

Contributions of Italian science in advancing lifespan extension through autophagy stimulation

E. Bergamini¹, G. Cavallini², A. Donati²

¹ Department of Food Science and Human Nutrition, campus Bio-Medico University of Rome, Italy

² Interdepartmental Centre on Biology and Pathology of Aging, University of Pisa, Italy

In their recent paper Tancini et al. reviewed advancements of non-italian science in lifespan extension through autophagy stimulation and future perspectives ¹. Here, it may be worthwhile to recall discoveries in Italian laboratories supported by MIUR (40% program), disclosing the way to successful intervention on aging in humans. Seminal work was the discovery that autophagy can be induced by giving fasted animals an antilipolytic drug (either 3,5-dimethylpyrazole or Acipimox) ². Treatment lowers blood FFA and glucose levels in less than 15 minutes, and lowers insulin and increases glucagon and glucocorticoids levels inducing liver autophagy in 30 min ³. A highly reproducible method for the investigation of endocrine-regulated autophagy and protein degradation was set and used to explore the endocrine and amino acid regulation of macroautophagy ⁴. A preliminary report that the autophagic response to stimulation by antilipolytic drugs decreases with increasing age was given at the 1987 binational Italy-US symposium on protein metabolism in Aging. Research advancements in following years were reviewed on the official journal of the Italian Gerontological and Geriatric Society as well as on international journals (e.g. ⁵). Briefly, results confirmed that the *in vivo* and *in vitro* function of autophagy declines with increasing age in ad libitum fed animals and that antiaging calorie restricted (CR) diets (both 40% restriction and every other feeding) may counteract these age-related changes; that protection by CR diets declines with increasing the age at the start of dietary interventions, co-varies with extension of life-span and parallels age-related changes in dolichol concentration, a novel lipid biomarker of membrane aging ⁶ and in the transduction of amino acid and hormone signaling; that treatment with Acipimox may increase autophagic response to fasting and intensify the beneficial antiaging effects of

a milder CR; that a long-lasting inhibition of autophagy (e.g. by chloroquine) may speed up the process of aging and that a long-lasting intensification of autophagy by antilipolytic drugs may delay the appearance of age-associated changes in rats (George Martin gave the name to treatment: PISA – Pharmacological Intensification of Suppression of Aging – see ⁷). Discovery that PISA may cause a selective degradation of older 8-OHdG rich mitochondria ⁸ and older peroxisomes ⁹ clarified the mechanisms of protection and gave a way to monitor efficacy non-invasively, both in animals and humans, by the assay of 8-OHdG output in urine ¹⁰. Finally, it was clarified that the stimulation of autophagy and apoptosis to clear cells and tissues from altered components is only a part in the antiaging mechanism of CR: to get full benefit, time of fasting should be followed by good nutrition, rich in omega-3 polyunsaturated fatty acids and red-wine antioxidants, to rise insulin and IGF-1 levels and foster replacement of the degraded altered organelles and cytomembranes with new ⁷. The full procedure was named D.A.N.I. (Dynamic Antiaging Nutritional Intervention). Thanks to the support of Rotary and Associazione Alberto Sordi (Roma), with the approval of the Italian Institute of Health (Istituto superiore di Sanità), full information is now available to Italian high-school students (and their families) for primary prevention of aging and associated diseases as a part in the regular biology program.

Discovery that antiaging caloric restrictions may act by a cyclically repeated activation of autophagic degradation and replacement of the degraded material with new prompted us to investigate which cell component is so difficult to be fixed that Nature decided that degradation is better than repair ⁷. The obtained results may shed light on the mechanisms of age-related cholesterolemia, of the beneficial effect of fish oil and of the

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■ Correspondence: Ettore Bergamini, Department of Food Science and Human Nutrition, Campus Bio-Medico University of Rome, via A. del Portillo 21, 00128 Roma - E-mail: ettore.bergamini@gmail.com

dangerous side effects of statin therapy. Evidence was found indeed that higher oxidative stress in membranes may activate HMGCoA-reductase, accounting for the age-related increase in the plasma level of cholesterol and in two tissue antioxidants, the biomarkers of aging dolichol and ubiquinone. The induction of autophagy by the administration of Acipimox did prevent these changes. Incidentally, data may clarify also the mechanisms of the beneficial effects of red wine polyphenols and resveratrol on cholesterolemia, and of the toxicity of statins (together with plasma cholesterol statins may decrease tissue dolichol and ubiquinone thus increasing risks of free radical-mediated tissue injury: rhabdomyolysis).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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