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Short Communication

Metabolic Flexibility for Metabolic Health: Role of Nutrition and Nutraceuticals

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Both lifespan and health span are influenced by nutrition, with nutritional interventions proving to be robust across a wide range of species. However, mechanisms by which nutrients and nutritional status may affect health span are not fully understood. Both health span and life span are closely linked to metabolic health and this condition mainly depends on metabolic flexibility. Metabolic flexibility is a term coined by Kelley et al. [1], and is conceptually defined as the ability to efficiently adapt metabolism by substrate sensing, trafficking, storage, and utilization, in response to availability and requirement of nutrients as well as by physical activity. In good health conditions, metabolic flexibility, i.e. metabolic plasticity, is essential to maintain energy homeostasis. As example, skeletal muscle of lean or physically active individuals showed a remarkable ability to adapt fuel preference to nutrient supply and was therefore designated as metabolically flexible. Upon consumption of a high-fat diet, lean subjects were able to increase Fatty Acid Oxidation (FAO) at the expense of glucose, whereas obese individuals were not [2]. Lean or physically active individuals also showed an increased expression of genes involved in fatty acid transport and oxidation compared with little or no change in their obese counterparts [3]. The ability to shift fuel source oxidation from carbohydrates to fats is generally related to metabolic health. Studies on mice showed that metabolic flexibility correlates with a healthy Respiratory Exchange Ratio (RER) resulting from the circadian shift between carbohydrate (value of 1.0) to lipid metabolism (value of 0.7) [4]. Mitochondrial dysfunction lead to a cellular shift toward a glycolytic phenotype, which is intimately linked, to a sedentary lifestyle and senescence. Metabolic flexibility is negatively correlated with aging and is disrupted in some pathological conditions, as in ectopic lipid accumulation which is causally linked to insulin resistance, in the context of obesity and metabolic syndrome [5]. Insulin-resistant obese patients manifest a lesser reliance on fatty acid oxidation compared with lean individuals and do not show increased fatty acid oxidation after fasting or reduced fatty acid oxidation after insulin infusion. Because of their inadequate responses to metabolic challenges, these patients are named "metabolically inflexible" [6]. Metabolic inflexibility is a hallmark of many age-related metabolic diseases but also plays a central role in, for instance, cancer and immune metabolism diseases. Conversely, metabolic flexibility is enhanced by lifestyle interventions including exercise training and controlled Calorie Restriction (CR), which are able to reduce obesity, visceral fat deposit and ectopic lipid accumulation [7]. Exercise, in particular, is a principal preventive strategy to improve metabolic flexibility at all ages and prolong healthy aging [8]. These interventions are able to favor mitochondrial function and improve substrate switching and metabolic health. Molecular and signaling pathways drive metabolic flexibility and often serve as metabolic sensors able to respond to different nutritional conditions or exercise. Pathways involved in metabolic flexibility are those mediated by Mammalian Target of Rapamycin (mTOR) and insulin/insulin-like Growth Factor-1 (IGF-1) which are generally stimulated in fed conditions, and by pathways activated by fasting, involving AMP-Activated Protein Kinase (AMPK), NAD^+-dependent sirtuin (SIRT) deacetylases and PPARγ coactivator 1-α (PGC1α) (see ref 11 for a review). Main sensor of low energy levels is AMPK, which mediates one of the "chief" step of metabolic flexibility represented by "glucose-fatty acid cycle" [9]. This step states that high glucose availability suppresses oxidation of fatty acids and vice versa [5]. In particular, during CR, the rise in AMP/ATP activates AMPK, which inhibits Acetyl-Coenzyme a Carboxylase (ACC), thus stimulating fatty acid uptake by the mitochondria via Carnitine-Palmitoyl Transferase 1 (CPT-1) and increasing FAO. In parallel, during CR, the increase of NAD^+ concentrations stimulates nuclear/cytoplasmic-localized SIRT1 and mitochondrial SIRT3 activity and leads to protein deacetylation and improved mitochondrial function. There is a reciprocal interplay between AMPK and SIRT, which contributes to metabolic adaptations during fasting conditions [10] as well as during aerobic exercise. This interplay leads to increased transcription, translation, and activity of the transcriptional coactivator PGC1α which is a main mediator of mitochondrial biogenesis and regulator of exercise-induced adaptations in the capacity of oxidative phosphorylation in skeletal muscle [11,12]. In the last years many food-derived natural compounds, also named nutraceuticals have been investigated in relation to their effects on most of the nutrient sensing pathways activated by CR and physical exercise, and potentially related to longevity and health span [13-15]. However, in our opinion there are only few controlled studies on the effects of single dietary components on biochemical pathways and enzymes able to improve metabolic flexibility. As example, one relevant aspect might be related to prevention of ectopic intracellular lipid accumulation. At this purpose biochemical studies on nutritional modulation of enzymes involved in substrate switching such as Pyruvate Dehydrogenase (PDH) and PDH kinase 4 (PDK4) as well as in pathways leading to cytosolic acetyl-coenzyme A (acetyl-CoA) accumulation could be of great interest. Nucleo-cytosolic acetyl-CoA has emerged as a central signaling node used to coordinate metabolic flexibility in response to a changing of nutritional status. In fact, cells utilize acetyl-CoA levels to integrate nutrient status with energy levels to ensure the proper funneling of substrate toward energy production

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or storage. In cytosol acetyl-CoA is generated by the enzyme ATP Citrate Lyase (ACLY) which catalyzes the cleavage of citrate to oxaloacetate and acetyl-CoA, a critical reaction linking cellular glucose metabolism and lipogenesis. Accumulation of acetyl-CoA in cytosol also favors protein acetylation and inhibits autophagy with a negative impact for metabolic health. Recently the involvement of ACLY in the progression and development of various chronic diseases has been comprehensively described [16]. Preclinical studies and clinical randomized trials showed the importance of ACLY activity in metabolism, supporting its inhibition as a potential therapeutic approach to treat atherosclerotic cardiovascular disease, nonalcoholic fatty liver disease and other metabolic disorders [17]. Among nutraceuticals Garcinia cambogia, which contains Hydroxycitric Acid (HCA) has been reported to play a role in inhibiting the enzyme ACLY [14]. However, the safety of this plant extract has been highly questioned [18]. In our opinion further studies are needed that address more exhaustive role of nutrition and nutraceuticals on pathways involved in regulation of metabolic flexibility as well as on any other process affecting cellular metabolic health.

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