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## Molecular and metabolic insights of creatine supplementation on resistance training

### Abstract

In recent years the research problem in the field of sports supplementation has changed to explain the metabolic mechanisms by which creatine (Cr) administration enhances the performance of certain sports or simply benefits the muscular adaptation. In this review for first time the biochemical mechanisms of Cr ingestion in a cell signaling insight were analyzed, focusing on energetic bioavailability enhancement and optimization of the temporal and spatial buffering of Cr/PCr/CK system. Moreover, intensification in proliferation and differentiation processes of muscle cells (IGF-I/PI3K/Akt-PKB, SPHK1/MAPK/p38/MRFs, mTOR, cellular swelling, mitotic activity of satellite cells, actin polymerization, and myoblast fusion) and inactivation and/or reduction in the expression of ergolytic metabolites (GSK3 $\beta$ , myostatin and AMPK regulation) were examined. In this way, we explained from a metabolic point of view the increase in muscle mass, strength, fatigue resistance, and performance of high intensity sports after Cr monohydrate supplementation.

**Keywords:** Cr/PCr/CK System, creatine monohydrate, muscle energy metabolism, MAPK, IGF-I, resistance training, high-intensity exercise.

## Perspectivas moleculares y metabólicas de la suplementación con creatina en el entrenamiento de fuerza

### Resumen

En los últimos años el problema de investigación en el campo de la suplementación deportiva ha cambiado al punto de explicar los mecanismos metabólicos por los cuales la administración de creatina (Cr) incrementa el rendimiento en ciertos deportes o simplemente beneficia la adaptación muscular. Esta revisión analiza por primera vez los mecanismos bioquímicos de la ingesta de Cr desde la perspectiva de señalización celular, enfocándose en la mayor biodisponibilidad energética de Cr y optimización de la acción buffer espacial/temporal que ofrece el sistema Cr/PCr/CK. Además, se examinan aspectos relacionados con el incremento en los procesos de proliferación y diferenciación de células musculares (IGF-I/PI3K/Akt-PKB, SPHK1/MAPK/p38/MRFs, mTOR, hinchamiento celular, actividad mitótica de células satélite, polimerización de actina y fusión de mioblastos) y la inactivación y/o reducción en la expresión de proteínas con funciones ergolíticas (GSK3 $\beta$ , miostatina y regulación de AMPK). De esta manera, se explican el aumento de la masa muscular, la fuerza, la resistencia a la fatiga y el rendimiento en ejercicios de alta intensidad, producidos por la suplementación con monohidrato de Cr, desde un punto de vista metabólico.

**Palabras Clave:** sistema Cr/PCr/CK, monohidrato de creatina, metabolismo energético muscular, MAPK, IGF-I, entrenamiento de fuerza, ejercicio de alta intensidad.

## Perspectivas moleculares e metabólicas da suplementação de creatina no treinamento de força

### Resumo

Nos últimos anos, o problema de pesquisa no campo da suplementação de esportes mudou ao ponto de explicar os mecanismos metabólicos pelos quais a administração de creatina (Cr) aumenta o desempenho em alguns esportes ou benefícios de adaptação musculares. Neste artigo, vamos analisar primeiro os mecanismos bioquímicos de ingestão da Cr a partir da perspectiva de sinalização celular, com foco em maior biodisponibilidade de energia de Cr e otimização de tampão temporais/espacial ação oferecida pelo sistema Cr/PCr/CK. Além disso, são considerados aspectos relacionados com o aumento da os processos de proliferação e diferenciação de células musculares (IGF-I/PI3K/Akt-PKB, SPHK1/MAPK/p38/MRFs, mTOR, inchaço celular, atividade mitótica da célula satélite, a polimerização de actina e de fusão de mioblastos) e inativação e/ou a redução na expressão de proteínas com funções ergolíticas (GSK3, miostatina e regulação da AMPK). Desta maneira, é explicado o aumento da massa muscular, força, resistência à fadiga e desempenho em exercícios de alta intensidade, produzidos pela suplementação com Cr monohidratada, a partir de um ponto de vista metabólico.

**Palavras-chave:** sistema Cr/PCr/CK, creatina monohidratada, metabolismo energético muscular, MAPK, IGF-I, treinamento de força, treinamento de alta intensidade.

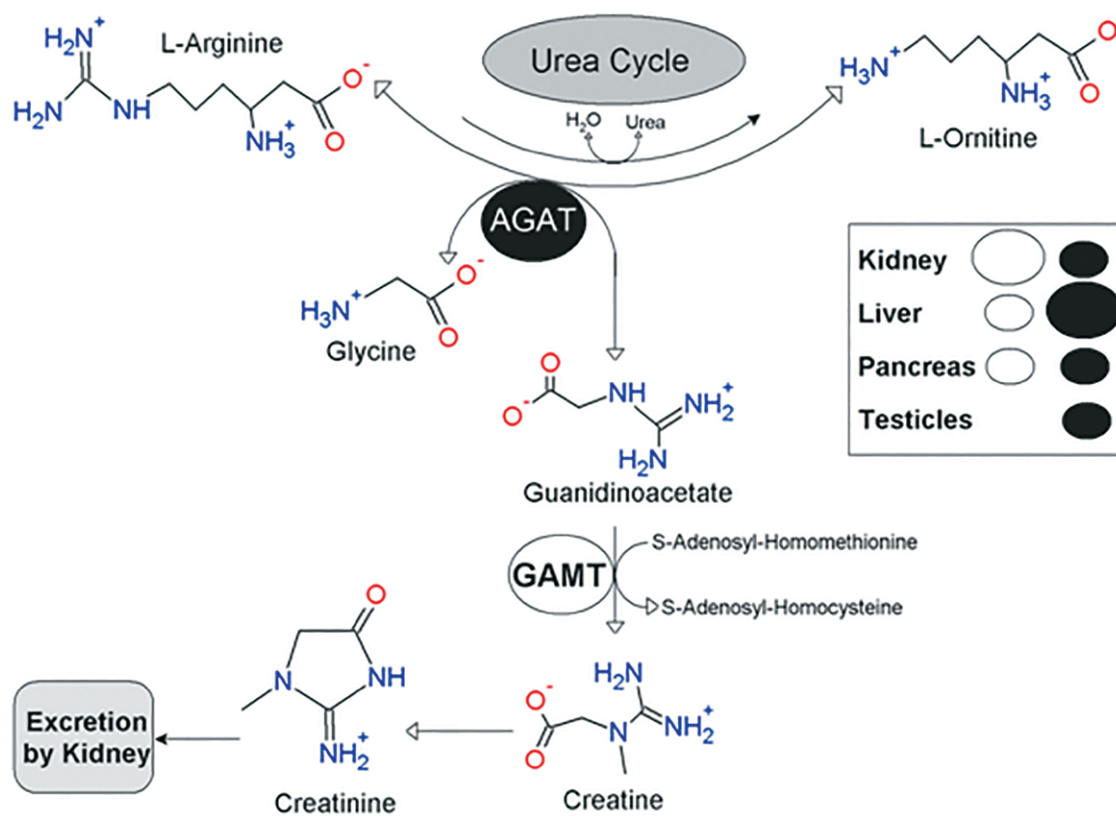
## Introduction

Creatine (Cr) was discovered in 1832 by the French scientist Michel Eugene Chevreul, who extracted from meat a new organic constituent and named it creatine, from Greek *κρέας* = *kreas* flesh (1). Cr or *N*-(aminoiminomethyl)-*N*-methyl-glycine (CAS 57-00-1, 2006) is a metabolite with a molecular dimension similar to an amino acid (2) which is synthesized mainly in liver, kidney, and pancreas (3). Endogenous synthesis of Cr starts with the transfer of the amidino group of arginine to the amino group of glycine by L-Arginine-Glycine amidinotransferase (AGAT - EC 2.1.4.1) yielding L-ornithine and guanidinoacetate (3). Then, guanidinoacetate is methylated at the original nitrogen of glycine using S-adenosylmethionine as donor of the methyl group. This reaction produces Cr and S-adenosylhomocysteine and is catalyzed by Guanidinoacetate N-Methyltransferase (GAMT - EC 2.1.1.2) (Figure 1) (4, 5).

On the other hand, Cr is degraded spontaneously through a mono-molecular reaction to creatinine (Crn, MW 113.1 g/mol), which is quan-

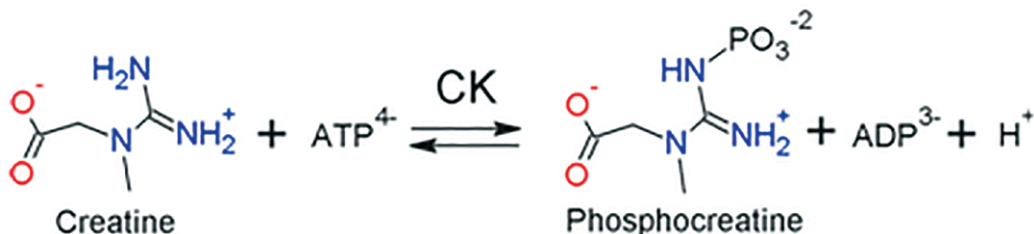
tatively excreted in the urine (6). The rate of excretion is estimated about 1.7% of the total Cr (TCr) body pool per day (7). Cr is primarily present in cells with high and intermittent energy (8). However, the tissues that store the highest concentrations of this metabolite do not synthesize it on their own but obtain it Cr from the bloodstream via a specific carrier (CreaT), nowadays denominated as SLC6A8 (9, 10, 11). Near 95% of the Cr reserves in the body are found in skeletal muscle and the other 5% remaining is distributed in heart, brain, liver, kidney, testicles, retina, and epithelial cells (8, 9, 12, 13). The average concentration of Cr in muscle tissue is 120 mmol/kg dry-mass (4). In muscle, Cr is found in a ~33% in natural form and the ~67% remaining in form of phosphocreatine (PCr), the energetically loaded form via creatine kinase (CK-EC 2.7.3.2), hence acting as a cellular buffer on H<sup>+</sup> ions (Figure 2).

High-energy phosphates, as PCr, provide the necessary energy for muscle contraction to the start-up of the activity and during explosive, short and high intensity exercise. In the periods of muscular inactivity, PCr is rapidly resynthesized, paradoxically this process requires the energy precedent of ATP hydrolysis from aerobic systems (14, 15).



**Figure 1.** Creatine Synthesis and Degradation.

Software; Advanced Chemistry Development / ChemSketch (Freeware) 11.02.



**Figure 2.** Creatine Kinase Reaction.

Software; Advanced Chemistry Development / ChemSketch (Freeware) 11.02.

Cr crystallizes from water as monoclinic prisms holding one molecule of water of crystallization per molecule of Cr (2), forming the popular dietary supplement known as Cr monohydrate, which makes part of the most frequent nutritional supplements used by amateur and elite athletes due to its ratified ergogenic effects on resistance training (16-27). However, the metabolic principles that explain the positive effects of Cr supplementation on athletic performance remains less understood currently.

## Creatine supplementation on fatigue resistance

The main event after Cr ingestion is the increase in serum and muscular Cr levels, without variations on ATP concentrations (24, 28, 29). For example, in response to higher doses (20 g Cr), serum Cr concentration increased by 50-fold (peak value of serum Cr is approximately  $2.17 \pm 0.66$  mM) 2.5 hours after ingestion. However, in response to lower doses (< 2 g Cr), the blood increase in Cr is insignificant (30). In skeletal muscle, Cr and PCr concentrations, before supplementation, are approximately 85 and 41 mmol/kg dry mass respectively, which equals to an intracellular TCr concentration of 40-50 mM (100-150 mmol/kg dry mass). Nevertheless, TCr levels increase by about 25% after Cr supplementation (31), and 37% if the Cr ingestion is accompanied of exercise (29). In this sense, it has been reported that Cr supplementation increases muscle PCr content approximately by 20%, generally from 70-90 to 85-105 mmol/kg dry mass (32). Accordingly, this suggests that the PCr/TCr ratio (do not confuse with the PCr/Cr ratio) diminishes after Cr supplementation at rest. Assuming equilibrium of the CK reaction, this decrease in PCr/TCr implies increased cytoplasmic ADP and decreased Gibbs free energy of ATP hydrolysis in muscle, which seems contrary to the reported ergogenic benefits of Cr supplementation. However, Braut *et al.* (33) showed that muscle concentrations of PCr and TCr increased linearly throughout 5 days of Cr supplementation (0.43 g/kg body mass/day) using  $^{31}\text{P}$  and  $^1\text{H}$  magnetic resonance spectroscopy (MRS). These results indicate that Cr supplementation does not alter the PCr/TCr ratio and hence the Gibbs free energy of ATP hydrolysis in muscle at rest. Indeed, during Cr supplementation the TCr muscle levels keep its normal homeostasis due to the increment in PCr and Cr by ~70% and ~30%, respectively. Meyer's (34) "electrical analog" model of respiratory control posits that the time constant ( $\tau$ ) for the exponential fall in muscle PCr concentration following the onset of muscle contractions is a function of the mitochondrial resistance and the metabolic capacitance. This capacitance leads to reduction of peak rates of ATP synthesis in cells with fluctuating energy consumption. Moreover, the capacitance allows repayment of energy "debt" during stages of high energy demand to occur between periods of low rates of energy consumption. The CK reaction concedes myocytes to sustain reduced mitochondrial volume, aid larger diameter fibers, and express faster isoforms of myosin (15). The Meyer's model predicts that an increase in mitochondrial density will result in a shorter  $\tau$  (that is, faster PCr concentration, [PCr], kinetics) and that an increase in metabolic capacitance, determined predominantly by the muscle TCr content, will result in a longer  $\tau$  (slower [PCr] kinetics) (35), and therefore benefits short duration high-intensity exercise. Currently, it is established that PCr concentration and  $\text{VO}_2$  vary with similar kinetic profiles from the start-up of the exercise until a new state of energy production by oxidative metabolism. This data display that regulation of mitochondrial respiration is intimately linked to ATP/ADP and PCr/Cr ratios, by means of CK reaction (36). Jones *et al.* (35) developed a study to analyze the effect of Cr supplementation (20 g/day x 5 days) on [PCr] kinetics using  $^{31}\text{P}$  MRS, following the onset and offset of both moderate-intensity and heavy-intensity exercise.

The results showed that Cr administration increments by ~8% the PCr/ATP relation consistent with the muscle TCr increase. Furthermore,  $\tau$  for [PCr] was enhanced after Cr loading phase for moderate exercise and subsequent recovery and for heavy exercise but not for subsequent recovery. These data demonstrate, for the first time in humans, that an increase in muscle [PCr] results in a slowing of [PCr] dynamics in exercise and subsequent recovery.

Cr supplementation, besides regulating the muscular ATP and ADP concentrations, enhances myocellular PCr levels generating an increase in  $\tau$  for [PCr] by means of a higher energy bioavailability of the CK system. This implies that ergogenic effects of Cr supplementation can be sustained from enhanced kinetic variables of PCr degradation process. Moreover, the augment of [PCr] generates a longer dependence of high energy phosphates metabolism to produce energy in a fast and effective way, also permitting less accumulation of fatigue-linked molecules as:

1. Inorganic Phosphate (Pi) and Hydrogen Ion ( $\text{H}^+$ ): During short periods of high-intensity exercise, Pi and  $\text{H}^+$  are accumulating within skeletal muscle originating apparition of fatigue through several mechanisms (37, 38). Cr supplementation has been shown to diminish the concentration of  $\text{H}^+$  (30, 35, 39, 40) and Pi (39, 41). These phenomena also lead to less hypoxanthine accumulation (30, 42, 43).

2. Cytosolic  $\text{Ca}^{2+}$  concentration: High  $\text{Ca}^{2+}$  concentrations due to energy deficiency and less sarcoplasmic reticulum uptake during exercise are strongly associated with fatigue (44, 45, 46). Cr administration seems to improve the  $\text{Ca}^{2+}$  uptake by sarcoplasmic reticulum  $\text{Ca}^{2+}$ -ATPase and parvalbumin (47, 48), while regulates the  $\text{Ca}^{2+}$  release during the excitation-coupling process (49, 50).

## Creatine supplementation in the increasing lean body mass and muscle strenght

Increment of muscle protein synthesis is one of the Cr supplementation effects after resistance training, although it has converted an important point of debate due to tuneless findings of some investigations (51, 52). Nevertheless, since more than two decades many studies have revealed that Cr supplementation accompanying a period of resistance training increases muscle fibers size with respect to control subjects (53, 54, 55, 56, 57). In addition, *in vitro* studies have shown an increment in myotubes diameter after Cr exposition with regard to controls (58, 59, 60). However, a molecular point of view is needed in order to explain the myocellular responses to Cr supplementation, generally involving larger cross-sectional area and subsequent lean body mass and strength gain.

Nutrient, hormonal, and contractile stimuli often (but not always) converge at mammalian target of rapamycin (mTOR), suggesting that this protein is an important modulator of protein synthesis (61). mTOR is part of two multiprotein complexes; mTORC1, which activates downstream S6 kinase (S6K, also known as  $\text{p}^{70\text{S6k}}$ , which in turn phosphorylates the ribosomal protein S6 and other factors involved in translation, initiation and elongation stimulating protein synthesis) and phosphorylates the inhibitory eukaryotic initiation factor 4E binding protein (4E-BP1); and mTORC2, which phosphorylates Akt (also called protein kinase B, PKB) at serine 473, this phosphorylation is required for maximum activation of Akt, thus regulating protein synthesis (62). Some investigations have analyzed the effect of Cr supplementation towards the proteins involved in the mTOR signaling pathway. Deldicque *et al.* (63) evaluated in a double-blind cross-over design the phosphorylation state of S6K1 and 4E-BP1 after Cr supplementation (21 g/day x day) in six men following 10 sets of 10 leg-press repetitions (every 5 s) at 70% of each individual 1-RM, and found that three hours post-exercise the

phosphorylation state of S6K1 increased by about 400% in both groups. However, the phosphorylation state of S6K1 returned to basal values 24 h post-exercise and Cr had no additional effect. In this way, the results of these investigations show that Cr supplementation has no effect on phosphorylation state of S6K1; notwithstanding, the association of S6K1 phosphorylation and muscle mass was demonstrated in human subjects after 12-weeks of resistance training; thus, it should be necessary the evaluation of long-term Cr supplementation on S6K1. On the other hand, though exists a potential Cr inhibition on 4E-BP1, it is important to stand out that 4E-BP1 phosphorylation is reduced during resistance exercise and is unchanged during post-exercise recovery. Thus, it appears that the contraction-induced increase in muscle protein synthesis is independent of changes in 4E-BP1 phosphorylation (61).

It has been demonstrated that Akt/PKB can activate directly the mTORC1 complex by phosphorylation on raptor or indirectly by means of phosphorylation and inhibition of the tuberous sclerosis complex (TSC) proteins 1 and 2 (62), moreover another novel negative regulator of mTORC1 is proline-rich Akt substrate-40 (PRAS40), which has been shown to bind mTOR via raptor to repress mTORC1 signaling. The inhibitory function of PRAS40 is reduced when phosphorylated by Akt/PKB (61). Additionally, mTORC1 is also positively regulated for amino acids, mainly leucine, by means of the vacuolar protein sorting-34 (Vps34) and mitogen activated protein kinase kinase kinase-3 (MAP4K3) (64). Finally, since synthesizing proteins is an energetically expensive cellular process, it is not surprising to find a specific regulator of mTORC1 function when energy is not sufficient. Indeed, mTORC1 has been shown to be inhibited by AMP-activated protein kinase (AMPK) through enhanced TSC2 activity and, recently, by phosphorylating raptor (61). Evidence suggests that Cr supplementation regulates the above upstream mTOR processes as we describe next.

Deldicque *et al.* (63) evaluated the effect of Cr supplementation (21 g/day x 5 days) on IGF-I and IGF-II mRNA expression pre and post-exercise in biopsies from vastus lateralis throughout RT-PCR, and found that in Cr group IGF-I and IGF-II mRNA expression at rest was increased by 30% and 46% than placebo, respectively. However, the mRNA expression measured after exercise was similar for the Cr and the placebo conditions. Burke *et al.* (65) reported a significant increase in intramuscular IGF-I concentration in Cr supplemented athletes (0.25 g Cr/kg mass dry x 7 days followed of 0.06 g Cr/kg mass dry x 49 days) following an 8 weeks-program of resistance training. In agreement with this, Snow *et al.* (66) determined the effects of Cr supplementation (0.8 g/kg body mass) and moderate intensity resistance training on the phosphorylation state of some proteins involved in the Akt/PKB pathway, finding that the phosphorylation state of Akt/PKB and GSK3 $\beta$  increased significantly in Cr supplemented group at 1 and 5 days. Safdar *et al.* (67) reported an increment in mRNA (2.1 fold) and protein (4.2 fold) content of Akt/PKB after Cr supplementation (20 g/day x 3 days followed of 5 g/day x 7 days) without changes in placebo group. Furthermore, Cr administration reduces the leucine oxidation rate and flux ratio mitigating the protein catabolism in men (68) and at the same time generates a greater bioavailability of arginine and L-homoarginine in the body (69), which correlates with NO production during exercise. Although there is not enough scientific support in humans, some authors claim that Cr supplementation and its inherent increased PCr/Cr ratio could inactivate the AMP-activated protein kinase (AMPK) since it was shown *in vitro* that high PCr concentrations reduce AMPK activity to 50% which means this kinase is sensitive not only to ATP/AMP but also to PCr/Cr ratio (70).

In this way, the increasing lean body mass after Cr supplementation can be related to the stimulation of signaling pathways as IGF-I, mainly PI3K/Akt-PKB/mTOR which plays an important role in the regulation of muscular hypertrophy, and the probable leucine and AMPK regulation on mTOR. Stepping aside the direct effect of Akt/PKB on mTOR regulation, a novel mechanism mediating the effect of GSK3 $\beta$  on muscle growth has been described recently. GSK3 $\beta$  is able to phosphorylate nebulin

localized to the Z-disk, thus preventing the interaction of nebulin with neuronal Wiscott-Aldrich syndrome protein (N-WASP), which is involved in actin assembly (62). Therefore, IGF-I/Akt-PKB signaling controls myofibril growth and maintenance via the GSK3 $\beta$ /nebulin/N-WASP pathway. This phenomenon could explain the findings of some researchers years ago. Dangott *et al.* (71) and Olsen *et al.* (72) showed that Cr supplementation increase the satellite cell population and its mitotic activity, while O'Connor *et al.* (59) showed that Cr stimulates the myoblast fusion *in vitro* and *in vivo* possibly mediated by actin polymerization.

In general, most of the investigations on Cr supplementation have reported an increase in the intracellular volume without notorious changes in extracellular volume (67, 73, 74, 75, 76), probably because of the high osmotic charge associated to the increase in Cr and Na<sup>+</sup> in cytosol. In fact, cell swelling has been marked as an anabolic signal (77), which in turn can stimulate the activation of osmosensing molecules as G protein coupled receptors in the MAPK pathway and sphingosine kinase (SPHK1), creating a positive feedback motif. This osmotic effect of Cr supplementation on SHPK1 and the MAPKs p38 and ERK6 was confirmed by Safdar *et al.* (67) as well as other studies have shown a p38 overexpression after *in vitro* (58) and *in vivo* (79) Cr administration. Activation of MAPKs is crucial for muscle adaptations and development after exercise (80). For example, JNK/SAPK is involved in the transcription process of CK via p53 whereas p38 plays an important role in the up-regulation of Myogenic Regulatory Factors (MRFs) and myostatin down-regulation (81). MRFs are transcription factors involved in the differentiation and maintenance processes of muscle cells with multiple regulation points throughout the myogenic lineage (these include the proteins MyoD, Myogenin, Myf5, and MRF4/Myf6/Herculin), regulating the expression of important proteins such as CK and Myosin Heavy Chain (82). Particularly, Cr supplementation has safe (84) and conserved effects on increasing MRFs expression (mRNA and protein) even with different administration protocols in humans (55, 83, 85, 86).

In particular, Cr supplementation during an exercise training program can increase the muscle mass and strength (87) by means of positive regulation processes, which include the higher IGF-I and IGF-II expression and following turning on of the well-established Akt/GSK3 $\beta$ /mTOR signaling pathway and the SHPK1/MAPK/MRF pathway and its downstream components activation by means of the creatine-induced cell swelling (all features pictured in Figure 3).

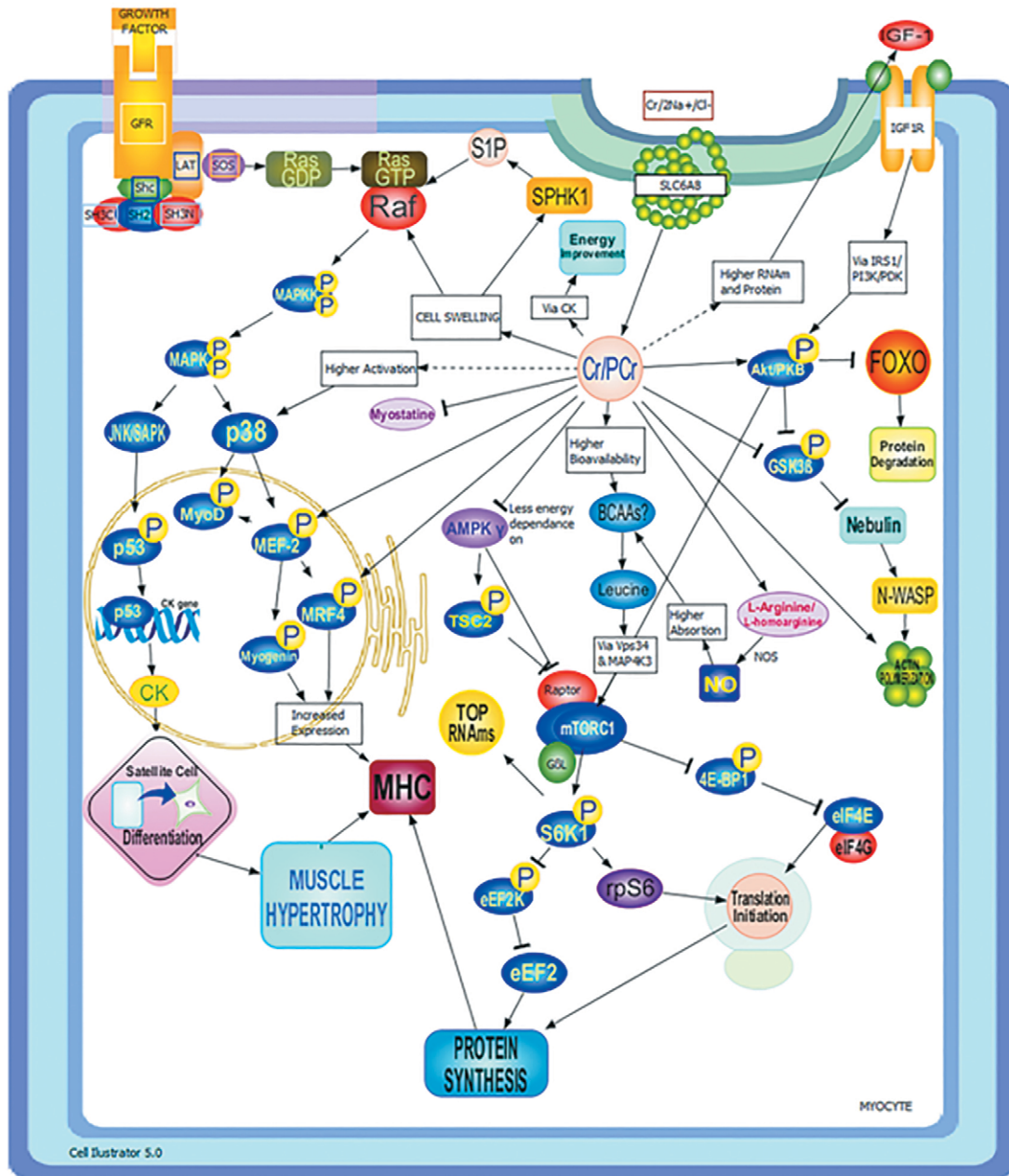
## Conclusion

In summary the ergogenic effects of Cr supplementation are absolutely dependent upon Cr accumulation in myocyte and the subsequent optimization of the Cr/PCr/CK system which serves as a spatial/temporal buffer of ATP regeneration in proximity to myocellular ATPases. In addition, this improvement in energy homeostasis leads to positive regulation of anabolic hubs (such as IGF-I and MAPK), which stimulate synergically the faster muscle growth and strength gain.

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**Figure 3.** Signaling events during Cr/Pcr accumulation in muscle. After supplementation, Cr enters to the myocyte through the Cr<sup>+</sup>/SLC6A8 favoring the muscular Pcr/Cr ratio. During resistance training the augmented Pcr/Cr ratio, besides preventing energy failure of ATP, increases the expression of IGF-I which activates Akt/PKB to possibly inhibit AMPK allowing indirect and direct activation of mTOR. Additionally, Cr effects on some amino acids homeostasis, especially leucine, regulate equally mTOR via Vps34 y MAP4K3. On the left side the Ras/MAPK pathway is represented. This activation can be mediated through growth factor binding or cell swelling via SHP1, both stimulated after Cr supplementation. Subsequent MRFs activation allows optimizing the remodeling and recovery processes of myocyte a posteriori to exercise training. Software; Cell Illustrator 5.0.

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