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Review Article

Nutritional Genomics: Genes and Polymorphisms in Energy Metabolism: An Overview

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Abstract

Recent studies have demonstrated the effects of nutrients on gene expression and their influence on skeletal muscle metabolism. Macronutrients play important roles, which through dietary signals control the metabolic programming of cells to maintain cell homeostasis, influencing specific gene expression. The effect of nutrients and their relationship to genes. In this review, we discuss advances in genetic studies of DNA polymorphisms and their association with energy metabolism. Various genes (AMPD1 C34T rs17602729, PPAR-α (PPARA) rs8192678, PPAR-D (PPARD) rs2016520, PPAR-G (PPARG) rs 1807282, PGC 1 a (PPARGC1A) rs8192678, PPP3RUDD1) 1807282, PPAR8GC 1a, PPP3RUDD1 (PPARD) UCP006 UCP006 UCP006 UCP006 UCP006 UCP006 PPARG (PPARG) 1807282, PGC 1a (PPARGC1A) rs8192678; rs33 (PPARGC1A) GC1A, rs1937 and CLOCK/BMAL1 have been implicated in various aspects of skeletal muscle energy. Future research is guaranteed to explore multigenetic traits to provide a deeper molecular understanding, with greater genetic predisposition and metabolically flexible tissue, skeletal muscle largely contributes to the metabolic adaptation of the entire body.

Keywords: Genetic; Athletes; Sports Performance; Nutrients; Macronutrients; Exercise; Metabolism

Introduction

Genetic expression is regulated by several steps that include transcription, processing, stability of messenger RNA (mRNA) and protein synthesis from mRNA, ribosome functions and RNA transfer (tRNAS) [1]. As well as a metabolically flexible tissue, skeletal muscle largely contributes to the metabolic adaptation of the entire body that occurs through the complex and coordinated regulation of multiple energy/nutrient sensing pathways [2].

Nutrients can influence and modify the expression of mRNA or miRNA directly and indirectly. Genetic molecular studies relate the impact of nutrients on gene expression [3]. Recent technological advances have made possible the annual publication since 2009 of the human genetic map for health-related performance and fitness phenotypes, more than 200 genes or genetic regions have been associated with physical performance, with more than 20 variants [4,5]. Each sport has unique requirements, each amateur athlete, whether amateur or high-performance athlete, can respond differently to the stimuli of the influence of genetic factors on physical performance [6]. Therefore, future studies can clarify more clearly the genetic influence on physical performance, on how genes interact (skeletal, cardiovascular, respiratory, nervous, etc) with the complexity of the nutrients extracted from the diet [5,6].

Macronutrients (proteins, carbohydrates and lipids) are the fundamental nutrients, strength and muscle contraction in exercises, important in the regulation of energy metabolism, as they are sources of energy and support for the synthesis of structural and regulatory units in cells [7-9].

Nutrition and genetic variation

For the maintenance of organic homeostasis, the interaction between nutrition, metabolism and gene expression is necessary [7]. Any imbalances in consumption (low or high) in macronutrients can result in disturbances in energy metabolism [9,10]. The evolution of science in recent years has demonstrated an understanding of the diversity of nutrient-mediated molecular mechanisms to regulate genes essential for their biological functions to carry normal metabolism [11,12]. In many cases, these gene variants have responses associated with aerobic capacity and muscle fiber composition as traits related to skeletal energy metabolism [13,16].

Genetic variants can undergo transient changes in energy metabolism in gene transcription include immediate transcription factors, in addition to myogenic regulators. Carbohydrates in food have sensitive effects on the expression of genes associated with cell adhesion, cell cycle and growth control, and lipids need transport and oxidation for mitochondrial metabolism [15], oxidative phosphorylation, transcriptional regulators gene expression and mitochondrial biogenesis [14], being an important source of energy and its derived substances have critical roles in the regulation of cell signaling [18]. Triglycerides (i.e., fatty acids and glycerol), are an important source of energy, and play a critical role in the regulation of genes and in the cellular adaptation of skeletal muscles [9]. Muscle adaptations, modulated by a single exercise session alter DNA binding activity for a variety of transcription factors, including PPAR, PPRAD and PPARGC1A [17,20]. PPARs are located in the regulatory region of genes involved in lipid and carbohydrate metabolism. Many studies have demonstrated muscle activity sustaining exercising the ability to transiently activate gene expression by macronutrients [19]. The expression of the GLUT4 gene, hexokinase and uncoupling protein (UCP) reaches its peak from 30 minutes to 3 hours after exercise [22,23]. As PPP3R1 5I/5D, UCP2 rs660339, UCP3 rs1800849 are involved in metabolic pathways associated with elite endurance athletes and mitochondrial regulation. AMPD1 C34T rs 17602729 [24,25] is related to the function of regulating energy metabolism, while TFAM has the function of regulating mitochondrial transcription and CLOCK/BMAL1 [26], participates in the regulation of energy metabolism and has an extensive network of genes controlled by the biological clock and its molecular alterations that lead to consequences in energy metabolism. Proteins are essential for strength, increase and/or maintenance of lean body mass, in addition to playing an important role in immune function and in the stability and subcellular localization of transcription factor complexes in the nucleus and mitochondria [20,23]. In this review, we discuss advances in genetic studies of DNA polymorphisms and their association with energy metabolism.

Genetic variants in skeletal muscle energy

Transcription factors are the main agents by which nutrients influence gene expression. The transcription factor nuclear hormone receptor superfamily, with 48 members of the human genome, is the most important group of nutrient sensors [17,18]. However, understanding transcription factors, that is, gene x nutrient can act at different times of gene expression, reflecting on the activation and/or repression of specific signaling pathways that regulate transcription and translation and gene expression responsive to energy metabolism and exercise [20,21]. Thus, transient DNA hypomethylation of specific promoter regions of ten genes results in increased mRNA expression in response to acute exercise, as well as.

Polymorphisms under study

In table 1 the genes, their respective SNP identification numbers and the implicit function of these genes in energy metabolism were selected. For all the genes under study, a variant was investigated for associations related to the regulation of skeletal muscle energy [37,38]. Most of these genes encode proteins that are associated with mitochondrial transcription, proliferation, regulation and biogenesis. Thus, we addressed this issue in a study focused on variants of genes in metabolic pathways (that is, genes mainly involved in TP, glucose, insulin and lipid metabolism, mitochondrial biogenesis, thermogenesis, regulation of the muscle fiber type composition [39,40].

Discussion

We investigated 10 polymorphisms in genes related to skeletal muscle metabolism and/or exercise metabolism in resistance and endurance. In this selected cohort, AMPD is an important regulator of muscle energy metabolism [25,26]: when converting AMP to inosine monophosphate with ammonia release, this enzyme alters the balance of the myokinase reaction for ATP production. which acts on skeletal muscle metabolism (saving adenine nucleotides) and is involved in the regulation of muscle glycolysis during rigorous exercises [41]. It was evaluated in a case-control study (n 104 resistant athletes vs. 100 controls) [41].

Resistance exercise induces many adaptations of skeletal muscle, including an increase in the capacity for oxidative metabolism of fatty acids (FA) and carbohydrates. The increase in the oxidation of AF is facilitated by the increase in the capacity for the uptake of AF by the myocyte [21], its subsequent mitochondrial transport and Beta-oxidation. PPARs are in the regulatory region of genes involved in the metabolism of lipids and carbohydrates. The PPARA gene has emerged as a candidate gene for the study of athletic ability due to its expression in lipid metabolism, glucose energy homeostasis and vascular inflammation [28,42]. In conditions of energy deprivation, activation promotes the capture, utilization and catabolism of fatty acids [16,20] in the liver, skeletal muscle and heart [42]. PPARD is also involved in skeletal muscle adaptive metabolic responses to environmental changes, such as prolonged fasting or physical exercise, controlling the number of oxidative myofibers [29,30]. Another study with rodents suggests that a key feature of PPARδ activation is the induction of skeletal muscle fatty acid oxidation [30,42]. After activation of PPARδ in mouse skeletal muscle, the fiber composition changes to oxidative type I with induction of fatty acid oxidation [43].

Decreased expression of the peroxisome proliferator-activated receptor-γ, coactivator-1α (PPARGC1A) may have consequences on insulin resistance by interfering with multiple cell functions, including mitochondrial function [31], lipid oxidation [31,32], angiogenesis and microvascular flow [44] as well as oxidative stress [32]. A study of human skeletal muscle cell cultures showed a higher degree of methylation of PPARGC1A when incubated with free fatty acids (FFA) [31,40]. Interestingly, cellular exposure fostered by saturated fatty acids [44], as well as ingestion of a high-fat diet for 3 days, resulted in reduced expression of PPARGC1A in young men [43,46].

Canonical protein phosphatase 3/calcineurin signaling (PPP3R1), is central to numerous physiological processes [33]. Scientific evidence demonstrates that calcineurin plays a key role in controlling systemic energy and body weight homeostasis [45,46]. In humans, calcineurin activation was associated with changes in skeletal muscle mitochondrial dynamics [47]. An exercise intervention trial in obese insulin-resistant adults further suggested that decreased activation of Drp1 upon exercise may facilitate lifestyle-mediated improvements in substrate metabolism and insulin sensitivity [46,47].

The consumption of the maximum rate of oxygen consumption depends on a variety of factors, such as maximum cardiac output and the capacity of cardiac and skeletal muscle to capture and use oxygen. In skeletal muscle internally, fiber type ratio is a useful marker in the functional properties of skeletal muscle, and a high proportion of slow-twitch Wbers is related to high mitochondrial volume, high oxidative capacity, and high resistance to fatigue [33,34].

Regarding the case-control studies and the allelogical frequencies of genes, we investigated intermediate phenotypes (maximum oxygen consumption and muscle mass composition) that are studied because they are related to energy metabolism, showing their linkage to modulation polymorphisms of important genes for endurance and endurance exercise [38]. In fact, the UCP2, UCP3 genes have been shown to influence muscle fiber composition and/or skeletal muscle metabolism [34,47,48].

UCP2 is expressed in body tissues and, according to Ricquier and Bouillaud (2000), its physiological function is related to the regulation of metabolism, thermogenesis induced by diet and body weight control [49,51].

UCP3, specifically expressed in muscle tissue, is related to the consumption of energy substrates and also to the control of body weight, being regulated by the availability and metabolism of energy substrates such as lipids and glucose [54]. The entry of these substrates into the muscle results in increased UCP3 expression, leading to increased energy expenditure [49]. Since skeletal muscle is considered to be a notable region for energy expenditure in humans and rodents, UCP3 may be an important mediator of adaptive thermogenesis [51]. The role of UCP2 and UCP3 in skeletal muscle is not yet fully understood and the possibilities of mediating thermogenesis or regulating lipid oxidation are discussed, especially when there is a high availability and low demand for this fuel [52]. According to Gong., *et al.* [53], the UCP2 and UCP3 gene expression in skeletal muscle is elevated during fasting to maintain temperature, as the muscle assumes the body's thermoregulatory function [49,52].

Mitochondrial transcription factor A (TFAM) is a key regulator of mitochondrial gene replication, repair, and transcription [35,42]. An ex vivo study demonstrated that TFAM overexpression in cardiomyocytes decreased mtH2O2 [50]. In contrast, adipose

tissue-specific deletion of TFAM decreased reactive oxygen species (ROS), increased mitochondrial fuel oxidation, and protected mice against obesity and IR [51]. Ji-Ho-Koh (2019) demonstrated that muscle-specific overexpression of human mitochondrial transcription factor (TFAM) attenuates fat gain induced by a high-fat diet (HFD) and insulin resistance (RI).

The molecular mechanism underlying circadian rhythms is a gene regulatory network composed of transcriptional-translational feedback loops referred to as the core clock [27]. The molecular clock elements that constitute a positive central clock turnover are two members of the PAS-bHLH family of transcription factors, Clock (Circadian locomotor output control kaput) and Bmal1 (Brain muscle arnt-like1) [36,37,54]. Coming from more than 600 different muscles in the human body, around 40 percent of total body mass, understanding the effects of exercise on molecular rhythms in individual skeletal muscles can provide a critical view of the systemic mechanisms that contribute to daily rhythms [27,36]. The central molecular gene Clock has also been shown to be critical for healthy skeletal muscle, as mutant mice exhibit approximately 30% reductions in normalized maximal strength at both the muscle and individual fiber level [54]. Most scientific studies on exercise and changes in circadian rhythms have been based on resistance exercise paradigms. Zambon., *et al.* reported that a session of 60 contractions was associated with changes in molecular clock gene expression in human skeletal muscle [55].

Conclusion

This narrative review aimed to demonstrate the results of genetic studies of DNA polymorphisms and their association with muscle energy metabolism.

Sports performance is multifactorial; recently, some genes (AMPD1, PPARs, UPCs, TFAM, CLOCK/BMAIL1 have been shown to be involved in transient DNA hypomethylation of specific promoter regions which results in increased mRNA expression in response to physical exercise, as well as in the regulation of energy of the body. skeletal muscle Athletes with variations in genotype experience changes in muscle energy metabolism during exercise Heritability for a specific phenotype is likely dependent and specific to the type of exercise Future research will allow evaluation of multigenetic traits to provide a deeper molecular understanding of reflection on the activation and/or repression of specific signaling pathways that regulate transcription and translation and gene expression responsive to energy metabolism, exercise and nutritional modulation that may allow an improvement in physical performance.

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