NUTRITIONAL ZINC, OXIDATIVE STRESS AND IMMUNOSENESCENCE: BIOCHEMICAL, GENETIC AND LYFE STYLE IMPLICATIONS FOR HEALTHY AGEING.

ZINCAGE PROJECT
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www.zincage.org

Summary
As we age, our bodies become less able to fight disease. Zinc is a key dietary mineral that seems to be connected with this process. Scientists know zinc levels in the body decline with age, and that supplementing the diet of the elderly with zinc can have a positive impact on cellular defects associated with age. There is a potential to improve the health of Europe's rapidly ageing population with simple, cheap zinc tablets. However, too much zinc can be toxic, and certain groups of people may have adequate zinc even in old age. A three-year Specific Targeted Research Project called ZINCAGE is studying the behaviour of zinc and its related physiology in the immune cells of Europe's elderly, with a view to generating advice on who could really benefit from zinc supplementation.

Scheme of the Workplan and ZINCAGE objectives
The project ZINCAGE (composed by n. 17 Partners from different European Countries) foresees the study of the zinc metabolism in order to reach healthy ageing. For this purpose, different approaches will be considered at genetic, biochemical, molecular and cellular levels with a final target on the efficiency of the immune system. The loss of this trace element provokes a general derangement of systems with subsequent weakness of the old organism to respond to oxidative stress induced by external damaging agents allowing the appearance of age-related degenerative diseases. However, the loss of zinc is not equal in all old individuals at, at the same time, the zinc deficiency is strictly correlated to free zinc ion bioavailability. Indeed, it may occur that some individuals are "high responders" to oxidative stress despite the content of zinc into the circulation is low. It depends by some stress related-proteins involved in the distribution and in the metabolism of zinc ions. The correct functions of these proteins lead to a satisfactory zinc ion bioavailability with subsequent good functioning of the immune system. This is the case in transient stress as it may occur in young-adult age and with a great surprising in successful ageing (nonagenarian/centenarian subjects). Therefore, the zinc-dependent stress-related proteins play a pivotal role in zinc metabolism to reach health longevity. Taking into account a different distribution of zinc ion bioavailability between normal ageing and successful ageing, a genetic background of these stress-related proteins might exist leading to a different distribution of zinc ion bioavailability within the ageing population. For this reason, a zinc supplementation is also foreseen in ZINCAGE exclusively in aged people with a defect in zinc metabolism at genetic level. Because of the relevance of zinc in cognitive functions, also these last aspects will be considered in the project before and after zinc supplementation for a complete healthy ageing. This will provide essential knowledge for recommending zinc supplementation levels in different populations in order to avoid zinc toxicity and enhance food safety. Thus, the project ZINCAGE is broken down into six work packages and will be conducted by six work package leaders in collaboration with other active partners. Dividing the project into six work packages is mainly based on the content of the specific research. Each of the six work packages constitutes a specific and complementary sub project involving the participation of several partners, bringing in their particular expertise in genetic or biochemical or molecular and cellular biology (Fig.1).

Zinc basics
In a healthy immune cell, zinc is captured within the structure of a protein called Metallothionein and stored. From here, it is released into the cell nucleus when

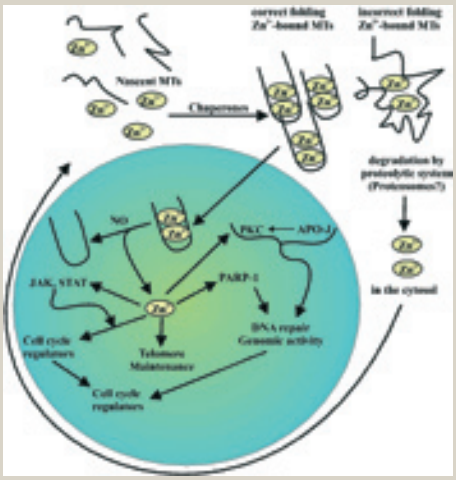
needed, forming a crucial component of enzymes involved in DNA and protein repair, cell division and chromosome maintenance (Fig. 2). Such processes, which are vital for an effective immune system, are found to be less efficient in old age. Metallothionein stops releasing its zinc in old people. There are several theories for why this happens, such as bad folding of the protein itself, or lack of a chemical that liberates zinc inside the nucleus. Without zinc, key proteins become oxidised and function badly. Failed maintenance of the protective sealed end of each chromosome, known as the telomere, is especially implicated in ageing being the telomere generally shortens with age.

Mediterranean diet keep you young
Scientists at ZINCAGE will study the activity of zinc in immune cells, called lymphocytes, taken from 800 people aged between 65-85, to find out which parts of the process are not functioning. They will also test whether faults can be corrected by supplementing the diet with zinc. Subjects will come from Germany, Poland, Greece, Italy and France. Scientists will look for differences between men and women, and are also keen to identify any differences between northern and southern Europe. Southern Europeans have longer life expectancy than northerners, which has been linked

to more balanced diet on zinc food content in the Mediterranean diet. The project will take samples of DNA from elderly subjects and look at the genes for proteins that interact with zinc. They will investigate whether or not the genes are different in subjects where zinc is not working properly as there may be a genetic tendency in certain groups to zinc deficiency in old age. Partners in the project will develop a DNA microchip to test the activity of all the genes associated with repair of DNA , and to diagnose problems that may be associated with zinc availability.

The secret of longevity

The same tests will be carried out on people who are ageing very well – having reached 90 or 100 – and on people suffering severe age-related degeneration. The researchers hope to find differences among these groups – perhaps nonagenarians retain perfect zinc functions or display discernible genetic differences in how their bodies deal with zinc. In addition, one of the aims of ZINCAGE is to provide a simple genetic screening method in order to identify people at risk of zinc deficiency and consequently the appearance of age-related diseases. The use of zinc supplements by these subjects may be useful to help them achieve successful ageing. ZINCAGE will advance our understanding of the role of zinc in the ageing immune system significantly and give European science a competitive edge in the field. The project should provide the basis for advice on who should take zinc supplements to ward off the frailties of old age.



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