Trace elements are key regulators of metabolic and physiological pathways known to be altered during the ageing process and therefore have the capacity to modulate the rate of biological ageing. Optimal intake is required to maintain homeostasis and to increase cell protection. Deficiencies are associated with specific illnesses. However, the contribution of commonly observed life-long sub-optimal intakes of trace elements to the development and severity of age-related chronic diseases is less appreciated. Additionally, reduce intake of several trace elements has been shown to be particularly challenging for elderly people. This review will use selenium as an example to illustrate how a trace element can influence ageing and how the Omics technologies could help to study the effect of trace elements on the ageing process. Although transcriptomics and proteomics approaches in animal models have so far enabled us to identify downstream targets of trace elements in pathways related to age-related diseases processes, future approaches of combining nutrigenomics with longevity studies in humans will help us to identify mechanisms whereby trace elements affect the ageing process.

Evidence is building up showing that caloric restriction, without malnutrition, extends lifespan in species ranging from yeast to non-human primates [3], but it appears, on the contrary, that inadequate/sub-optimal intake of micronutrients contribute to the development of chronic diseases. In his “Triage theory”, B. Ames suggested that this could reflect the need for an organism to re-allocate micronutrients according to triage priorities to favour short-term survival over long-term wellbeing [4,5]. The consequences of this re-allocation may remain unnoticed in the day-to-day experience but are likely to show up late in life as cancers, Alzheimer’s disease, Parkinson’s disease, diabetes and cardiovascular diseases.

On the other hand, the beneficial effects of caloric restriction are associated with alterations in metabolism, particularly the insulin/insulin-like growth factor 1 (IGF-1) pathways, which could reflect an evolution mechanism to ensure survival of a species during period of food shortage [3]. Many genetic manipulations affecting nutrient-sensing pathways including the insulin and mTOR (mammalian target of rapamycin) pathways mimic the effect of caloric restriction on lifespan in yeast, worm, flies and mice and support this hypothesis [3].

This review will firstly discuss in general terms how trace elements affect ageing and then use Selenium (Se) as an example to illustrate how trace elements influence the ageing process. Furthermore, the review will also illustrate how the so-called “Omics technologies” can be used to unravel the modes of action of trace elements and to identify biomarkers to define the optimal intake for health at the molecular level.
How do trace elements affect the ageing process?

Trace elements act on processes known to be altered during ageing such as the immune function (Se, Zn, Cu) [6–10], oxidative stress (Zn, Se, Cu, Fe, Mn) [11], insulin sensitivity (Se, Zn) [12,13] and cognitive function (Se) [14,15].

Trace elements can act on the ageing process, and therefore modify the rate of biological ageing, at three different levels: (1) they modulate oxidative damage and DNA repair capacity; (2) trace elements intake is reduced in elderly people and (3) life-long/long-term inadequate intake of trace elements may increase the risk for age-related diseases (see Fig. 1).

The capacity of trace elements (such as Se, Zn, Mn) to reduce oxidative damage or enhance repair capacity relies on capacita to act as essential co-factors for anti-oxidant enzymes such as Cu, Zn-superoxide dismutase, Mn-superoxide dismutase, catalase (Cu, Fe), and the different types of glutathione peroxidases (Se). These enzymes are crucial to limit oxidation of lipids, nucleic acids or proteins occurring in chronic diseases (such as cancers and cardiovascular disorders) and in ageing. Additionally, zinc (Zn) is active in more than 300 proteins and over 100 DNA-binding proteins, including the tumour suppressor protein p53, a Zn-binding transcription factor acting as a key regulator of cell growth and survival upon various forms of cellular stress. p53 is mutated in half of human tumours and its activity is tightly regulated by metals and redox mechanisms. Disruption of Zn-binding from the p53 structure, for example by toxic metals such as cadmium, alters its conformation and inactivates its DNA-binding capacity, resulting in a loss of the capacity of the tumour suppressor to respond to DNA damage [16–18]. Additionally Leccia et al. observed that Zn protects human skin fibroblast from UVA-induced DNA damage and apoptosis [19]. Other studies have shown that Se could also limit DNA damage. For example, using a canine model, Waters and collaborators showed that the relationship between Se status and the extent of DNA damage within the prostate followed a U-shaped and that Se concentrations associated with the lowest level of DNA damage in the aging dog prostate remarkably parallels the Se concentration in men that minimizes prostate cancer risk [20].

In addition, some trace elements have been shown to increase repair capacity. For instance, in human leukocytes, bleomycin-induced DNA damage is repaired more efficiently in the presence of Se, as selenomethionine [21]. Similarly, Seo and collaborators showed that Se, in the form of selenomethionine, could induce a DNA repair response in normal human fibroblasts in vitro, and protects cells from DNA damage [22].

On the other hand, malnutrition, interaction with medication, reduced digestion and absorption are common in older people and contribute to reduced intake of some trace elements (see Fig. 1).

Several trace elements pose particular challenges regarding intake in older adults, including iron (Fe), Zn and Se. These elements are vital to enzymatic activity, free radical scavenging, and protein functions. However, there is a lack of data available on the actual requirements for these elements in the elderly population [23]. Indeed, if total energy intake declines with age, it seems that, on the contrary, requirements for many nutrients increase to maintain organ function [24].

Finally, life-long low or inadequate intake of trace elements can impact on the ageing process and has been linked to disease development in the older age. The health implications of long term inadequacy of trace element intake have not yet been thoroughly examined. Zn deficiency, for instance, has been suggested to contribute to oesophageal cancer in humans, and was shown to induce oesophageal tumours in rats exposed to a single low dose of a nitrosamine [25,26].

Evidence suggests that trace elements affect the ageing mechanism, however the link between the ageing process and trace elements remains often unclear or at least indirect. New perspectives are emerging with the so-called “Omics technologies” (genomics, transcriptomics, proteomics, metabolomics) to further elucidate the role of trace elements on the ageing process. As mentioned above, ageing is a complex process, involving the accumulation of changes in gene expression, protein modifications and influenced by genetic components. Applying the “Omics” approach, which allow the translation of genetic information into biological function, and the construction of networks integrating the different levels of the biological information flow from gene-to-function, could contribute to a better understanding of the role of trace elements in the ageing process. In particular, this approach could help to identify and develop good biomarkers of the ageing process and of trace elements to monitor the effects of trace elements on ageing.

Selenium (Se) will be used here as an example to illustrate how nutrigenomics can help to unravel the effects of trace elements on ageing, because (a) a strong body of evidence now supports a role for Se and Se status in the ageing process and associated diseases and (b) several biomarkers of Se are available, and some of them having been associated with age-related diseases.

Selenium, ageing and age-related diseases

Se is a trace element essential for human health. It is a key component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defence systems, and immune function. The biological functions of Se are exerted by selenoproteins in which Se is incorporated in the form of the amino acid selenocysteine. In humans, 25 genes coding for selenoproteins have been identified [27] and include several glutathione peroxidases (GPx), the plasma Se-transport protein selenoprotein P (SePP), thioredoxin reductases, and iodothyronine deiodinases.

The fundamental roles of Se in the healthy immune response, the regulation of inflammatory pathways, the protection against some forms of cancers and the reduction of cardiovascular disease mortality suggest that assessment of Se requirement has the potential to influence the prevalence of chronic diseases [28,29]. However, as the geographical distribution of Se in soil is highly variable, availability of Se to populations differs greatly between countries. Levels are notably low in parts of China and New Zealand and sub-optimal in most European countries and Africa [30,31]. Long term implications of low Se intake are not fully understood but growing evidence from the literature show an increased mortality and prevalence of chronic diseases correlated with low intake of Se. Additionally, as for many other micronutrients, Se inadequacy is common in older people. In particular, it was reported that Se intake is reduced in elderly people and that Se status declines in an age-dependent manner [32]. Similar results were observed in men who took part in the National Health and Nutrition Examination Survey (NHANES III) carried out in the United States (http://www.ars.usda.gov/ba/bhnrc/fsrg). The observation that Se inadequacy is common in older people suggests that requirements may increase with age.

Se and longevity

The Epidemiology of Vascular Ageing (EVA) study recently established a relationship between Se status and longevity. This 9-year longitudinal study, involving 1389 free-living participants aged 59–71 year, was carried out on a French elderly population. The authors observed a significantly higher mortality in people with low plasma Se at baseline and an association between plasma Se concentration and mortality by cancer, suggesting that inadequate Se intake may increase the vulnerability to diseases [33]. Additionally, the EVA study revealed that decrease in Se status over time
Fig. 1. Effects of trace elements on the ageing process. The ageing process corresponds to the accumulation of cellular damage in response to stress, lifestyle and environmental factors over time and lead ultimately to age-related disease and death. Trace elements, as part of a healthy diet, have the potential to decrease the rate of biological ageing by limiting damage and increasing repair capacity. On the other hand, inadequate intake of trace elements over several decades has been shown to contribute to the accumulation of damage and development of age-related diseases. Additionally, in elderly people, the risk of nutritional factors increases and counterbalances the protective influence of trace element. The weight of these different factors over time is schematised by triangles.

was associated with cognitive decline, as evaluated by neuropsychologic test [14], and dysglycemia in French elderly males [12] which are both commonly observed during ageing.

Supporting the findings from the EVA study, a similar effect of Se on the reduction of all-cause and cancer mortality was observed in the 12-year follow NHANES III study carried out on 13,887 adults in the US population [34]. Additionally, the Women’s Health and Aging Studies (WHAS) I and II, two complementary, population-based studies designed to evaluate the causes and course of physical disability in older women living in the community, showed that low serum Se and total carotenoid concentrations are associated with an increased risk of death among older women, in the US population [35].

However a limitation of these studies is that they do not allow determining whether low Se is a cause or a consequence of the disease or ageing process. In particular, it is known that in inflammatory conditions, expression of selenoproteins, such as the plasma selenoprotein P, is inhibited [36].

Se and prostate cancer

In addition to its role on longevity, Se and Se supplementation have been suggested to protect against the development of some cancers. A particularly interesting example is the case of prostate cancer. Originally the Nutrition Cancer Prevention trial (NPC), carried out in the USA, designed to evaluate whether Se supplementation of 200 µg/d Se in 1312 subjects could reduce the risk of basal and squamous (nonmelanoma) skin cancers, showed no protective effect against these skin cancers but reported an overall significant reduction in total cancer mortality and incidence for lung, colorectal, and prostate cancers. Approximately 60 percent fewer new cases of prostate cancer were observed among men who had taken Se for 6.5 years than among men who took the placebo [37,38]. However a key observation from the NPC study was that beneficial effects of Se supplementation were greater for male participants with low baseline Se status (<106 µg/L). This study led to the design of a similar, but much larger, intervention trial, called the Se and vitamin E Cancer Prevention Trial (SELECT study), carried out on 35,533 US men. Like the NPC, the SELECT study was a double-randomized placebo-controlled study in which people were given 200 µg/d Se or 400 IU/d vitamin E or a combination [200 µg/d Se + 400 IU/d vitamin E] or placebo. However, the men recruited had already a high mean baseline Se status (136 µg/L) contrary to the ones that took part in the NPC study. The study did not show any significant reduction of prostate cancer incidence but an adverse, though non-significant, increase in type 2 diabetes mellitus incidence in the Se supplemented group [39]. A similar effect on diabetes incidence was as well recently reported from the NPC study [40].

The Physicians Health Study (PHS), carried out more recently as a nested case–control study (including 1286 cases and 1267 controls) in the US population, may reconcile partially the inconsistent results on prostate cancer risk from these two randomized trials. The authors found the association between prediagnostic Se levels with prostate cancer risk and progression was significantly modified by a genetic variation on the 15 kDa selenoprotein (SEP15) gene, with carriers of the G allele with high Se status having a significant lower risk of prostate cancer mortality [41].

Similarly, we recently observed, in the EPIC-Heidelberg nested case–control cohort involving 248 prostate cancer cases and 492 matched controls, a significant association between serum Se concentration and prostate cancer risk modulated by the genotype for rs1050450 in the GPX1 gene and a significant association between genotype for rs7579 in SEPP1 and prostate cancer risk [42].

These studies demonstrated that genetic components can influence Se requirements and should therefore impact on the design of
future intervention studies. In particular, to avoid adverse effects of Se, there is a need to define good biomarkers of Se status are required as well as Se intake required to optimize these biomarkers. These results revealed as well that the relationship between prostate cancer and Se is not yet completely elucidated and that indiscriminate use of Se supplements may not be advised because of differences in baseline Se and possible genetic influences. Additionally, these studies suggest a particular role of GPx1 and SeP15 in the healthy function of the prostate tissue or in the disease development.

Role of selenoproteins in human health and diseases

It is believed that most beneficial effect of Se occurs through the function of selenoproteins, designating them as prime candidates for studying the molecular mechanisms of action of Se in disease prevention. Mechanistic approaches revealed their implication in multiple pathways crucial to disease development prevention such as for example antioxidant defence systems, reduction of DNA damage and increase in DNA repair, immune function, calcium homeostasis, protein folding/misfolding, protection against lipid peroxidation [21,22,28,43,44].

Epidemiological data from association studies linking genetic variations in selenoprotein genes to disease risk have shown that single nucleotide polymorphisms (SNPs), which altered the expression or function of one selenoprotein, can increase the risk of multiple disorders [45].

In the case-control study carried out on a Czech population, including 832 colorectal cancer cases and 705 controls, we reported that genotypes for three SNPs in the selenoprotein P (SEPP1), in GPx4 and in the selenoprotein S (SELS) genes were associated with increased colorectal cancer risk [46]. Interestingly these polymorphisms induce a base change in regions of the gene that regulate the level of the synthesis of the corresponding protein [47–49]. Additionally, we found that the risk of colorectal cancer due to presence of the SNPs in GPX4, SEPP1 and SELS genes was modulated by genetic interactions with SNPs in other selenoprotein genes and those genetic interactions were overlapping with the biological interactions of the corresponding proteins [46].

In particular, interactions between SNPs in the SEPP1 gene and other selenoproteins reflect the key role played by selenoprotein P in Se transport and delivery to organs [50]. When dietary levels of Se are low, SNPs combinations could modulate Se bioavailability altering and selenoprotein levels and activity in specific organs. As a result, these SNPs combinations could impact on the balance between inflammation, cytokine production, redox status and oxidative damage, favouring the switch towards cancer.

This effect of SNPs in the SEPP1 gene on Se bioavailability is supported by findings from the SelGen intervention trial in which we showed the effects of SNPs on the protein function. As mentioned above, SEPP is the major selenoprotein in the plasma and contains about 65% of total plasma Se [51]. The protein is synthesized in the liver from dietary Se and secreted in the plasma where it transports Se to other organs to deliver Se for the synthesis of downstream selenoproteins. In humans, the protein contains 10 selenocysteines and exists in the plasma as two different isoforms of respectively 50 and 60 kDa molecular mass respectively [52]. The Se/protein ratio of the 60-kDa isoform is higher than that of the 50-kDa form [52]. To date, SEPP is the best biomarker of active Se [50].

In the SelGen study, 75 healthy volunteers were prospectively genotyped for 2 SNPs in the SEPP1 gene (rs3877899 and rs7579) and supplemented with 100 μg/d sodium selenite. We showed that genotypes for these two polymorphisms affected the proportion of plasma isoforms of SEPP protein, the synthesis of downstream selenoproteins in blood cells and plasma of volunteers [48,53]. Genetic variations in the SEPP1 gene may affect the capacity of the protein to deliver Se for synthesis of downstream selenoproteins, thus influencing the cellular response to oxidative stress.

Selenium targets age-related disease pathways

Transcriptomics and proteomics approaches have been used to further understand the phenotypic consequences of variations in Se status and unveiled Se targeted pathways. Interestingly, many of the observed changes in expression occur in pathways which are proposed to be in the ageing process and age-related diseases.

In the colon of mice fed on a diet marginally deficient in Se, comparable to variations observed in human dietary intakes, the mTOR and insulin signalling pathways as well as the protein biosynthesis, inflammatory response and Wnt signalling pathways were the most affected by reduction in Se availability [54]. As described above, mutants in the insulin and mTOR pathways extend lifespan in yeast, worm, flies and mice [3] and modulation of expression of cancer-related pathways (such as Wnt, mTOR, TGF-pathways) may contribute to the higher susceptibility to colorectal cancer in Se deficient conditions reported in some studies [55–57]. Interestingly similar effects on the protein biosynthetic pathway were observed in healthy human volunteers from the SelGen study, in response to Se supplementation [58].

Supplementation of rats with Se, as sodium selenite, altered levels of plasma proteins haptoglobin, apolipoprotein E, transthyretin and fibrinogen [59]. These proteins have been linked to age-related diseases including neurological and cardiovascular disorders [60–62]. However, these changes were detected at supra-nutritional doses of Se. Further investigations using nutritionally relevant doses of Se compatible with variations commonly observed under physiological conditions in the human diet are now required to identify potential novel biomarkers influenced by Se status.

These approaches provide new perspectives to study the role of Se on the ageing process and age-associated diseases as they show that Se can modulate the expression of potential biomarkers of ageing. These molecular targets and pathways could be used to further study the role of Se on ageing.

Conclusions

Trace elements play a crucial role in metabolic functions which are altered during the ageing process. The relationship between ageing and trace elements is complex: (a) trace elements can decrease damage and increase repair, (b) intake of trace elements is reduced in older people and (c) incidence of age-related diseases may be increased by life-long inadequate intake of trace elements.

Epidemiological data have helped to clarify the existence of a link between ageing and some trace elements but failed to identify whether the observed changes were a cause or a consequence of the disease/ageing process. Association studies between polymorphisms in genes related to a specific trace element and disease risk have suggested a role of some factors in the normal function of tissues/disease development and could help to identify individuals at high risk of developing age-associated diseases or disabilities.

In the case of Se, its role on the ageing process and prevention of age-related diseases depends upon a complex combination of Se status, Se bioavailability (reflecting the capacity of selenoprotein P to deliver Se to organs), genetic variations in selenoprotein genes, and the regulation of downstream metabolic pathways involved in the ageing process. The use of dietary intervention to prevent the development of chronic diseases has to be approached with caution to avoid potentially harmful effects of Se supplementation.
To conclude, biomarkers of trace elements could help to (a) understand influence of trace elements on metabolic pathways, (b) identify cause/effect relationships between genetic factors, trace elements and other environmental factors, and the main chronic diseases and (c) refine requirements for sub-group populations.

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