CHAPTER EIGHTEEN

Personalized sports nutrition: Role of nutrients in athletic performance

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18.1 Introduction to personalized nutrition: "One size does not fit all"

Since ancient times, nutrition has always been considered an essential condition for maintaining good health. Hippocrates of Kos, the father of medicine, said in 460 BC: "Let food be thy medicine and medicine be thy food." His observations led to associative evidence between diet and health by highlighting how food is able to interfere with our body's physiology by not only acting as an energy provider, but as a modulator of the health/disease balance in a different way for each individual (Tsiompanou and Marketos, 2013) depending on the personal characteristics. Somehow it can be considered a precursor of modern nutritional genomics.

It is fundamental to consider that although nutrients act by modulating some physiologic functions in a dose-dependent manner, each individual responds differently depending on its genotypic and phenotypic characteristics (Ferguson et al., 2016). Therefore, the recommended daily doses suggested by the international nutrition guidelines, based on studies on large populations rather than specific genotypes or phenotypes, should be used with enough flexibility to account for the plethora of genetic, epigenetic, and environmental factors contributing to health and disease in each individual.

Nutritional genomics is a new branch of nutritional medicine based on the concepts of functional genomics and personalized medicine. Empowering the individual biochemical data with genomic data allows the customization of a specific diet for each individual, based on the genotypic characteristics and the nutrients modulatory action on gene expression (Camp and Trujillo, 2014).

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18.1.1 Gene-nutrient interactions: The era of nutrigenetics and nutrigenomics

In the past decade, growing evidence that molecular components in macro- and micronutrients act as potential dietary signals influencing the metabolic status of cells has been collected. Further, the link between genetic polymorphisms in key steps controlling metabolic pathways and the development of chronic diseases such as cardio-metabolic and gastrointestinal diseases has been elucidated. The use of -omics techniques is now allowing to analyze with a systemic approach the response of the whole body to nutrients. Genomic, proteomic, and metabolomic analyses can be used to identify individual molecular characteristics relevant to the definition of a personalized nutritional regime for each individual, depending on the beneficial or negative effect of dietary factors (Müller and Kersten, 2003).

At the genetic level, two terms, nutrigenetics and nutrigenomics, have been developed to indicate subfields focused on the intricate relationships between nutrients, genes, and biological systems.

Nutrigenetics aims to analyze and understand how our genetic background with individual genetic polymorphisms can modulate nutrients absorption, distribution, metabolism, and elimination (ADME), thus affecting response to diet.

Nutrigenomics focuses on the individual sensitivity to nutrients in terms of influence on gene and protein expression and, subsequently, metabolite production, thus providing actionable information on the effects of diet and allowing effective dietary-intervention strategies to prevent diet-related diseases (Mutch et al., 2005).

These two terms are strictly related and should be considered as a single entity when applied to clinical nutritional analyses. Today, genomic tools, such as quantitative techniques (RT-PCR) and high-density microarray and other -omics techniques, equipped with advanced systems biology-oriented informatics can be used to create nutrient-gene interaction networks to analyze for each individual the influence of each nutrient on the entire organism, thus achieving a weighed nutritional regime for wellness maintenance.

18.1.2 Could nutritional genomics be applied to personalized sports nutrition?

One of the most effective applications of nutritional genomics can be in athletic performance. Nowadays every athlete playing sports such as bodybuilding, running, soccer, etc., must conjugate physical activity with a personalized nutritional regime in order to maximize muscle growth and athletic performances. The genetic variability between individuals can affect muscle strength, skeletal structure, heart and lung size, tendon elasticity, etc., leading to different human phenotypes, ultimately influencing sports performance.

Genetic analysis demonstrates that the chances of an individual to have an optimal sporting genotype are lower than 1 in 20 million and with the increase of polymorphisms the score decreases correspondingly (Puthucheary et al., 2011).

Basal muscle mass and response to training are two main factors contributing to muscular performance. Genetic factors account for about 50%–80% of interindividual variation in body mass and this has an important impact on muscular growth response (Puthucheary et al., 2011). Moreover, endocrine functions, muscle fibers composition, psychological aspects, and nutrition can have genotype-associated differences and influence athletic performance.

In particular, influences between genes and nutrients can affect the amount and the type of nutrients ingested with food and, subsequently, bodily functions.

Despite genetic testing for predicting sports performance and talent identification being continuously on the rise in the market, nutrigenetic and nutrigenomic analysis are less known and applied because of the complexity of the interpretation of the functional roles of different polymorphisms in nutrition, especially because every polymorphism can affect directly or indirectly different other genes, proteins or metabolic pathways. More research is needed to clarify the complex gene-nutrient associations' network that could be then used to determine which types of nutrients should be integrated for each individual, and which are not necessary or potentially dangerous.

18.2 Genes, nutrients, and nutraceuticals in athletic performance

18.2.1 Proteins and carbohydrates

Amount and type of proteins and carbohydrates in a personalized nutritional regime are crucial for muscle growth and sports performance.

In recent years significant progress has been made in describing the mechanisms regulating the complex pathways coupling gene expression and protein synthesis and how genetic variability can influence them by starting from the absorption of key nutrients necessary to activate these processes.

Protein intake and amino acids absorption and metabolism are crucial for muscle growth. Genetic differences can affect the amounts of bioactive peptides derived from protein sources and consequently the use of them for muscle activity and growth. Different foods have different protein qualities in terms of the amount of limiting amino acids. Leucine, for example, is a key factor for protein synthesis and enhances the activity of key kinases that regulate the beginning of translation processes such as the mTOR signaling pathway. Genetic polymorphism in LAT1 and LAT2 gene which encode for BCAA amino acid transporters could influence the absorption rate of leucine after ingestion contributing to reduce the amount of leucine available for protein synthesis (Kühne et al., 2007). Further, more than 20 *mTOR* single nucleotide polymorphisms (SNPs) have been identified that contribute to cell overgrowth and cancer development, with seven highly correlated SNPs (rs2536, rs2295080, rs1883965, rs1034528, rs17036508, rs3806317, and rs1064261) (Zining et al., 2016; Wang and Proud, 2006).

The hyperfunctionality of the mTOR pathways due to genetic polymorphisms have an impact on muscle growth and athlete performance in terms of nutrients absorption and protein synthesis. Based on this genetic evidence nutritional strategies concerning the amount of carbohydrates and protein ingested with diet and supplements have to be correctly performed.

In 2009, the pan-European study DiOGenes (diet, obesity, and genes) analyzed the impact of amount and qualities of proteins in weight management in five different diets, measuring in 773 individuals more than 30 plasma proteins such as vascular factors, adipokines, insulin and related hormones, growth factors, satiety hormones, etc. The diet with a moderate increase in protein intake and a modest reduction in the glycemic index of food was related to weight loss. Interestingly, the angiotensin-converting enzyme (ACE) was the one having the most relevance to body weight. In particular, the reduction in ACE due to this diet was related to weight loss in 8 weeks. It is not clear whether ACE-related body weight regulation and dietary protein are strictly related, but numerous genetic polymorphisms in the ACE gene have been revealed to influence the association of circulating level and activity of the ACE protein and weight management. In sports nutrition, people carrying a mutation in the ACE gene are highly recommend to adopt a correct diet regime to prevent fat mass accumulation (Chou et al., 2012).

In terms of body weight management and sports performance, proteins have proved to be a perfect ally. Protein intake has been shown to modify the association between genetic variation in FTO (obesity-associated gene) and body weight measurements in some ethnocultural groups. Higher protein intake (>18% of total daily caloric intake) protects against the obesogenic effects of some FTO genotypes and lead to better individual metabolic profiles. The benefits of high-protein weight management diets have previously been demonstrated, and the results have further suggested a link between FTO, protein intake, and body weight. Clarifying the mechanism that regulates this gene-diet interaction is a clear direction for future research to improve lean muscle mass for bodybuilders among others (Merritt et al., 2018; Jefferson and Kimball, 2001; Muñoz et al., 2017).

Another important aspect in sports nutrition for muscle structure and function is the amount of key amino acids required for collagen synthesis which is a crucial protein in tendon and bone and is also found in both the epimysium and perimysium of skeletal muscle where it acts as a supportive structure in muscle tissue. Collagen synthesis requires proline, lysine, and vitamin C. People carrying polymorphic binding site of the Sp1 transcription factor in the gene (COL1A1, COL1A2) encoding the alpha chain of type I collagen, which are associated with lower grip and biceps strength (Van Pottelbergh et al., 2001), have to increase the daily intake of lysine, proline, and vitamin C through diet or high-quality supplements.

Today, we know that protein and carbohydrates have to be co-ingested to stimulate protein synthesis and muscle growth. In particular, insulin pathways are crucial for muscle

hypertrophy. At the same time, insulin polymorphisms can affect the rate of glucose absorption and muscle hypertrophy. Insulin-like growth factor-I (IGF-I) plays a key role in exercise-associated muscle growth and development. The regulatory region of the promoter of the IGF-I gene is labile. Reports in the literature have suggested that the IGF-I protein plays a major role in strength training (ST)-induced skeletal muscle hypertrophy and strength improvements. A microsatellite repeat in the promoter region of the IGF1 gene has been associated with IGF-I blood levels and phenotypes linked to IGF-I in adult. Kosket et al. demonstrated that IGF1 promoter polymorphism may influence the strength response to ST (Kostek et al., 2005).

Another work demonstrated that the genetic variation C-1245T (rs35767) in the promoter region of the IGF-I gene was associated with higher circulating IGF-I levels, and possibly with increased muscle mass in athletic and nonathletic Israeli populations. The study suggested a contribution for the relatively rare IGF-I TT genotype to endurance performance, and in particular to power sports excellence in Israeli athletes (Ben-Zaken et al., 2013). Different polymorphisms affect the IGF-1 pathway and modulating the amount and the time of carbohydrates ingestion with food during the day seems to be a promising strategy to improve sports performance. It can be speculated that individuals carrying IGF-1 polymorphisms with reduced IGF-1 pathway functionality have to integrate with more whole-grain carbohydrates and high-quality proteins to induce protein synthesis and muscle and brain performances.

Carbohydrates and protein intake with food or supplements is a widely used strategy for muscular recovery and protein synthesis. Genetic and biochemical studies demonstrate that different carbohydrates have different metabolic responses. Fructose ingestion, for example, has been shown to suppress the stimulation of the exercise-induced glucose transporter (GLUT4) in rat skeletal muscle, impairing the expression of genes involved in "remodeling"/postexercise muscle growth; fructose intake alters the expression of genes involved in oxidative metabolism, mitochondrial biogenesis, and proteolytic genes in skeletal muscle. This negative effect of fructose ingestion has been observed for most of these genes both in sedentary people and in those who do exercise, and besides altering the adaptive response of GLUT4, it has also been shown that ingestion of fructose could compromise skeletal muscle responses to exercise by modulating glycogen storage and mitochondrial biogenesis by altering PGC-1α, FNDC5, NR4A3, GLUT4, Atg9, Lamp2, Ctsl, Murf-1, and MAFBx/Atrogin-1 in the skeletal muscles of both sedentary and exercised animals. These results highlight how fructose could compromise the expression of genes involved in metabolic adaptation of skeletal muscles. High fructose intake with diet or supplement may impair skeletal muscle response to exercise, thus limiting sports performance in athletes (Pereira et al., 2017).

On the other hand, long-term glucose uptake contributes to the development of obesity and type 2 diabetes mellitus (T2DM). Obese people tend to eat foods containing glucose, which can lead to glucose dependence, increased glucose in the blood and intestinal

lumen, and exposure of intestinal enterocytes to a high level of glucose in the diet. Recent studies have documented a role for enterocytes in glucose detection. One study was conducted aimed to identify the relevant target genes and the molecular pathways regulated by the high amount of glucose in a well-established in vitro epithelial cell culture model of the human intestinal system (Caco-2 cells). Data on microarray gene expression showed that 679 genes were altered (297 upregulated and 382 downregulated) with high glycemic treatment. The results provide valuable information regarding the molecular and genetic aspects in response of enterocytes to high levels of glucose, which is the main nutritional contributor to the development of obesity and T2DM (type 2 diabetes) (Boztepe and Gulec, 2018).

Studies on bowel and obesity have largely focused on intestinal glycemic detection and reduction of intestinal glucose uptake through delayed carbohydrate breakdown in enterocytes, while the mechanisms by which enterocytes respond to high levels of glucose had not been previously studied. Thus, the identification of candidate genes (e.g., TXNIP) involved in intestinal glucose control for absorption during high glucose uptake adds a new piece of information. In addition, enterocytes exposed to high blood sugar may communicate, possibly via LCN15 (lipocalin 15), with endocrine cells in the gut or in peripheral tissues. This work demonstrates glucose-dependent genetic regulation in enterocytes and has identified important target genes that will facilitate further investigations into the control of glucose metabolism in enterocytes during high glucose uptake (Boztepe and Gulec, 2018; Muñoz et al., 2017).

Goda (2000) showed the molecular mechanism of nutrient intake in modulating intestinal gene expression, cloning 5′ flanking regions of two disaccharidase genes, namely sucrase-isomaltase (SI) and lactase-hydrochloride hydrolase (LPH). Oral feeding of a sucrose-containing diet in rats increases SI mRNA and LPH mRNA levels within 3 h. Among the monosaccharides tested, fructose gave rise to more important mRNA levels of SI and LPH genes, which were accompanied by a coordinated increase in the mRNA levels of two microvillar hexose transporters (SGLT1 and GLUT5). It was shown that fructose, but not glucose, increased the transcription of SI, LPH, and GLUT5. Analysis of the DNase I fingerprint of the rat LPH gene showed that the protected region retains the same sequence of *cis* elements (CE-LPH1) in the LPH gene (Goda, 2000).

At the gene level, it has also been discovered that AGP rs699 and IRS2 rs1805097 SNPs show a significant association with overweight individuals (BMI $P > 85$). The variants rs699, rs1805097, and rs17817449 were significantly associated with BMI and the variant of UCP3 rs1800849, with waist circumference. It is thus important in athletes to monitor these SNPs and not exceed in a high caloric meal (Muñoz et al., 2017).

Muscle energetic metabolism is a key process with genotypic diversity throughout athletes. In particular lactate production in anaerobic glycolysis is highly accumulated during high-intensity exercise and may influence the incidence of muscle injuries.

Lactate transport across the plasma membrane is mainly mediated by proton-linked monocarboxylate transporters (MTC1 and MTC4) that play a crucial role in intracellular pH homeostasis (Massidda et al., 2015). Genomic analyses revealed an association between lactate transporter defects in skeletal muscle and easy fatigue and muscle cramping upon exercise due to delayed removal of protons accumulated during anaerobic work and consequentially and higher risk for muscle injuries. A well-known polymorphism in the MCT1 gene (rs1049434 A/T) is associated with higher lactate levels in response to high-intensity training in subjects carrying the TT genotype because of an increased H+ concentration during exercise which lead to metabolic acidosis (Cupeiro et al., 2010; Fedotovskaya et al., 2014). This factor might compromise extreme performance in healthy individuals or athletes. Indeed, Fedotovskaya et al. (2014) have shown that the TT genotype and T allele are significantly under-represented in endurance athletes compared to controls. Despite controversial, in severe metabolic acidosis bicarbonate therapy seems to be beneficial (Sabatini and Kurtzman, 2009). In our context, we can hypothesize a utility of bicarbonate administration to individuals carrying the rs1049434 TT genotype of the MCT1 gene in order to reduce H+ concentration and improve endurance performance.

Recently, a work by Collins underlined the role of the AMPD1 rs17602729 gene polymorphism in exercise-induced myopathy and increased perceived pain posttraining. People carrying at least one T variant require longer rest periods between bouts of weight training. Adenosine monophosphate deaminase (AMPD) is a very important regulator of muscle energy metabolism during exercise playing a central role in the salvage of adenine nucleotides as well as the determination of energy charge. It has been shown that physical activity lowers skeletal muscle AMPD activity and part of the population who express the mutant AMPD1 T allele [2% of the Caucasian population are homozygous (TT genotype) and approximately 20% are heterozygous (CT genotype)] are vulnerable to muscular cramps, pain, and premature fatigue during exercises (Collins, 2017; Ginevičienė et al., 2014). A nutrigenomic approach to people carrying almost a T allele in AMPD1 gene might involve carbohydrate drinks for endurance athletes and creatine monohydrate supplementation for strength athletes in order to reduce muscle soreness and to accelerate muscle recovery.

18.2.2 Lipids

Genetic variability in lipid regulating genes has been studied in the last decades and the influence of these genetic polymorphisms on lipid plasma levels can suggest new dietary strategies to personalize a balanced diet regimen for athletes.

It is well known that the effect of dietary changes on plasma lipid concentrations differs significantly between individuals (Jacobs et al., 1983). Some individuals appear to be relatively insensitive (hyporesponders) to dietary intervention, while others

(hyperresponders) have significant improvement (Loktionov, 2003). In this regard, low-fat diets can cause reduced HDL (Katan et al., 1997) which can be particularly harmful to some subjects. For example, it has been shown that individuals with a predominance of small dense particles of LDL (subclass model B), a phenotype that is associated with an increased risk of coronary heart disease, benefit more from a low-fat diet (Jansen et al., 2002) compared to those with the subclass A variant (larger LDL).

Currently, there is considerable support for the idea that interindividual variability in response to dietary changes is determined by genetic factors, especially for different phenotypes for lipids and lipoproteins (Bertolini et al., 2004). Indirect evidence to support this hypothesis stems from the general observation that the phenotypic response to the diet is determined in part by the baseline value of the phenotype itself and that it is influenced by genetic factors (Williams et al., 1986). However, taking into account the complexity of lipid metabolism, the main problem is how to identify and clarify the many potential interactions between genes and diet.

Blood lipid response to a given dietary intervention could be dependent on the effect of both diet and gene variants. Brahe et al. investigated SNPs and diet mutual role in blood lipid profiles for 240 SNPs in 24 candidate genes, selected for their involvement in lipid metabolism pathways, and identified one significant interaction between LPIN1 rs4315495 and dietary protein that resulted in a decrease in TAG concentration for minor allele carriers on the high-protein weight maintenance diet. Adjusting for multiple testing, no other effects of SNPs or SNP-diet (protein content or GI) mutual contribution on blood lipid profile were detected after weight loss or after the 6-month ad libitum weight maintenance diet. People carrying this SNP should improve their protein intake in diet to prevent TAG increases especially for athletes with high caloric diet (Brahe et al., 2013) (Fig. 18.1).

An important and well-recognized factor in sports performance is the PPARα gene which encodes the peroxisome proliferator-activator receptor alpha, a central regulator of expression of other genes involved in fatty acid metabolism, which has been found positively associated with endurance athlete status. PPARα shows increased expression in tissues involved in fatty acids utilization such as liver, skeletal muscle, and cardiac muscle. Activation of PPARα promotes uptake, utilization, and catabolism of fatty acids by upregulation of genes involved in fatty acid transport, as well as in peroxisomal and mitochondrial fatty acid metabolism. Differences in genotype distribution of PPARα polymorphism between professional soccer players and sedentary volunteers have been investigated by Proia et al. In this study the authors found some variations in genotype distribution of the rs4253778 PPARα polymorphism between professional soccer players and sedentary volunteers. In particular, the G allele was significantly more frequent in soccer players compared with healthy controls, as was the GG genotype; No significant correlations were found between lipid profile and genotype background (Proia et al., 2014).

It is well-known that dietary PUFAs have effects on diverse biological processes such as insulin action, cardiovascular function, neural development, and immune function,

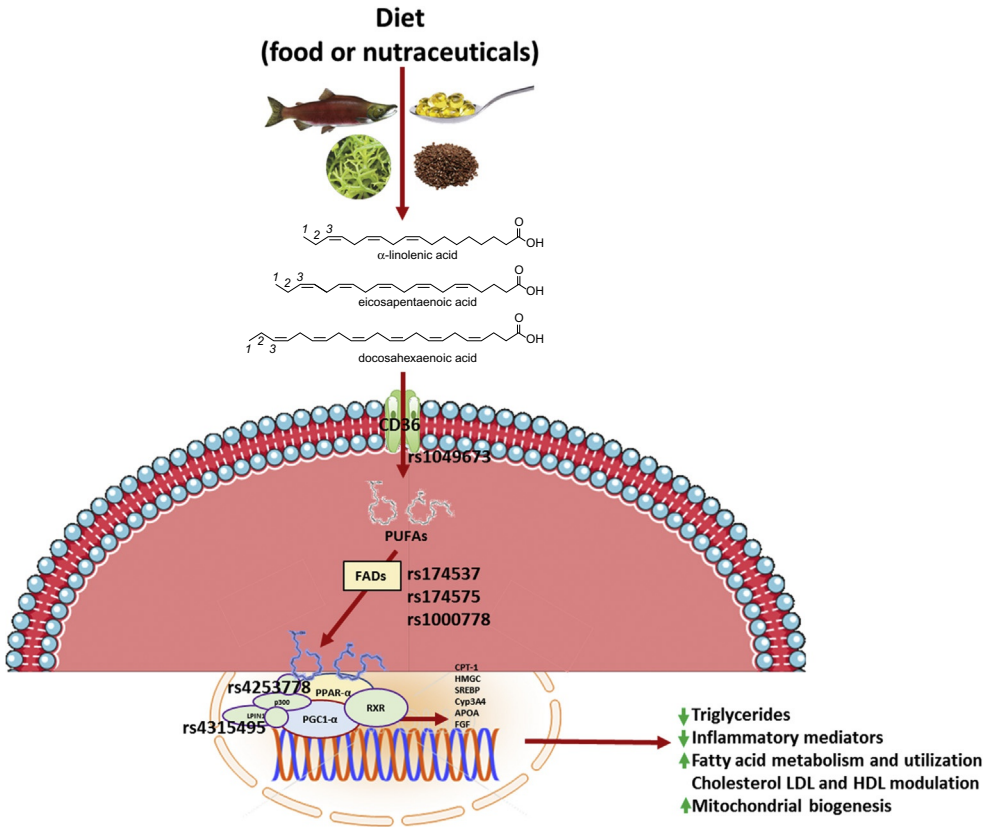

Fig. 18.1 Nutrigenomics of dietary PUFAs. Polymorphisms (SNPs) affecting PUFAs kinetics and dynamics.

some of them mediated via PPARα. Additionally, dietary PUFAs (in particular omega-3 fatty acids) activate, both directly and indirectly, other transcription factors such as liver X receptor, hepatocyte nuclear factor-4, and sterol regulatory element binding protein, which in turn mediate to some extent other biological processes affecting the expression of specific genes.

Health benefits of omega-3 fatty acids have been recognized for more than 40 years; however, there are gaps of knowledge in their mechanisms of action. This is due to the complexity of the action of omega-3 fatty acids, that have pleiotropic effects at the cellular level and act directly or indirectly through a wide range of metabolic pathways. Recently, nutrigenomics has contributed to a better understanding of the molecular mechanisms linked to the health benefits of omega-3 fatty acids. The use of nutrigenomics in this research field has been successfully applied in various human and animal models. For example, several detailed analyses of omega-3 PUFAs nutrigenomics have recently been

published using human blood mononuclear cells (Bouwens, 2009; Rudkowska et al., 2013), and on different tissues in animal atherosclerosis models (Gladine et al., 2012, 2014) that have contributed to a better understanding of the cardioprotective role of omega-3 PUFAs. All these studies show that the dietary intervention with PUFA omega-3 induces a substantial modulation of transcriptome, proteome, lipidome, and metabolome. Moreover, in all the experimental models used, the main pathways affected by the omega-3 PUFAs are related to inflammation, lipid metabolism or oxidative stress, while the main transcriptional regulators involved in these effects are NFκB and PPAR, both associated to crucial pathways in sports nutrition and athletic performance.

Other important data come from a study conducted by John P. Vanden Heuvel in which he concludes that diets rich in omega-3 fatty acids have long been associated with a reduced risk of CVD and prevention of some types of cancer. These effects could result from expression regulation of genes known to be "fatty acid receptors" (Skulas-Ray et al., 2010). It is estimated that genetic variation can explain a large portion of interindividual variability in o3-PUFA levels. FADS1 and FADS2 express the key enzymes involved in converting o3-PUFA into longer chain products. Several SNPs in these genes are associated with significant decreases in the percentage of o3-PUFA incorporated into serum lipids. Similarly, variations in genes encoding for other enzymes involved in the metabolism of fatty acids such as 5-LOX and polymorphic COX-2 can explain interindividual differences in levels and reactivity to o-PUFAs.

Many of the fatty acid receptors described above have genes with prevalent SNPs that are associated with the differential response to dietary intervention with o3-PUFA. For example, the carriers of the 162Val variant of PPARA and Ala12, the PPAR/G isoform generally respond to the supplementation of EPA and DHA with a greater reduction of serum triglycerides. Treatment with o3-PUFA is often associated with decreased circulating triglycerides and inflammatory mediators. However, the molecules responsible for producing beneficial responses vary within the population with polymorphic alleles in genes that encode lipoproteins such as APOE4 and cytokines like TNFα, among others. Indeed, several studies have shown an association between beneficial effects and polymorphisms of o3-PUFA in APOE, Gene FABP2, and TNF (Heuvel, 2012).

In terms of sports performance, it is widely recognized the importance of o-3 fatty acid in a personalized nutritional regime. Omega-3 fatty acids have to be taken at least after physical activity with a meal rich in lipid-like EVO oil or with proteins, better at night. The genetic variability should be addressed by varying the omega-3 daily intake depending on the genetic and lifestyles characteristics of the athlete.

18.2.3 Vitamins and minerals

An increasing number of studies in recent years have highlighted the importance of molecular nutrition as a potential determinant of health and disease (Jeukendrup and

Gleeson, 2018). In particular, the ability of minerals and vitamins to regulate the expression of genes and the production of proteins through the modulation of transcription and translation is now recognized. In sports nutrition, the daily amount of minerals and vitamins should be taken into consideration in order to provide the right dose of each micronutrient to each athlete in a personalized way. In particular, new nutrigenomic studies are now highlighting the important role of the correct daily intake of some minerals and vitamins to maximize sports performance and allow the body to recover properly after exercise (Jeukendrup and Gleeson, 2018).

18.2.3.1 Vitamin D

Vitamin D is a fat-soluble pro-hormone that can be consumed in the diet as cholecalciferol (vitamin D3) or ergocalciferol (vitamin D2) and activated in the skin in response to sunlight. Its nuclear receptor (VDR) modulates over 200 genes that transcribe proteins involved in maintaining bone health and calcium homeostasis, muscle function and mitochondrial antioxidant systems, autoimmune regulation, and synthesis of steroid hormones, among others.

About 200 polymorphisms in the vitamin D receptor gene (VDR) are known and others have been identified to be involved in vitamin D metabolism, therefore it is very easy to go into vitamin D deficiency for genetic reasons.

The expression of VDR decreases with age and the VDR genotype is associated with lean mass and strength in older men and women. Furthermore, there are strong relationships between vitamin D status and muscle function, especially in elderly patients. There is evidence that hypovitaminosis D is associated with a decline in muscle function. Vitamin D supplementation has beneficial effects on muscle strength, balance, and gait in various conditions although there are differences that can be explained with a dose of supplementation, a form of vitamin D and discrepancies in the threshold to define the deficiency/insufficiency (Beckett et al., 2014; Halfon et al., 2015; Potera, 2009; Puthucheary et al., 2011; bt Khaza'ai, 2018).

Vitamin D3 also plays a fundamental role in muscle with high-intensity exercise-induced damage and inflammation that are modulated by MAPK-NF-kB activation. High-intensity exercise activates p38 MAPK, which can stimulate nuclear translocation of p65 of NF-kB, as well as the gene expression of TNF-a and IL-6. Therefore, supplementation with vitamin D3 may be useful in rapid recovery or in protecting muscle damage from constant training (Choi et al., 2013).

Daily vitamin D intake is also essential for the modulation of insulin signaling and vitamin D can be used as a coadjuvant in the prevention of T2DM. However, vitamin D levels are responsible for the alteration of the pathophysiology of the DM2 gene due to the interaction of the mechanism of action VDR, DBP, 1-α-hydroxylase in skeletal and nonskeletal organs (Palomer et al., 2008).

It is thus important to monitor vitamin D3 plasma levels and to assess if some SNPs are presently known to be associated with the reduction of the amount of the active form of vitamin D3. It is suggested to perform a genomic analysis to assess vitamin D3 associated polymorphisms and quantify the daily dose of vitamin D3 needed.

18.2.3.2 Folate (as vitamer 5-methyltetrahydrofolate), methionine, choline and vitamin B

Folate (as vitamer 5-methyltetrahydrofolate), methionine, choline, and vitamin B12 are critical in carbon metabolism, which is the main source of methyl donors for cellular methylation reactions. These reactions include essential DNA synthesis and repair processes, DNA methylation, cell proliferation, and amino acid synthesis. Folate can be used in the de novo generation of methionine and, as such, the consumption of folates and other donors of methyl groups determine the availability of methyl groups for methylation reactions. Therefore, folates and other methyl group donors may indirectly influence miRNA profiles via alteration of DNA methylation status or may have an impact on miRNA expression levels through other methylation reactions. Altered functioning of catalytic enzymes in homocysteine (Hcy) metabolic pathways linked to gene mutations may lead to inhibition of certain pathways and elevation of plasma Hcy level (Ahmetov et al., 2016; Morton and Close, 2015).

Methylenetetrahydrofolate reductase (MTHFR), methionine synthase (MTR), methionines synthase reductase (MTRR), and betaine-homocysteine methyltransferase (BHMT) are enzymes in the Hcy remethylation pathway and interact with each other. Complex interactions between variations of corresponding genes, especially interactions between functional polymorphisms, can contribute to Hcy metabolic disorder and associated diseases. Sports nutrition is traditionally rich in protein and could alter the folate/Hcy pathways especially if not coupled with good vegetable intake. Thus, athletes should monitor this pathway measuring Hcy plasma level and through genetic analysis (rs1801133, rs1801394, rs1979277, rs1805087, rs18013940, rs492602, rs3733890, and rs6586282 SNPs associated to the folate/Hcy pathway thus introducing folic acid or directly the active form methylfolate and vitamin B6 and B12 with diet or supplements to prevent hyperhomocysteinemia (Suidasari et al., 2017).

Low folate consumption has been associated with an increased risk of muscle soreness and fatigue, muscle breakdown, and muscle strength. Vitamin B6 has also been found to be essential for the expression of genes useful for the repair and health of skeletal muscle (Beckett et al., 2014).

18.2.3.3 Minerals

Dietary trace element supplementation can result in an improvement in athletic performance. Athletes have a higher than normal requirement for minerals and an inadequate diet directly affects athletic performance.

Both iron deficiency and magnesium deficiency can result in a significant reduction in exercise performance. There is evidence that dietary magnesium intake may be suboptimal in some individuals, thus dietary supplementation of this element may be useful in some population groups. At the same time, iron supplements can improve athletic performance in individuals severely deficient in this element. If iron supplements are used, it is important that the level of supplementation is not excessive, as excess iron in the diet can result in an induced zinc deficiency (McDonald and Keen, 1988).

Interindividual variation in iron uptake and metabolism could be explained by polymorphisms in genes governing iron homeostasis. Several studies have examined the hemochromatosis (HFE), transferrin receptor-1 (TFR1), and TMPRSS6 genes in relation to iron storage and absorption. SNPs in these genes were strongly associated with lower serum iron concentration and other hematological variables (Wallace, 2016).

In marked contrast to iron and magnesium, there is little evidence for the idea that zinc deficiency influences exercise performance in humans. Despite this fact, zinc supplements have been widely advocated for the athlete, on the basis that intense exercise can result in changes in zinc metabolism. If zinc supplements are used, it is important that they are not excessive, as excess zinc in the diet can result in a secondary copper deficiency (McDonald and Keen, 1988).

Zinc, copper, and manganese are essential cofactors for the enzyme superoxide dismutase (SOD). SOD is a major antioxidant enzyme, which plays a vital role in the clearance of ROS. Among the isoforms of SOD, copper-zinc superoxide dismutase (SOD1, CuZn-SOD) with copper (Cu) and zinc (Zn) in its catalytic center is localized in the intracellular cytoplasmic compartments, and manganese superoxide dismutase (SOD2, Mn-SOD) plays an important role as a primary mitochondrial antioxidant enzyme. Numerous SOD polymorphisms have been detected, but only a few SNPs have been shown to have an impact in clinical practice. SOD1 +35A/C (rs2234694) which is located adjacent to the splice site (exon3/intron3 boundary), SOD2 Ala16Val (rs4880) which has been suggested to alter protein structure and function (C/T substitution in exon 2, codon position 2, amino acid position 16) and catalase −21A/T (rs7943316) which is located inside the promotor region just proximal to the start site, are the main SNPs. During physical activity ROS production increases and at the same time, antioxidant enzymes activity increases. Athletes carrying SNPs in the SOD enzymes might not be able to down-modulate excessive oxidative stress, which can lead to muscle damage in the long term. Another aspect is prolonged hyperglycemia due to genetic background or high caloric diet, which increases reactive oxygen species and modifies structure and function of lipids, proteins, and other molecules taking part in chronic vascular changes. Low activity of scavenger enzymes such as in people with SOD polymorphisms can accelerate this pathological condition leading to chronic diseases such as diabetes. In these athletes, supplementation with zinc, copper, and manganese might be interesting to

normalize SOD activity and prevent excessive oxidative stress and related-chronic conditions (Beckett et al., 2014; Flekac et al., 2008).

Nutrigenetics and nutrigenomics are comparatively new tools with which to study micronutrients. A critical evaluation of available data, incorporating omics technologies, strongly suggests that the intake or dietary supplementation with micronutrients should be optimized at an individual level.

18.2.3.4 Focus: *Caffeine ergogenicity and sports performance in athletes*

Caffeine (1,3,7-trimethylxanthine) is one of the most widely used performance-enhancing drugs. The performance-enhancing effects of caffeine have been known for over 100 years and are well replicated in both endurance-based activities and repeated high-intensity efforts (Guest et al., 2018).

The ergogenic effect of caffeine is related to several different mechanisms including a competitive adenosine receptor antagonist which reduce adenosine's downregulation of arousal and nervous activity and increase neurotransmitter release and muscle firing rates, an increase in adrenaline secretion and cellular ion release, and a decrease in pain perception. All of these mechanisms may improve caffeine ergogenic effects (Pickering and Kiely, 2018).

In terms of kinetics, plasma caffeine concentrations appear at about 15 min post-ingestion, peaking after about 60 min, with a 3- to 4-h half-life followed by an extensive liver metabolism by cytochrome P450 enzymes (primary CYP1A2), into paraxanthine, theophylline, and theobromine.

The general recommendation suggests the ingestion of 3–6 mg/kg of caffeine approximately 60 min prior to exercise despite recent research has shown high inter-individual variation in the ergogenic effects of caffeine with a wide variety of caffeine doses and timings.

The responses variations following caffeine ingestion are polygenic phenomena, mediated by multiple interacting genes and some genome-wide association studies have discovered SNPs associated with this behavior (Rahimi, 2018).

An SNP within CYP1A2 gene, rs762551, affects the speed of caffeine metabolization. Individuals with AA homozygotes ("fast metabolizers") tend to produce more of this enzyme and therefore metabolize caffeine more quickly. Conversely, C allele carriers ("slow metabolizers") tend to have slower caffeine clearance. The variable effects of this SNP are most well established in regard to health, with myocardial infarction and hypertension risk increased in slow metabolizers consuming moderate (3–4 cups) amounts of coffee, whilst fast metabolizers exhibit a protective effect of moderate coffee consumption. These studies prompted attention to how the CYP1A2 polymorphism might alter caffeine ergogenic effects in sports performance (Pickering and Kiely, 2018).

Womack et al. showed a significant effect of CYP1A2 genotype on the ergogenic effects of caffeine in trained male cyclists, with AA genotypes displaying a significantly

greater performance improvement than C allele carriers through two 40-km cycle time trials, following consumption of either 6 mg/kg of caffeine or placebo 60 min beforehand. These findings suggest that caffeine has a greater ergogenic effect for CYP1A2 AA genotypes than C allele carriers (Womack et al., 2012).

Recently, Guest et al. demonstrated that both 2 and 4 mg/kg caffeine improve 10-km cycling time in athletes carrying the AA genotype with no effect in those with the AC genotype and diminished performance at 4 mg/kg in those with the CC genotype concluding that CYP1A2 genotype might be examined when deciding whether athletes should use caffeine for enhancing sport performance and in which dose (Guest et al., 2018).

In conclusion, there is substantial variation in sports performance between individuals following caffeine ingestion. Understanding these differences, in part related to genetic variation between individuals, might lead to the development of personalized caffeine consumption guidelines for athletes.

18.3 Phytonutritional epigenomics: Role of phytonutrients in athletic performance

Epigenomics is the study of the complete set of epigenetic modifications on the genetic material of a cell, known as the epigenome. Epigenetic modifications are reversible modifications on a cell's DNA structure or histones that affect gene expression without altering the DNA sequence. DNA methylation, histone modifications, chromatin remodeling, noncoding RNA, are deeply interconnected layers all playing a role in epigenomic modifications that ultimately affect DNA expression (Romani et al., 2018). Epigenetic characteristics are specific to the individual and can represent key molecular patterns predisposing toward higher or lower physical performance capacities. By the same token epigenetic effects may also play a role in athletic potential (Ehlert et al., 2013).

Molecules with epigenetic effects can potentially be used to manipulate the epigenome and thus modulate DNA expression, by acting on one or more of the players of the "epigenetic orchestra" and of their mutual interactions, thus achieving genotype-phenotype interactions of therapeutic interest. In sports nutrition, an epigenomic approach could be applied to reduce muscle inflammation, to faster muscle recovering or to stimulate endogenous antioxidant systems. Given their multiple molecular effects, plant-derived molecules or whole phytocomplexes could be used to achieve a personalized therapeutic approach (Buriani and Fortinguerra, 2015; Buriani et al., 2017). Plant-derived molecules such as curcumin and resveratrol can modulate transcription factors (Nf-kB, NRF2, PGC1-a, FoXO3, AMPK, Sirt1) which lead to the transcription of key proteins involved in mitochondrial biogenesis, antioxidant systems, glucose and lipid homeostasis, and DNA repair which, in turn, ameliorate sport performance (Mead, 2007; Balogun et al., 2003; Lagouge et al., 2006).

Two important examples of the use of phytocomplexes or plant-derived molecules are provided by curcumin and resveratrol. Curcumin (diferuloylmethane), is a component of the spice turmeric (*Curcuma longa*) phytocomplex, which has been part of the traditional Asian medicine for centuries. In sports nutrition, turmeric and in particular curcumin may be potentially useful to prevent loss of muscle mass. Inhibition of NF-kB activity is of particular interest for the potential use of curcumin in the treatment of muscle wasting since NF-kB activation is a key step in the pathway leading to loss of muscle mass (Alamdari et al., 2009).

In a work by Delecroix et al. (2017), supplementation with curcumin and piperine each day between 48 h before and 48 h after exercise-induced muscle damage (EIMD) showed an effect on the recovery of some aspects of the muscle function. When the recovery period between competitions was short, a curcumin and piperine supplementation could be an effective recovery strategy to attenuate muscle damage. The recovery in sprint mean power output was moderately faster in the condition where the players consumed curcumin and piperine rather than placebo (Delecroix et al., 2017).

Another work assessed the effect of curcumin in EIMD and delayed onset muscle soreness (DOMS), which impact subsequent training sessions and activities of daily living (ADL) even in active individuals. In sedentary or diseased individuals, EIMD and DOMS may be even more pronounced and occur even in the absence of structured exercise. Curcumin supplementation resulted in a significantly smaller decrease in CK (−48%), TNF-α (−25%), and IL-8 (−21%) following EIMD compared to placebo supporting the use of oral curcumin supplementation to reduce the symptoms of EIMD (McFarlin et al., 2016).

Resveratrol (3,5,4′-trihydroxystilbene) is a natural phytoalexin which has been shown to improve oxidative stress levels in skeletal muscles of aged rats. As muscle disuse and reloading after disuse increases oxidative stress, resveratrol supplementation could improve muscle regeneration after disuse. Bennet et al. demonstrated the effect of resveratrol in improving muscle mass after disuse in aging (Bennett et al., 2013).

Another work by Sun et al. showed that exercise combined with resveratrol supplementation exhibit antiobesity functions in the long term due to enhanced mitochondrial biogenesis. This effect could be exploited by athletes aiming to reduce body fat and increase lean muscle mass. In order to obtain optimal resveratrol plasma concentrations, at least 200 mg of trans-resveratrol should be orally given at morning (Sun et al., 2018; Wang and Sang, 2018).

Another important aspect of resveratrol supplementation in sports performance is the effect on glucose control and insulin sensitivity. The latter is a new hot topic in bodybuilding, and there are some very valid reasons for that. In fact, one of the most important physiological tasks during a physical transformation like bodybuilding is making your body use insulin as much efficiently as possible, and resveratrol seems to be a promising molecule for this. A meta-analysis of 11 randomized controlled trials aimed to quantitatively evaluate the effects of resveratrol on glucose control and insulin sensitivity.

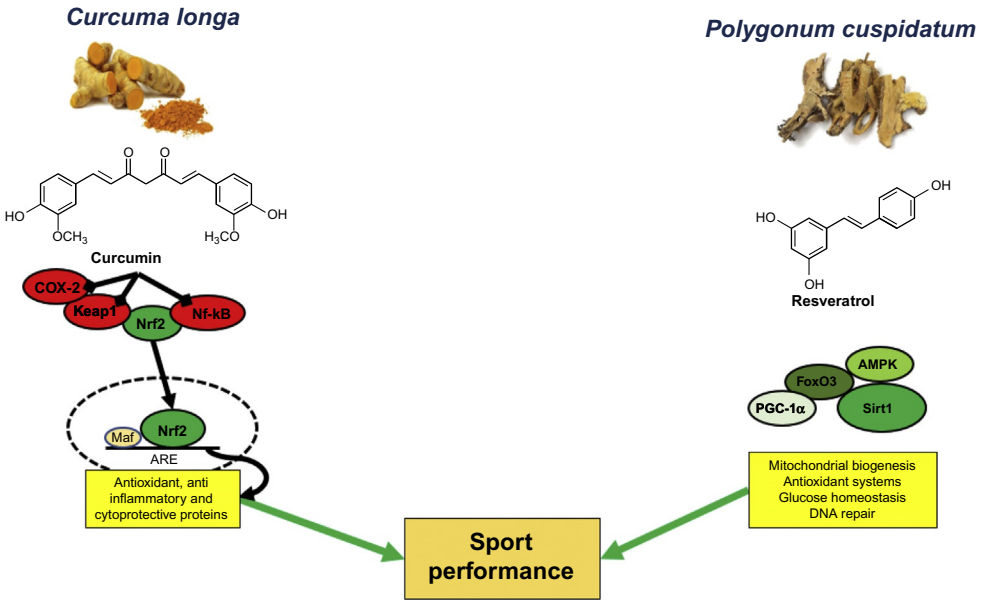

Fig. 18.2 Phytonutritional epigenomics of curcumin and resveratrol.

Resveratrol significantly improved glucose control and insulin sensitivity in persons with diabetes or prediabetes but did not affect glycemic measures in nondiabetic persons. These results suggest that resveratrol can be useful for those athletes who have high glycemic index and insulin resistance to ameliorate insulin actions in muscle absorption and growth (Liu et al., 2014; Baur et al., 2006) (Fig. 18.2).

18.4 Conclusion

In sports nutrition, the use of genetic information to personalize a nutritional regime can be applied to maximize athletic performances. However, for the majority of nutrients, there are still very little data or none at all, on the role of genetic polymorphisms on their ADME and the impact of these in athletic performance. In many cases, the application of nutritional genomics to sports performance is extrapolated from data of single polymorphisms analyzed for other conditions, or in specific diseases, so it will be necessary to confirm the data in athletes.

Further, individual network analysis comparing gene-nutrient associations, and genetic polymorphisms should be performed to understand in deep the physiological global status of an athlete in order to personalize a nutritional effective regimen. These applications of genomics in sports will gradually improve as the availability improves of progressively more informed and complete -omics databases as well as systems biology-oriented software.

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Further reading

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