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Micronutrient–gene interactions related to inflammatory/immune response and antioxidant activity in ageing and inflammation. A systematic review

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ABSTRACT

Recent longitudinal studies in dietary daily intake in human centenarians have shown that a satisfactory content of some micronutrients within the cells maintain several immune functions, a low grade of inflammation and preserve antioxidant activity. Micronutrients (zinc, copper, selenium) play a pivotal role in maintaining and reinforcing the performances of the immune and antioxidant systems as well as in affecting the complex network of the genes (nutrigenomic) with anti- and pro-inflammatory tasks. Genes of pro- and anti-inflammatory cytokines and some key regulators of trace elements homeostasis, such as Metallothioneins (MT), are involved in the susceptibility to major geriatric disease/disorders. Moreover, the genetic inter-individual variability may affect the nutrients' absorption (nutrigenetic) with altered effects on inflammatory/immune response and antioxidant activity. The interaction between genetic factors and micronutrients (nutrigenomic and nutrigenetic approaches) may influence ageing and longevity because the micronutrients may become also toxic. This review reports the micronutrient–gene interactions in ageing and their impact on the healthy state with a focus on the method of protein–metal speciation analysis. The association between micronutrient–gene interactions and the protein–metal speciation analysis can give a complete picture for a personalized nutrient supplementation or chelation in order to reach healthy ageing and longevity.

1. Introduction

Ageing is an inevitable biological process that is accompanied by gradual and spontaneous biochemical and physiological changes including increased susceptibility to diseases, adverse environmental conditions and loss of mobility and agility. Alterations in the neuroendocrine–immune interactions as well as in the antioxidant capacity also play a fundamental role in ageing. The inability of an organism in coping with these changes may lead to the onset of some degenerative age-related diseases. As a result, the "remodelling theory of ageing" has been proposed (Paolisso et al., 2000). Various nutritional factors are directly linked with these phenomena as for instance in restoring neuroendocrine-immune network, the metabolic harmony and the capacity to respond to oxidative stress (Meydani, 2001). Approximately, 40 micronutrients (vitamins, essential minerals and other compounds required in small amount for normal metabolism) have been reported as essential components of the diet (Alvarez Leon et al., 2006). The dietary intake of essential micronutrients is often inadequate in the elderly due to several causes (Ames, 2006). First of all, the poor socio-economic condition present in a large part of old people may lead to a consumption of inexpensive foods deficient in micronutrients, such as carbohydrates (Kant, 2000). The gap is worsened by loss of appetite, lack of teeth, intestinal malabsorption and decreased requirement of energy that lead, as a final result, to frailty, disability and mortality (Semba et al., 2006).

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Some authors have reported that the deficiency of micronutrients in ageing is strictly related to global impairments of the immune functions, metabolic harmony and antioxidant defence by external noxae with subsequent onset of age-related diseases (Failla, 2003). Indeed, many micronutrients contribute directly or indirectly to the biological activity of some antioxidant enzymes (superoxide dismutase, SOD; glutathione peroxidase, GPx; catalase), to the efficiency of the immune system, to the metabolic harmony, to keep under control the inflammatory state and, as such, to maintain the correct functioning of many body homeostatic mechanisms with subsequent achievement of the longevity (Mocchegiani et al., 2008c) and, finally, to the maintenance of metabolic function especially in preventing mitochondrial decay (Ames, 2006). In this last context, feeding studies in old rats have shown that mitochondrial metabolites and antioxidants protect the neuronal cells from neurotoxin- and oxidant-induced toxicity and oxidative damage but especially they delay the normal senescence of human diploid fibroblasts and the oxidant-induced senescence (Liu et al., 2002). With advancing age, an increased oxidative damage to proteins and lipid membranes, particularly in mitochondria, causes a deformation of the structure of enzymes, with a consequent decrease of enzyme activity as well as substrate binding affinity for their substrates. An increased level of substrate by micronutrients restores the speed of the reaction as well as mitochondrial function, thus delaying mitochondrial decay and ageing (Liu et al., 2002). In contrast, recent longitudinal studies in dietary daily intake in human nonagenarians/centenarians (successful ageing) have shown that an adequate consumption of micronutrients as well as a satisfactory content of some trace elements within the cells lead to good performances in several immune functions, to metabolic compensation and preservation of the antioxidant activity (Chernoff, 2001). In this context, polyunsaturated fatty acids, highly sensitive to reactive oxygen species (ROS), decrease in liver mitochondria from human centenarians, a feature that could represent a protective mechanism to favour longevity (Anantharaju et al., 2002). Therefore, nutritional factors can play a pivotal role for healthy ageing and longevity. However, the effects of the nutrients are strongly influenced by genetic factors, in particular by genes involved in inflammatory/immune response and antioxidant activity. The genes of IL-1, IL-6, TNF-α pro-inflammatory cytokines, of IL-10 anti-inflammatory cytokine, of HSP70 chaperone and the regulators of trace elements homeostasis, Metallothioneins (MT), seem particularly relevant because they are involved in the susceptibility to major geriatric disorders, such as diabetes, osteoporosis, osteoarthritis, dementia, cardiovascular diseases (CVD) and infections (Franceschi, 2007; Mocchegiani et al., 2006a,b). Indeed, up to 25% of the variation in human lifespan is heritable (Mitchell et al., 2001); the rest is due to environmental and life style factors, which impact on the ageing process contributing, as such, to a large inter-individual variability. Therefore, current problems are to understand how the interaction between genetic factors and nutrients may influence the ageing process and longevity in view of the high impact of gene expression, protein production and epigenetic mechanisms in regulating the life span (Mattson, 2008). Some dietary patterns fave shown very different impact on long-term disease occurrence and survival. In this context, a strong evidence for a beneficial effect of higher compliance to the "Mediterranean" dietary pattern on causes of death, including those ones by CVD and cancer, has been reported (Mitrou et al., 2007). Anyway, it is also commonly accepted that the complex interactions of multiple polymorphisms play a key role in how individuals may respond to dietary interventions (nutrigenetic approach) or how some nutrients may affect the gene expressions (nutrigenomic approach) (Darton-Hill et al., 2004). For each nutrient, there is a window of intake between the Recommended Dietary Allowance (RDA), (defined as the dietary intake sufficient to meet the requirement of 97% of healthy individuals in a particular stage of the life and gender group), and the tolerable upper limit (UL), which is the highest nutrient intake that can be achieved without incurring risk of adverse health effects for most individuals in the general population (Stover, 2006). Although worldwide research on genetic variation that requires a different RDA or UL is still in progress, several genes and alleles have been suggested to affect nutrient utilizations (Mocchegiani et al., 2012a). During this last decade, it has been recognized the pivotal role played by some micronutrients (zinc, copper, selenium) in maintaining the correct functioning of many body homeostatic mechanisms with subsequent achievement of longevity (Mocchegiani et al., 2008c). Taking into account the influence of these nutrients in many genes involved in inflammatory/immune response and antioxidant activity (Mocchegiani et al., 2012a), the micronutrient–gene interactions are fundamental to escape many age-related diseases and to achieve healthy longevity. We report the specific role played by the most relevant micronutrient–gene interactions in ageing with a focus on the precise determination of their specific transporter proteins, by means of the method of protein–metal speciation analysis (Malavolta et al., 2012). As such, the association between micronutrient–gene interactions and protein–metal speciation analysis may give a complete picture of the personalized micronutrient supplementation or chelation (in the case of nutrient overload) in order to reach healthy ageing and longevity.

2. Micronutrients, immune efficiency, antioxidant response, ageing

2.1. Zinc, immunity, antioxidant response and ageing

Zinc (Zn) is an essential micronutrient required for many cellular processes, including the correct function of the immune system and antioxidant response. Zinc homeostasis and signaling, acting as a "second messenger", are both critical in immune activation and against oxidative stress (Powell, 2000; Chasapis et al., 2012). An imbalance in zinc homeostasis is associated with the development of chronic diseases. Zinc deficiency (genetic or nutritional) causes significant impairment in both adaptive and innate immune responses, promotes systemic inflammation and impaired antioxidant defence (Fraker and King, 2004; Chasapis et al., 2012; Wong and Ho, 2012). A plethora of data indicates that a significant portion of the aged population has inadequate zinc intake with a decline in zinc state with advancing age (Mocchegiani et al., 2013b).

Zinc deficiency in the elderly seems to be due to many factors related to the ageing process, such as inadequate mastication and psychosocial factors leading to a reduction of zinc-rich foods (bovine, ovine and pork meat, hard cheese, nuts, cocoa, eggs) intake, altered intestinal absorption, alteration in zinc transporter proteins, drug interactions and competition between zinc and other bivalent minerals (copper, iron, calcium and selenium) or vitamins (Mocchegiani et al., 2013b). The intracellular zinc homeostasis is regulated by buffering Metallothioneins (MT), i.e. the major storage proteins for zinc, and by zinc transporters (ZnT and ZIP families) for cellular zinc efflux and influx, respectively, that mediate the intracellular zinc signaling. The main reasons why intracellular zinc levels are compromised during ageing have been traced to the increased expression of MT (Mocchegiani et al., 2007) and to the defective zinc transporters, which could result in increased sequestration of zinc and low intracellular free zinc content (Mocchegiani et al., 2013b). Specifically, MT preferentially bind zinc but in ageing they are unable to release zinc in order to be used by other Zn-dependent antioxidant enzymes and proteins related to the efficiency of the immune system. Indeed, zinc, acting

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