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GENERAL INFORMATION

Molecular biology and genetics in nutrition

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Abstract
The biomolecular principles of nutrition are basic for the understanding of the surgical patient's nutritional requirements. The catabolic processes carried out for the use and utilisation of macronutrients are extremely complex and are closely related. The tricarboxylic acid cycle has the role of a metabolic crossroad in which the products of the catabolism of carbohydrates, proteins and lipids play important roles in order to obtain useful energy for the synthesis of ATP in the mitochondria. The adaptation of metabolic processes to different physiological situations faced by a patient is a well-documented phenomenon regulated by molecular, hormonal, nervous and genetic factors. Nutrition genetics studies how the nutrients ingested in the diet interact with and modify the genome. It has two main fields of study, nutrigenetics and nutrigenomics. Nutrigenetics studies the interactions between individual genes and specific dietary nutrients, whereas nutrigenomics has a collective approach that studies how certain food compounds regulate the genetic material. Nutrition genetics foresees breakthroughs in nutritional science through the creation of personalised diets focused on molecular, genetic and epigenetic aspects. It will also aim for the prevention of metabolic diseases through the sequencing of the genome of each patient, the use of molecular studies that focus on the mechanisms of the target genes and biological markers testing.

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PALABRAS CLAVE
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Biología molecular y genética en nutrición

Resumen
Las bases biomoleculares de la nutrición son fundamentales para comprender el porqué de las necesidades nutricionales del paciente quirúrgico. Los procesos catabólicos llevados a cabo para la utilización y aprovechamiento de los macronutrientes son extremadamente complejos y estrechamente relacionados entre sí. El ciclo de los ácidos tricarboxílicos tiene el papel de encrucijada metabólica en la que los productos del catabolismo de los carbohidratos, proteínas y lípidos juegan papeles importantes, con el fin de obtener energía útil para la síntesis de ATP en la mitocondria. La adaptación de los procesos metabólicos a las distintas situaciones fisiológicas a las que se enfrenta un paciente es un fenómeno bien documentado, regulado por factores moleculares, hormonales, nerviosos y genéticos. La genética en nutrición estudia cómo los nutrientes ingeridos en la dieta interactúan y modifican al genoma. Tiene 2 principales campos de estudio, la nutrigenética y la nutrigenómica. La nutrigenética estudia las interacciones entre genes individuales y nutrientes específicos de la dieta y es de carácter individual, mientras que la nutrigenómica tiene un enfoque colectivo que estudia cómo ciertos compuestos de la alimentación regulan el material genético. La genética de la nutrición prevé grandes avances en la ciencia de la nutrición, por medio de la creación de regímenes alimenticios personalizados enfocados en aspectos moleculares, genéticos y epigenéticos; también buscará la prevención de enfermedades metabólicas por medio de la secuenciación del genoma de cada paciente, estudios moleculares que se enfoquen en los mecanismos de los genes diana y en pruebas de marcadores biológicos.

Molecular biology and genetics in nutrition

Nutrition is a complex field because of the existence of a large number of essential nutrients, identification of chemical compounds with unclear or unknown biological functions, different requirements of many cell types in the body and their different adaptation to each physiological situation, symbiotic relationship between humans and microorganisms that live in the digestive tract and the huge number of genetic and epigenetic variables that create the need for individualised approaches and are tailored to the characteristics of each individual. Molecular basis is the first step to understanding all the processes related to nutrition. These make up a vast knowledge that goes beyond the scope of this paper so it will instead focus on the major components of food, their main metabolic pathways, the relationships between these pathways and the energy produced from these catabolic processes. Nutritional genetics is an emerging science that has attracted much interest in recent years due to advances in understanding the genetic material. It seeks to understand and adapt to the inherent genetic variations of each individual and thus expand the scope for nutritional therapies in order to prevent or treat diseases or complications.

The main result of the digestion of carbohydrates, proteins and lipids is to reduce the size of molecules so that they can be absorbed more efficiently; these molecules are small peptides and amino acids from proteins, monosaccharides and disaccharides obtained from carbohydrates and fatty acids and monoglycerides obtained from lipids[1]. These basic constituent molecules are absorbed into the bloodstream and transported to different tissues and cells where they will be metabolised for energy production or synthesis of biomolecules.

Energy metabolism is the general process through which cells receive the energy they need to perform all their vital functions such as growing, multiplying, synthesising proteins and replicating genetic material, among others. Adenosine triphosphate (ATP) is the main source of cellular energy and is the result of the coupling between the oxidation of nutrients and availability of substrates[2]. There are two mechanisms for the synthesis of ATP, the first is substrate-level phosphorylation[3] in which the ATP is synthesised through the transfer of phosphate groups from high-energy compounds to adenosine diphosphate (ADP). This process takes place in the mitochondria through the tricarboxylic acid cycle and cytoplasm during glycolysis. The second and most important mechanism for ATP synthesis is oxidative phosphorylation[4] consisting of ATP synthesis from ADP and inorganic phosphate (Pi). This process is carried out only in the mitochondria and is the mechanism that produces the greatest amount of ATP in most human cells.

Metabolic reactions are processes that function as energy transducers where redox reactions play a key role in the synthesis of ATP[5] in these reactions. The electrons removed from fuel molecules are transferred to two transporting coenzymes, nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide and (FAD), which are converted to their reduced forms, NADH and $FADH_2$. Oxidative phosphorylation depends on the transfer of electrons from NADH or $FADH_2$ to oxygen forming water[6]. Electrons are transported through a group of protein complexes located in the inner mitochondrial membrane. These protein complexes form the electron transport chain and enable the distribu-

tion of free energy between the reduced coenzymes and oxygen as well as a more efficient conservation of energy[7].

Electron transfer between the protein complexes of the electron transport chain is associated with pumping hydrogen protons from the mitochondrial matrix to the intermembrane space of the mitochondria. This pumping action generates a proton motive force, which is the combination of the pH gradient across the inner mitochondrial membrane and transmembrane electrical potential[8]. Together this leads to the synthesis of ATP from ADP and Pi by activation of the ATP synthase.

Energy transmission between reduced coenzymes and oxygen directs the ATP synthesis. This is why it is important to understand the origin of these coenzymes. In aerobic respiration, the products resulting from the degradation of nutrients converge in the main metabolic crossroads, the tricarboxylic acid cycle. In this pathway the acetyl group of acetyl-CoA, which comes primarily from glucose catabolism, fatty acids and amino acids, is oxidised to CO_2 with the concomitant reduction of electron transporting coenzymes (NADH[9] and $FADH_2$[10]) (Fig. 1). This cycle is composed of eight reactions that start with the condensation of acetyl-CoA and oxaloacetate to generate citrate. The remaining seven reactions in the cycle serve to regenerate the oxaloacetate used in the first reaction and also to perform four oxidation reactions in which the energy released is used for the reduction of NAD^+ and FAD to NADH and $FADH_2$ coenzymes[11], which will donate its electrons to oxygen through the protein complexes of the electron transport chain[12]. In addition to the aforementioned processes, during the tricarboxylic acid cycle an ATP molecule[13] is formed directly, which is an example of substrate-level phosphorylation. The cycle of tricarboxylic acids can only be carried out under aerobic conditions[14] because, even though oxygen does not play a role in the cycle, the regeneration of NAD^+ and FAD is carried out in the electron transport chain, which only works in the presence of oxygen as a final electron acceptor[15].

Glycolysis is the metabolic pathway in which a glucose molecule is broken down into a series of enzymatically catalysed reactions giving two pyruvate molecules[16]. During the initial phase of this process, also called the energy expenditure phase, two ATP molecules are reversed, the first to activate glucose and second to activate the fructose 6-phosphate reaction catalysed by phosphofructokinase-1 (PFK-1). Part of the energy derived from the breakdown of ATP remains in the formation of the phosphate-ester bonds of glucose 6-phosphate and fructose-1,6-diphosphate. This process is called activation and its purpose is to make the molecules more reactive to facilitate progress in the pathway[17] (Fig. 2).

In the second phase of glycolysis, also known as the energy pay-off phase, most of the energy obtained from the oxidation of glyceraldehyde 3-phosphate is retained in the 1,3-bisphosphoglycerate phosphate acyl group, which is highly energetic. Subsequently, part of the 1,3-bisphospho-

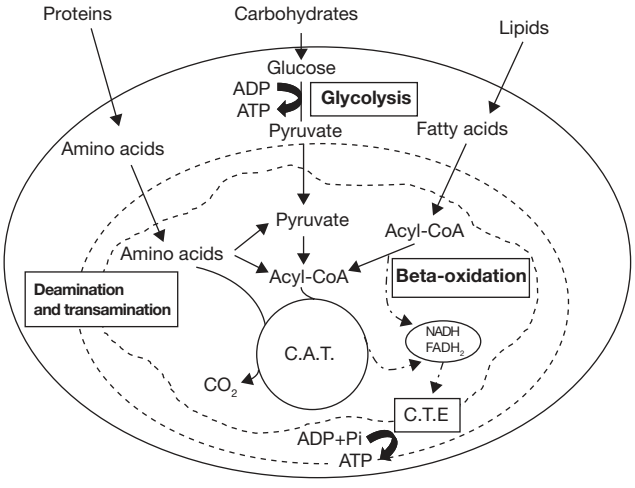

Figure 1 Protein, carbohydrates and lipids degradation result in amino acids, pyruvate and fatty acids, respectively. These molecules converge in the tricarboxylic acid cycle (TAC) within the mitochondria (---) for complete oxidation to CO_2, with concomitant reduction of NAD^+ and FAD to NADH and $FADH_2$. The flow of electrons (—) ranges from β-oxidation and TAC to the electron transport chain (ETC) located in the inner membrane of the mitochondria and where the oxygen functions as final acceptor of these electrons. The electron transport through the protein complexes of the ETC will result in ATP synthesis.

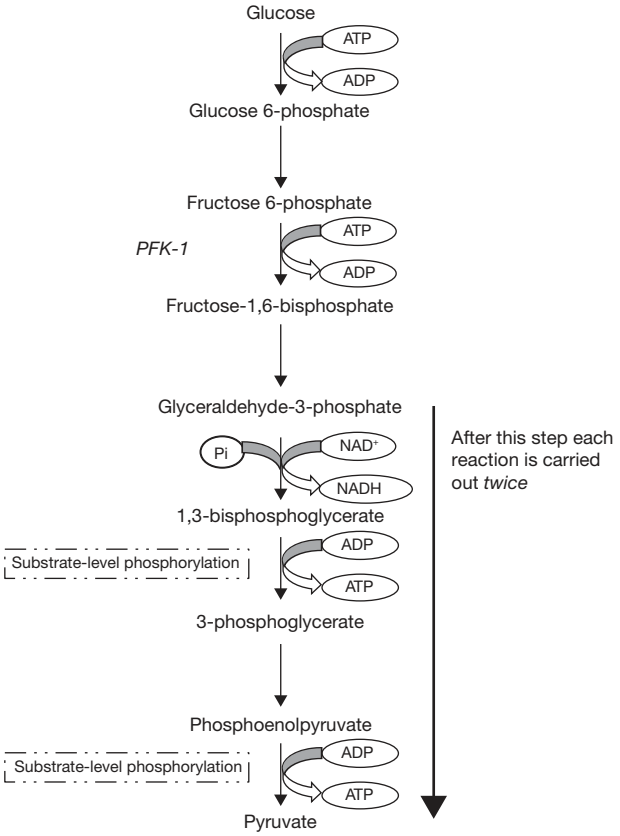

Figure 2 Glucose is catabolised in glycolysis in order to obtain pyruvate, ATP and NADH. In the first stage, called the energy investment phase, the expense of two ATP molecules is observed. In the second stage, called phase energy pay-off phase, there is a gain of four ATP molecules, two NADH molecules and two pyruvate molecules. From the breakdown of fructose 1,6 bisphosphate in two glyceraldehyde-3-phosphate molecules, the reactions are carried out twice.

glycerate energy, released during conversion to 3-phosphoglycerate, is used in the first substrate-level phosphorylation pathway (Fig. 2), resulting in an ATP molecule. The second phosphorylation at a substrate-level occurs during the conversion of phosphoenolpyruvate (PEP) to pyruvate. PEP is a macroergic compound because of its phosphate-ester bond and conversion of PEP to pyruvate is associated with phosphorylation of ADP[18]. For a complete oxidation, molecules of pyruvate generated in glycolysis are transported into the mitochondrial matrix where they are converted to acetyl-CoA in a reaction catalysed by the dehydrogenase pyruvate complex[19] as mentioned above. Acetyl-CoA will be introduced to the tricarboxylic acid cycle.

Proteins undergo a digestion process carried out by different enzymes throughout the digestive tract. Upon digestion they result in different- sized peptides and amino acids[20]. To understand the role of amino acids in energy metabolism, it is important to know that nitrogen is part of the amino acid structure and that this must be removed by specific enzymes so that the amino acids can be metabolically useful[21]. There are at least 20 amino acids, each of which requires a specific degradation pathway[22]. Amino acids undergo two types of basic reactions, transamination and deamination[23]. Transamination reactions are characterised by the existence of aminotransferase enzymes that convert amino acids into their respective alpha ketoacids by transferring the amino group from the amino acid to an alpha-ketoacid[24]. Deamination reactions remove the amino group from the amino acid and convert it to ammonia[25]. In the liver, the oxidative deamination of the glutamate results in the alpha keto glutarate (which is a tricarboxylic acid cycle intermediate[26]) and ammonia, which is converted to urea and excreted[27]. Deamination reactions in other organs form ammonia, which is incorporated into the glutamine to generate glutamate[28], the main transport for amino groups in the blood[29]. All amino acids can be converted to tricarboxylic acid cycle intermediates by deamination and transamination reactions[30] directly or through pyruvate or acetyl-CoA conversion (Fig. 1).

The β-oxidation of fatty acids is a process in which units formed by two carbons are removed progressively from the carboxyl end of the fatty acids[31]. The process is comprised of four reactions and generates acetyl-CoA and acyl-CoA with the simultaneous reduction of FAD by the acyl-CoA enzyme dehydrogenase and the reduction of NAD^+ by the β-hydroxyacyl-CoA dehydrogenase[32] (Fig. 3). The acetyl-CoA obtained as one of the products of this reaction is used in the tricarboxylic acid cycle[31] and the reduced coenzymes will be used in the electron transport chain (Fig. 1).

The aforementioned metabolic processes are strictly regulated[33] and several factors control the use of glucose, fatty acids and amino acids for different cell types. Not all cells have the enzymatic machinery and/or cellular compartments needed to use the three essential macromolecules; for example, erythrocytes lack mitochondria[34], are unable to oxidise fatty acids and amino acids, and only use glucose as an energy source. Even in cells that can use the three substrates, their preference and use may be altered by the physiological state of the cell such as in states of starvation, trauma or stress[35]. Different signals dictate how cells adapt to each situation; these may be hormonal[36], nerve, enzyme[37] and genetic[38] signals. Changes in

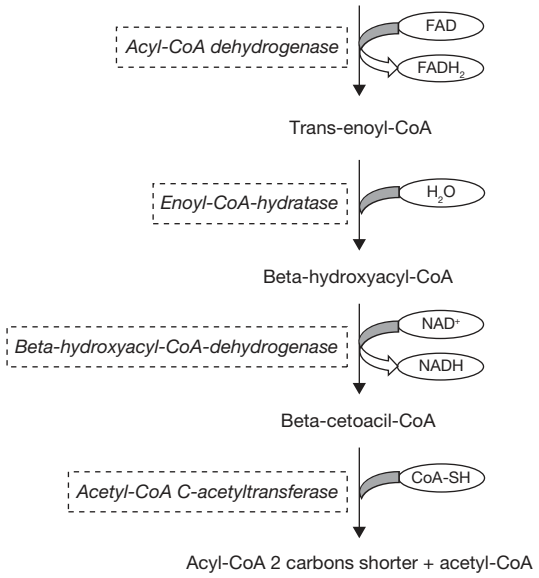

Figure 3 β-oxidation serves as a source of acetyl-CoA to be used in the tricarboxylic acid cycle and the NADH and $FADH_2$, which will be used as electron donors in the electron transport chain.

cell metabolism are regulated by kinase activated by AMP (AMPK). AMPK is an enzyme that detects the energy values available for cellular functions, responding to the decrease of free energy reflected by an increase in the rate of AMP/ATP[39]. Activation in the skeletal muscle and other tissues increases the activity of the ATP-generating processes (fatty acid oxidation, glycolysis, etc.) and inhibits processes that require ATP and can be reduced without compromising cell welfare (synthesis of proteins and triglycerides, etc.)[40]. The decrease in AMPK activity seems to have opposite effects[41].

Genetics in nutrition

Nutritional genomics studies the interactions between nutrition and the human genome and is formed by the combination of nutrigenomics and nutrigenetics[42]. Nutrigenomics studies, in collective terms, the role of nutrients in the regulation of gene expression[43,44]. The main field of study of nutrigenomics are the interactions that take place between genes by modifying transcriptome transcription factors, proteome protein expression and production of metabolites in the metabolome[42]. To better understand nutrigenomics, identifying nutrients is helpful (carbohydrates, proteins, lipids and bioactive compounds) as well as substrates which, by binding to its receptors (also called transcription factors), signal DNA transcription[44]. For example, high cholesterol levels cause a third of all cardiovascular diseases in the world and it is expected that by 2020 the leading causes of death worldwide will be cardiovascular diseases such as heart attacks, angina and atherosclerosis, among others[45]. A 10% reduction in blood cholesterol could reduce up to half the risk of cardiovascular disease[45]. Nutrigenomics seeks to modify the course of the disease through dietary modification.

Nutrigenetics is the study of variations in the DNA sequence in response to specific nutrients, to thus uncover the relationships between individual genes and specific dietary compounds[43,45]. An example of this interaction is that between folate and the *MTHFR* gene (5,10-methylenetetrahydrofolate reductase). The *MTHFR* gene codes an enzyme that catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate; 5-methylenetetrahydrofolate is a cofactor in the re-methylation of homocysteine to methionine. Methionine is an essential amino acid, a main source of sulphur in the body and has important functions in the modulation of protein and cellular activity, regulation of gene expression[45] and production of neurotransmitters[45]. There is a polymorphism in the *MTHFR* gene that produces two types of proteins: the reference (C), which functions properly and the thermolabile version (T), which has lower activity[45]. People who have two copies of the sequence of the reference gene (CC) or one copy of each (CT) seem to have a normal metabolism of folate[45], whereas the population with two copies of the defective thermolabile version (TT) and a folate deficiency accumulates homocysteine and presents a deficiency of methionine, which increases the risk of early cognitive decline and vascular diseases such as hypertension and stroke[45]. Individuals with the thermolabile version (TT) treated with folic acid supplements rapidly metabolise the excess homocysteine restoring the balance of methionine[45].

With the completion of the Human Genome Project in 2003 and the sequencing of the human genome, creating personalised nutritional regimens has become feasible again, based on molecular nutrition, genetic factors and epigenetic factors. The science of nutrition aims to create nutrigenomics profiles based on the sequencing of the genome of each patient using molecular studies that focus on the mechanisms of target genes and on biological markers such as the environment the individual has and is exposed to and its effects on the body, concentration of a specific hormone or the presence of biological substances.

Biochemical tests to identify biomarkers will be used to obtain measurable parameters of the expression of certain genes in stages prior to the onset of a disease, which serve as indices to assess the likelihood of developing various diseases, which might be preventable at an early age with an adequate diet[42].

Nutrigenomics promises to prevent metabolic diseases such as diabetes or lipid disorders. As these conditions have complex and multifactorial origins and a strong genetic factor, they need a comprehensive treatment that bases itself on the genetic polymorphism of each individual, with the purpose being prevention in order to avoid treatment. To achieve the widespread use of genetics in nutrition, obstacles must be overcome including the need to properly understand the molecular mechanisms controlling homeostasis at the biochemical, cellular and organic level, and the ability to visualise patients' genome quickly, reliably and affordably, which will allow health personnel to design appropriate nutritional diets[42-45].

Conflict of interest

The authors declare no conflict of interest.

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