repressed cardiac muscle growth and function [96]. On the contrary, genetic deletion of myostatin from hearts prevents skeletal muscle atrophy in heart failure [97]. Clinical studies have shown that serum levels of myostatin and myostatin expression in heart biopsies are higher in patients with advanced heart failure and/or congenital heart disease in comparison with healthy subjects [98, 99]. However, myostatin contribution to heart disease is still under debate [100].

New data have indicated that myostatin is a key regulator of bone structure and loss of myostatin increases osteogenesis of bone marrow-derived mesenchymal stem cells, however its osteogenic effect is ablated by muscle unloading [101]. These data indicate that myostatin possibly alters muscle mechanosensitivity. Furthermore, myostatin deficiency brings about faster bone regeneration after fracture and bone structure in myostatin-null mice differs in comparison with wild-type littermates [102, 103].

Recently it has been demonstrated that myostatin action in skeleton is not limited to osteogenic pro-

Table 1. *Effects of myostatin overexpression and knockout in skeletal muscle and adipose tissue*

Effect	Myostatin overexpression	Myostatin knockout
Skeletal muscle		
Protein synthesis	Depressed	Increased
Satellite cell activity	Depressed?	Increased?
Fiber-cross-sectional area	Depressed	Increased
Myosin-heavy-chain II b expression	Depressed	Increased
Muscle mass	Decreased	Hypertrophy
Fiber type distribution	-	More IIb fibers
Mitochondria number	-	Decreased
Mitochondrial respiration	-	Uncoupled
Oxidative metabolism	-	Decreased
Glucose disposal, insulin sensitivity	-	Improved
Glutathione system	-	Stimulated
SOD and CAT activity	-	Decreased
Adipose tissue		
Fat mass	-	Decreased
Adipocyte size	-	Decreased
Adipocyte insulin sensitivity		Improved?

cess and bone structure. In vitro study has shown that chondrogenesis and chondrocyte proliferation are negatively affected by myostatin suggesting that myostatin elimination has a potential improving of bone repair [104].

Myostatin and muscle wasting

Despite mentioned above studies concerning the relationship between myostatin activity, muscle mass, obesity and type 2 diabetes there are data indicating that myostatin may be a target of therapy in muscle wasting observed in cachexia, sarcopenia and inherited muscle dystrophic disorders [105].

In addition, prolonged absence of myostatin in myostatin-null mice markedly reduced sarcopenia in old animals [106, 107]. The latter effect of myostatin deletion is at least partially due to adverse myostatin effect on satellite cell activation and self-renewal [108].

Moreover, myostatin blockade induced by its antibodies injected for three months to *mdx* mice – animal model of Duchenne muscular dystrophy resulted in elevation of body and muscle mass, muscle size and strength [109]. Similarly, myostatin inhibition with its antibody slows muscle atrophy in rodent models of amyotrophic lateral sclerosis [110].

Interestingly, long-term enhancement in muscle mass and strength may be induced by single administration of myostatin inhibitors to both wild-type and dystrophic mice [111]. However, it has been noted that at least 40% decrease in myostatin level in mice is needed to induce significant muscle growth [112].

Studies concerning myostatin action in human muscle wasting are scarce. However, it has been demonstrated that in old men skeletal muscle are characterized by elevated levels of myostatin mRNA together with depressed number of receptors of anabolic agents such as growth hormone (GH) and insulin-like growth factor -1 (IGF-1) [113].

Myostatin and physical activity

It has been well documented that muscle features are under genetic control with pronounced (50-80%) contribution of genes in determination of muscle mass which is of special importance in sport performance but especially in disciplines with high contribution of speed and strength [114-115]. Thus, it is not surprising that during last years many studies focused on myostatin response to single exercise and training.

However, data concerning training effects on myostatin expression and activity are equivocal.

It has been demonstrated that in untrained males 12 weeks of heavy resistance training (3 times a week, three sets of 6-8 repetition at 85-90% of 1 RM) resulted in increased body mass, lean body mass and strength [116]. Myostatin mRNA expression and myostatin in muscle biopsy was elevated despite increased protein synthesis. In addition, in response to training significant elevation in follistatin – myostatin inhibitor, and glucocorticoid receptor density has been noted. Thus, it has been postulated that in this mode of training not myostatin but other factors positively affect muscle mass.

On the contrary, in other study resistance training with similar schedule induced significant elevation in muscle mass, but circulating myostatin response to training was highly differentiated (+ 5.9 to – 56.9 %) with mean decrease of 20 +/- 16 % [117]. Additionally, no changes in plasma IGF-1 was noted and in consequence it was suggested that muscle mass is not solely affected by myostatin and growth factors.

However, it is worth noting that discrepancies concerning myostatin response to strength training at lest partially may be due to the time course of training-induced effects. Louis et al. [118] have demonstrated that in response to a single bout of resistance exercise myostatin mRNA gradually decreases and peaks 8 h post-exercise and 12 and 24 h post-exercise is still decreased, but to much lesser extent. Moreover, until 2 h after exercise significant elevation in muscle mRNA including proteolytic enzymes has been noted. Thus, timing of human muscle biopsy seems to determine results concerning factors affecting muscle growth.

Furthermore, the subjects' training status possibly affects myostatin response to resistance exercise, since short-term resistance exercise induces downregulation of myostatin exclusively in trained participants [119]. Additionally, animal studies have indicated that myostatin response to short-term strength training is related to specific contraction types and is more pronounced by eccentric than after concentric and isometric training [120].

However, it should be stressed that myostatin depression in response to strength training and its positive role in muscle hypertrophy is not a long-lasting phenomenon. Jespersen et al. [121] have found that in young trained subjects myostatnin mRNA expression in the muscle significantly increased with 3-90 days of detraining together with rapid type II fiber atrophy observed after 10 days of detraining. These data may be of special importance for sport practice and training schedule in athletes.

The relationship between myostatin action and exercise capacity was also studied with respect to endurance training. It has been demonstrated that in myostatin null mice characterized by muscle hypertrophy metabolic plasticity is retain and skeletal muscle oxidative potential is elevated in response to endurance training [122-124]. Human studies have shown that endurance training (6 months, 40-55 $\dot{V}O_2$max) significantly (by 37%) decreases myostatin protein in the muscle in insulin-resistance subjects [125]. In addition, muscle myostatin was markedly and positively

correlated with insulin sensitivity. This relationship has been confirmed in mice by inducing insulin resistance by myostatin injection.

The above data suggested that myostatin expression in the muscle is diminished in response to endurance training and that there is a causal association between myostatin and insulin sensitivity. Therefore, it seems feasible that an improvement in insulin sensitivity following endurance training is at least partially due to attenuated myostatin expression.

A few studies concern the relationship between myostatin expression and performance. Mosher et al. [126] have shown that mutation in the myostatin gene identified in the whippet dog breed resulting in doubled muscle phenotype known as"bully" whippet and much better running performance together with no other health abnormalities. On the other hand, human studies have indicated that myostatin gene polymorphism influences at least selected indices of muscle strength such as vertical jump performance, with no effect on 30 m running time [127]. In consequence, it has been postulated that myostatin polymorphism affects the ability to produce peak power during muscle contractions.

Accordingly, it has been postulated that strength performance may be improved by myostatin inhibition [128]. Such a procedure became possible because Ramazanov et al. [129] have demonstrated that sulphated polysaccharides isolated from brown algae *Cystoseira canariensis* bind to circulating myostatin. However, in men no effect of this chemical on circulating myostatin, muscle mass and strength in response to heavy resistance training has been noted [130].

Summing up, numerous studies have demonstrated an important role of myostatin in muscle growth and fiber characteristic, but also in adipose tissue. Thus, it seems that muscle-originated protein is a possible link between two greatest body tissues with fundamental role in the regulation of metabolic processes. Moreover, it could not be excluded that genetic variants of myostatin play a significant role in inherited predispositions for physical efforts demanding high muscle strength, but much more studies are needed to elucidate this issue.

Declaration of interest

The authors declare no conflicts of interest.

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