Available online at www.sciencedirect.com
ScienceDirect
Mechanisms of Ageing and Development 128 (2007) 92–105
Mechanisms of Ageing and Development
www.elsevier.com/locate/mechagedev

Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans

Claudio Franceschi [a,b,c,e,*], Miriam Capri [a], Daniela Monti [d], Sergio Giunta [e], Fabiola Olivieri [e], Federica Sevini [b], Maria Panagiota Panourgia [b], Laura Invidia [a], Laura Celani [b], Maria Scurti [b], Elisa Cevenini [b], Gastone C. Castellani [b,f], Stefano Salvioli [a,b,c]

[a] *Department of Experimental Pathology, University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[b] *Centro Interdipartimentale "L. Galvani", University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy*
[c] *ER-GenTech laboratory, via Saragat 1, 44100 Ferrara, Italy*
[d] *Department of Experimental Pathology and Oncology, University of Florence, Viale Morgagni 50, 50134 Florence, Italy*
[e] *I.N.R.C.A., Department of Gerontological Sciences, via Birarelli 8, 60121 Ancona, Italy*
[f] *DIMORFIPA, University of Bologna, Via Tolara di Sopra 50, 40064 Ozzano dell'Emilia, Italy*

Available online 20 November 2006

Abstract

A large part of the aging phenotype, including immunosenescence, is explained by an imbalance between inflammatory and anti-inflammatory networks, which results in the low grade chronic pro-inflammatory status we proposed to call *inflammaging*. Within this perspective, healthy aging and longevity are likely the result not only of a lower propensity to mount inflammatory responses but also of efficient anti-inflammatory networks, which in normal aging fail to fully neutralize the inflammatory processes consequent to the lifelong antigenic burden and exposure to damaging agents. Such a global imbalance can be a major driving force for *frailty* and common age-related pathologies, and should be addressed and studied within an evolutionary-based systems biology perspective. Evidence in favor of this conceptualization largely derives from studies in humans. We thus propose that inflammaging can be flanked by *anti-inflammaging* as major determinants not only of immunosenescence but eventually of global aging and longevity.

Keywords: Inflammaging; Inflammation and anti-inflammation; Human studies; Aging and longevity; Systems biology

1. Aging is an adaptative process (remodelling) performed by an integrated panel of evolutionary selected mechanisms

Damaging agents are produced by the organism as a consequence of normal (inescapable) metabolic processes (e.g. reactive oxygen species, ROS, from oxidative metabolism) or derive from the exposure (also inescapable) to a variety of physical (e.g. UV rays from sun exposure) or biological (viruses, bacteria, parasites) agents. Collectively they represent *the environment*, and a clear distinction between internal and external environment is very difficult if not impossible. The body is equipped with a panel of mechanisms in order to counteract and neutralize the negative effects of such agents. Among the most important, we can list the following:

1. at the *molecular* level: DNA repair mechanisms, production of heat shock proteins and other chaperones, turn-over of proteins and organelles, anti-oxidant and detoxifying systems;
2. at the *cellular* level: apoptosis and autophagic cell death, phagocytosis and scavenging of damaged cells, cell senescence, replacement of dead cells by progenitors derived from stem cells (cell and tissues renewal);
3. at the *systemic* level: immune and inflammatory responses, stress response, neuroendocrine response;
4. at the *organismal* level: behavioral/avoidance responses aimed to minimize danger and damage.

All these types of responses contribute to survival in an integrated way, and it can be predicted that the *global* rate of

* Corresponding author at: Department of Experimental Pathology, University of Bologna, via S. Giacomo 12, 40126 Bologna, Italy.
Tel.: +39 051 2094743; fax: +39 051 2094747.
E-mail address: claudio.franceschi@unibo.it (C. Franceschi).

0047-6374/$ – see front matter
doi:10.1016/j.mad.2006.11.016

aging and the final longevity attained by a species is (more than) the sum of all these mechanisms (*adaptation or remodelling capacity* at the level of different species). During evolution a *positive* selection process occurred in order to maximize the efficiency of these defense mechanisms *as a whole*, because they were critical to maintain a healthy status and consequently to maximize reproductive capacity and fitness.

In 1991, a seminal conference of the New York Academy of Sciences organized by Gaetano Crepaldi, Vincent Cristofalo, Claudio Franceschi and Jan Vijg, was devoted to this topic starting from the basic idea that defence systems play a major role in the aging process (see the volume edited by Franceschi et al., 1992).

It is interesting to highlight an assumption and a prediction of such a perspective:

- a basic assumption in the field of aging research is that the fundamental biological mechanisms playing a major role in the aging process are highly conserved throughout evolution and that, accordingly, extrapolation from model systems to humans is quite reasonable. Comparative data on single genes or gene families all along evolution fit with this assumption. However, it is also clear that, despite such a basic conservative scenario, major changes also occurred in evolution, particularly regarding biological *regulatory* processes and integration between and among pathways, and that *major differences among species* also emerged during evolution. This consideration is particularly important for *H. sapiens*, and its *biology*, including aging. Here, we face a major problem which has been poorly addressed and which would deserve much more attention, i.e. a sort of *ecological perspective* regarding the different lifespan of the different species. It is possible to speculate that, owing to the extremely complex relationship and interactions among different species in a defined environment and the reciprocal constraints in terms of predator/prey, their lifespan should fit a general, ecological equilibrium. In other words, we can speculate that the unexpected *plasticity and malleability* of the aging process and longevity which are emerging in biogerontology have strong evolutionary basis, being a sort of prerequisite to allow adaptation to *ecological* changes, requiring a plastic and malleable lifespan of all the species being part to the specific environment, in order to attain a general ecological equilibrium among species.
- a major prediction is that the different longevity of individuals *within a species* can be explained by assuming a different *individual adaptation and remodelling capacity*, based on (the combination of) subtle differences among individuals regarding the efficiency of the above mentioned set of defense mechanisms, evolutionary selected for a certain level of efficiency in each species as a whole. Thus, the variants which play a role in human longevity at the individual level belong to repertoires of differences which have been selected by evolution at the population level.

2. Advantages and success of model systems: the crucial importance of the reductionist approach

Usually the above mentioned mechanisms thought to play a role in aging and longevity are considered separately, and a variety of approaches and model systems have been set up in order to assess the role played by each of them in the aging process. This is the case for example of DNA repair mechanisms, and indeed interesting results have emerged (Hasty et al., 2003). This approach has been followed in all fields of biology, and the molecular biology and genetics of aging is full of this kind of successful findings. This approach is *reductionist* by definition, and it can be applied only to *model systems*, the basic assumption being that the more *simple* is the organism the more successful will be the investigation on the fundamental ‘‘cause’’ of aging and longevity. Model systems fit basic requirements of scientific research, and indeed experimental animals are genetically well characterized (usually inbred) and the environment is very well *controlled* and kept *constant*. This setting assures another basic requirement of scientific research, i.e. the possibility to *replicate* the results in different laboratories.

After so many years of this type of successful research, it is timely to evaluate if this is the only (or major) strategy to pursue and whether other approaches are needed and can be added to the list.

3. Studies on human aging and longevity: the Cinderella of biogerontology

In this review, we will argue that the approach which exploit model systems and allows exciting, ‘‘mechanistic’’ experiments of molecular biology and molecular genetics, although still *fundamental*, must be enriched and accompanied by and extended to more *systemic* approaches. In particular, we will argue that much more space and credit should be given to studies on humans.

Research on aging and longevity has been dominated by studies performed in model systems, such as yeast, worms and flies, and results from studies in humans have been considered a sort of second class studies. Indeed, in most reviews on aging and longevity published in ‘‘major’’ journals, very little attention has usually been paid to results obtained in human studies. Even science follows ‘‘fashions’’, but this attitude has been an obstacle to realize that some of the results obtained in humans, which did not emerge clearly from studies in model systems, are of primary importance to understand the contribution of genetics to longevity (Fig. 1). While human biogerontologists know, take into account (quote) and are inspired by findings in experimental animals and model systems, the reverse is quite unusual. Rarely experimental biogerontologists consider (quote) or are inspired by results and conceptualizations elaborated during the study of human aging and longevity. A more balanced ‘‘bilateral’’ perspective is recommended, at every level of scientific research (funding and training, among others), taking into account that the final aim of our studies as biogerontologists is not only to ‘‘know’’ and