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Research Article

The Impact of Associations of Various Polymorphisms of Common Metabolic Genes with Muscle Energy Metabolism: An Overview

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Abstract

In recent years, studies have demonstrated the identification of the effects of nutrients on gene expression and their influence on skeletal muscle metabolism. Macronutrients are important dietary signals that control the metabolic programming of cells and play important roles in maintaining cellular homeostasis, influencing specific gene expression. The use of state-of-the-art sequencing, microarray and qPCR array to investigate the expression of transcripts, genes and miRNAs has a crucial impact on the understanding and quantitative measurement of the impact of nutrients and their interaction with genes. In this review, we demonstrate the results of genetic studies of DNA polymorphisms and their association with physical performance. Ten gene variants were identified to show discrete associations with skeletal muscle metabolism (AMPD1 C34T rs17602729, PPAR-α (*PPARA*) rs8192678, PPAR-D (*PPARD*) rs2016520, PPAR-G (*PPARG*) rs 1807282, PPARGC1A rs8192678, PPP3R1 5I/5D, UCP2 rs660339, UCP3 rs1800849, TFAM rs1937 and CLOCK/BMAL1 with macronutrient interaction.

Keywords: Gene Expression; Macronutrients; MicroRNA; Exercise; Nutrition

Introduction

Gene expression is regulated by several mechanisms, including transcription, processing, messenger RNA (mRNA) stability, protein synthesis from mRNA, ribosome functions and transfer RNAs (tRNAs) [1,2]. Dietary nutrients can modify mRNA or miRNA expressions directly and indirectly. Studies have demonstrated knowledge about the nutritional impact on gene expression and the accumulation of related data has opened a new era of science [3]. The annual publication of the human genetic map for health-related performance and fitness phenotypes, as of 2009, more than 200 genes or genetic regions have been associated with physical performance, with more than 20 variants [4,5]. A great challenge when trying to describe the influence of genetic factors on physical performance, since all sports have unique physical requirements and these requirements may differ between amateur and high-performance athletes [6]. Therefore, any study of the genetic influence on physical performance, of how genes interact (skeletal, cardiovascular, respiratory, nervous, etc.) with food is one of the most complex human characteristics [5,6].

Macronutrients, mainly proteins, carbohydrates and lipids, are of fundamental importance in sports performance, as they are sources of energy and support for the synthesis of structural and regulatory units of cells [7,9]. With the tools of nutrigenomics, it is now possible to understand the epigenetic mechanism [8,10,11]. A hypothetical model that shows the effects of macronutrients on gene expression, as well as on the phenotypes of an organism (Figure 1).

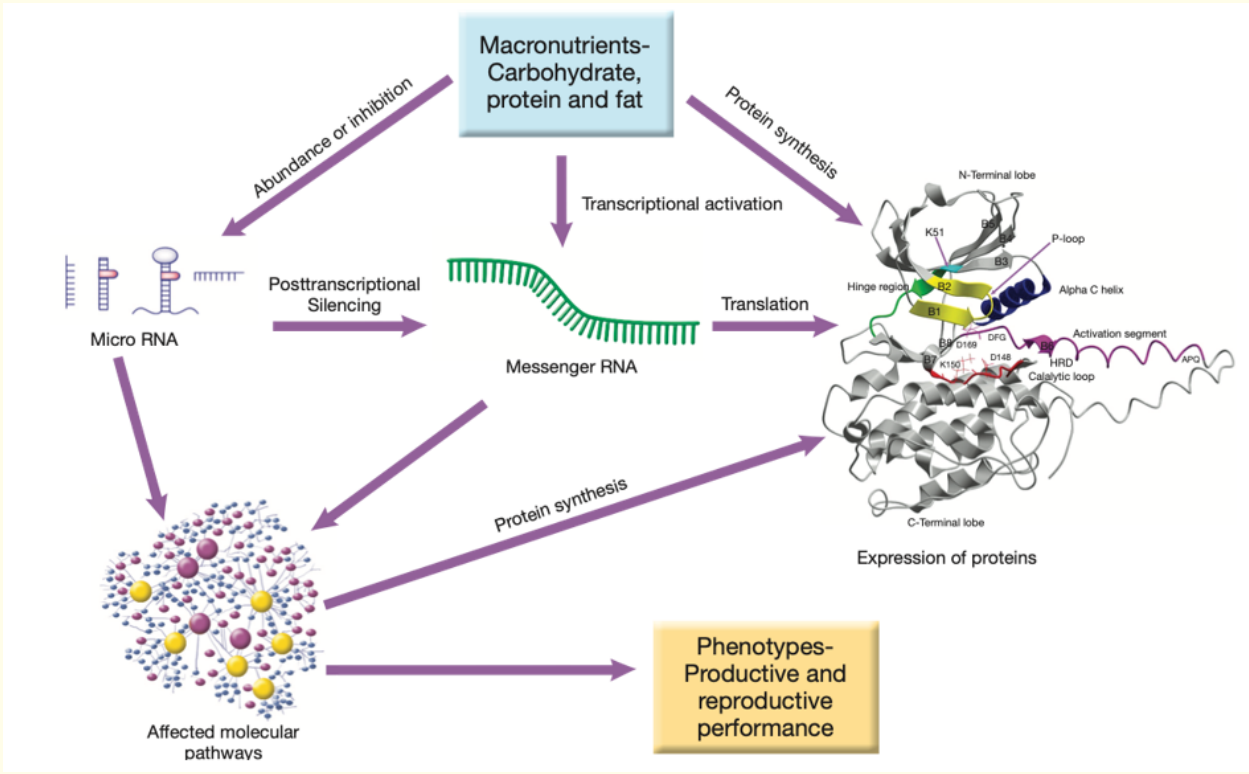

Figure 1: Diagram showing complex interaction between nutrients and genes. The components of this figure were adapted from Sohel, M (2016).

Any imbalance in macronutrients can result in developmental and functional disorders. Carbohydrates are one of the primary sources of energy, having a strong influence on the expression of genes involved in metabolic pathways, predominantly those related to skeletal muscle [12,14]. The amount of carbohydrates in the diet also has a dramatic effect on the expression of genes associated with cell adhesion, cell cycle and growth control [14,15]. Proteins are important, as they contribute to muscle structure (repair and construction) and physical performance [9,13,15]. Although proteins are not a primary energy source, they can be used as an energy source in specific circumstances, being composed of 20 amino acids in the human body. Dietary fat (fatty acids) is an important source of energy and its derived substances have critical roles in the regulation of genes and cell signaling, being used in sports as an energy mediator, through the ketogenic state [9,10,16]. Advances in science have been demonstrating the understanding of the different molecular mechanisms used by nutrients to regulate genes that are essential for their biological functions to carry out normal metabolism [10]. In several cases, these gene variants have been associated with aerobic capacity and the composition of muscle fibers as traits related to energy metabolism in elite athlete [11,14,16]. Advances in science have demonstrated an understanding of the different molecular mechanisms used by nutrients to regulate essential genes for their biological functions to carry out normal metabolism [10,12]. In several cases, these gene variants have been associated with aerobic capacity and the composition of muscle fibers as traits related to energy metabolism in elite athletes [10,11,17]. In this review we demonstrate the results of genetic studies of DNA polymorphisms, nutrients and their association with physical performance.

Genetic variants in energy metabolism

Transient changes in gene transcription include immediate transcription factors, in addition to myogenic regulators. Carbohy-

drates [16] and lipids, need transport and oxidation for mitochondrial metabolism, oxidative phosphorylation, transcriptional regulators of gene expression and mitochondrial biogenesis [17, 18]. At a regulatory level, for example, a single exercise session alters DNA binding activity for a variety of transcription factors, including PPARA, PPRAD and PPARGCIA 14,1 [7,17,20]. Many studies have already shown that sustained muscle activity exerts the ability to transiently activate the expression of many genes by macronutrients [19]. For example, the expression of the GLUT4 gene, hexokinase and uncoupling protein (UCP)-3 reaches its peak from 30 minutes to 3 hours after exercise [23,24]. While PPP3R1 5I/5D, UCP2 rs660339, UCP3 rs1800849 are involved in interrelated metabolic pathways to be associated with elite endurance athletes. AMPD1 C34T rs 17602729 [26,27] regulates the metabolism of muscle energy, while TFAM participates in the regulation of mitochondrial transcription and CLOCK/BMAL1 [28], regulates the metabolism of skeletal muscle and has an extensive network of genes controlled by the clock and the deregulation of its molecular clock lead to consequences in energy mestabolism.

Protein stability and subcellular localization of transcriptional factor complexes within the nucleus and mitochondria are also affected [20,25].

Thus, transient DNA hypomethylation of specific promoter regions of genes occurs precedes the increase in mRNA expression in response to acute exercise, as well as the interactions between gene and nutrient (Table 1).

Gene (Full name)	**Polimorfismo**	**Associated phenotypes and interactions**	**References**
AMPD1 Adenosine monophosphate deaminase 1	rs17602729 C34T	Genes related to the regulation of muscle energy metabolism catalyzing the deamination of adenosine monophosphate in inosine monophosphate, being stimulated after intense short-term exercises.	[26,27]
PPARA peroxisome proliferator activated receptor alpha	rs4253778	Genes related to role in lipid metabolism, energy metabolism. It is activated under conditions of energy deprivation and during metabolic and physiological	[16,20,29]
PPARD peroxisome proliferator activated receptor delta	rs2016520	Genes related to the regulation of muscle energy. Receptor-specific muscle overexpression increases the number of muscle fibers with high oxidative metabolic capacity. Regulates fatty acid oxidation, glucose utilization, mitochondrial biogenesis, angiogenesis, muscle fiber type, PPARGC1A, UCP2, UCP3 expression	[17,30,31]
PPARG peroxisome proliferator activated receptor delta	Rs1801282 Pro12 ala	Genes related to central transcriptional regulation of adipogenic and lipogenic programs, insulin sensitivity and glucose homeostasis	[16,20,32]
PPARGC1A Peroxisome proliferator-activated receptor □ coactivator 1-□	rs8192678	Genes related to a transcriptional activator through the recruitment and co-regulation of multiple transcription factors that regulate skeletal muscle gene expression. Regulates fatty acid oxidation, glucose utilization, mitochondrial biogenesis, thermogenesis, angiogenesis, co-activates PPAR□, PPAR□; regulates TFAM.	[17,33,34]
PPP3R1 Protein phosphatase 3, regulatory subunit B, alpha isoform (calcineurin subunit B)	5I/SD	Genes related to the generation of amino acids and ribose for the synthesis of proteins and nucleotides. Regulates energy metabolism / hypertrophy of skeletal muscle and heart, the expression of PPARA, PPARD, PPARGC1A	[35]

UPC2 Uncoupling protein 2	rs660339 55Val	Genes related to energy metabolism. Decouples oxidative phosphorylation from ATP synthesis; regulates lipid metabolism and energy expenditure	17,36]
UPC3 Uncoupling protein 3	rs1800849 T	Genes related to energy metabolism. In skeletal muscle, it can protect against fat-induced insulin resistance in muscle by converting intramiocellular fat into thermal energy. regulates lipid metabolism and energy expenditure, transports fatty acid anions out of mitochondria	[36,37]
TFAM Mitochondrial transcription factor A		Genes involved in the regulation of mitochondrial transcription, mitochondrial proliferation and mitochondrial biogenesis	[36,38]
CLOCK/BMAL1		Skeletal muscle-related genes controlled by the clock, and molecular clock dysregulation, which can interfere with energy metabolism. Divergent modalities of exercise can interact with the circadian rhythm, resulting in potent metabolic effects.	[28,39]

Table 1: Transcription factors and transcription coactivators to the regulation of muscle energy.

Transcription factors are the main agents through which nutrients influence the gene expression [10]. The nuclear hormone receptor superfamily of transcription factors, with 48 members of the human genome, is the most important group of nutrient sensors [17,18]. Thus, the understanding of transcription factors and the gene x nutrient interaction 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 exercise [20,21].

Conclusion

In this review, we demonstrate the results of genetic studies of DNA polymorphisms, nutrients and their association with skeletal muscle metabolism.

Sports performance is multifactorial; recently, several genes (AMPD1, PPARs, UPCs, TFAM, CLOCK/BMAIL1 have been implicated in various aspects of skeletal muscle energy. Athletes with variations in the genotype experience changes in muscle energy metabolism during exercise. Heritability for a specific phenotype is probably dependent and specific to the type of exercise. Future research will allow the assessment of multigenetic characteristics to provide a deeper molecular understanding of the 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 can allow an improvement in physical performance.

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