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VISIONS AND PERSPECTIVES

Contribution of invertebrate models to aging and longevity studies

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Abstract

This paper summarizes pros and cons of the invertebrate models involved in aging and longevity. The worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster* are the two models that have given the major contributions on this topic. Furthermore, we also discuss the possible contribution of recent theories on aging and inflammation to understand the complex phenotype of aged soma, from invertebrates to humans.

Key Words: aging; longevity; invertebrates

Introduction

According to Kirkwood (1985) animal species keep a balance between energy investments in maintenance, growth and repair on one hand and reproductive activity on the other hand, and this balance is related to aging. Despite the great variability present among the animal kingdom, invertebrates and vertebrates use a common pool of highly conserved molecules combinatorially assembled under the constrain of selection for fitness (Ottaviani *et al.*, 1997, 2007; Franceschi *et al.*, 2000). We surmized that same or similar molecules found in invertebrates are present in vertebrates and in these higher forms of life their function remains basically similar. However, Nature has apparently made new uses of these old molecules, while at the same time evolving towards more complex and centralized functions and organs (Ottaviani *et al.*, 1991). The molecular mechanisms able to affect aging and longevity are also involved in the capability of the organisms to cope with a variety of stressors (Franceschi *et al*., 2000). Furthermore, a prediction of these arguments is that the processes that extend lifespan and longevity in invertebrates will have a counterpart in vertebrates, including humans.

However, one of the major differences between invertebrates and vertebrates is the appearance of the acquired immune response, characterized by high levels of specificity and memory. Likely, the immune system is, at a higher level of biological organization and complexity, the counterpart of the anti-stress response network identified in invertebrates as the major determinant of survival. In this context, invertebrates respond to stressors utilizing the same basis set of molecules found in vertebrates, but in the last, the stress response becomes more specialized and specific, involving an evolutionary well maintained network of responses (Ottaviani and Franceschi, 1996).

The study of the mechanisms that underlie aging and longevity was conducted primarily in invertebrates without forgetting yeast, while human studies were considered secondary and only recently they have assumed considerable importance. With regards the human model, we have proposed the inflamm-aging theory, that represents the major characteristic of the aging process (Franceschi *et al*., 2000). Indeed, the ability to cope with a variety of stressors and the concomitant progressive increase in the proinflammatory status is considered a major cause related to a continuous, lifelong antigenic load and stress.

In this paper the main invertebrate species used as models for the study of aging and longevity are reported.

The invertebrate models used in aging and longevity studies

The worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster* are the two models that have given the major contributions to the knowledge of the molecular mechanisms underpinning aging and longevity. It should be noted that in 1978, 451

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references were listed on this topic for *D. melanogaster* (Van Heukelem, 1978). *C. elegans* is important for the study of aging as in this metazoan it was shown for the first time that single-gene mutations are able of extending maximum lifespan. In particular, the mutations of 4 genes *age-1*, *daf-2*, *spe-26* and *clk-1* induce a life extension of more than 40 %. The overexpression of *tkr-1* in transgenic worms increases the longevity 40 - 100 % and confers increased resistance to heat and ultraviolet irradiation (see for review Lithgow, 1996; Murakami and Johnson, 1998). The effects on *C. elegans* longevity and resistance to infection were also observed in worms fed with Lactobacilli and Bifidobacteria (Ikeda *et al.*, 2007; Komura *et al.*, 2010). With regards *D. melanogaster*, Spencer *et al.* (2003) found a group of gene called “aging genes” (*methuselah*, *Indy*, *InR*, *Chico*, *superoxide dismutase*) that extend the fly lifespan by up to 85 %. Further experiments using axenic cultures and antibiotic treatment showed that the presence of bacteria during the first week of adult life of flies enhanced longevity by 30 - 35 %. Conversely, the presence of bacteria in the last stage of life caused a slight decrease (Brummel *et al.*, 2004). The addition of *Escherichia coli* to the diet significantly prolonged the fly longevity in the two Oregon R *D. melanogaster* strains, selected for different longevities: a short-life with an average adult lifespan of 10 days and a long-life standard R strain with an average adult lifespan of 50 days. Furthermore, it has also been observed modifications on the structure and the histochemical reactivity of the fat body. The increased survival was associated with a great amount of glycogen accumulated in fat body cells from both strains. In aged control animals, fed with standard diet, lipid droplets were seen to be stored in fat body of short-lived, but not long-lived flies (Franchini *et al.*, 2012).

For what the increased survival is concerned, it is important to mention that recently Blagosklonny and Hall (2009) suggest a new view, *i.e.,* that "excessive growth is driving for aging", involving basic shared molecular pathways and processes such as the evolutionary conserved TOR pathway. TOR, the target of the antifungal drug rapamycin, has been described from yeast *Saccharomyces cerevisiae* to higher eukaryotes, and its decreased activity has been found to slow aging in yeast, *C. elegans* and *D. melanogaster* (Katewa and Kapahi, 2011; McCormick *et al.*, 2011).

A different approach in the study of aging and longevity is represented by the medfly populations of *Ceratitis capitata* in the wild (Carey *et al.*, 2008), where unlike the laboratory animals, it is not possible to control the experimental conditions. In this study, a new method for estimating age structure in insect populations was proposed, and it revealed that the major modifications were found in field populations, demonstrating that middle-aged individuals are common in the wild, and revealing the extraordinary lifespan of wild-caught insects.

According to Abel *et al.* (2009), bivalves are another excellent model to study aging since several parameters can be evaluated. For instance, the shell can provide information for determining the individual age and, at the same time, provides information on changes in environmental conditions that could influence the life of animals. It was also noted how different molluscan lifestyles regulate the balance between ROS production and antioxidant defense, playing an important role in the determination the maximum lifespan. Buick and Ivany (2004) suggested that one of the processes in extending bivalve lifespan from high latitudes could be the seasonal limitations of light and food availability.

However, other valuable model for the aging study are potentially available among marine invertebrates characterized by the "negligible senescence", *i.e.*, animals that do not show an increase in mortality rate or a decrease in fertility, physiological function or disease resistance with age (Finch and Austad, 2001). In this context, a list is reported by Bodnar (2009).

A new theoretical scenario

Within an evolutionary perspective, the theoretical field of aging has been dominated by few major theories, such as the mutation accumulation theory (Medawar, 1952), the antagonistic pleiotropy theory (Williams, 1957) and the disposable soma theory (Kirkwood, 1977). In this paper we would like to discuss some of the implications of the more recent and above-mentioned conceptualization of Blagosklonny and Hall (2009). This quasi-programmed hypothesis prompted us in extending the inflamm-aging theory to invertebrates. Indeed, inflammation is an ancestral and highly conserved process which plays a fundamental physiological role for survival from invertebrates to *Homo sapiens*. In a more general perspective, the age-related inflammatory process, which develops and increases with aging, owing to a lifelong persistent antigenic load as well as to other stimuli (accumulation of senescent cells), might be interpreted as a quasi-programmed extension to later life of the physiological tendency to activate inflammation and tissue repair crucial for survival in young age. Accordingly, we not only predict a major role of the gut microbiota in life extension in the invertebrates (Ottaviani *et al.*, 2011), but we also suggest that inflamm-aging, and the underpinning molecular mechanisms and pathways, will also play a prominent role in invertebrate models of life extension. This extension to invertebrates of the inflamm-aging theory can be complemented by the recently advanced hypothesis of metaflammation (Hummasti and Hotamisligil, 2010). This conceptualization suggests that an excess intake of nutrients is the driving force triggering the inflammatory status characteristic of obesity and metabolic diseases, such as metabolic syndrome and diabetes in humans and mice. Thus, at least two inflammatory process, inflamm-aging and metaflammation, have been identified, which likely affect aging, age-related diseases and longevity. We surmize that a theoretical merging of inflamm-aging and metaflammation could be useful to understand, at least in part, a variety of major topics in the aging field, such as the negative effects of excess nutrient and the positive effects of caloric restriction, the positive effects of inflammation for

Table 1 Major advantages and disadvantages of invertebrate model systems in comparison to humans

Advantages
• the relative simplicity of their systems • the rapid generation time • the short life-span • the small size • standardization of the environmental conditions, including diet, temperature, among others • easy possibility to perform genetic studies
Disadvantages
• inbreeding • artificial environment, including diet, temperature, among others • altered cycle of day and night • less complex immune system • scarce knowledge of the gut microbiota • scarce knowledge on mitochondrial DNA • scarce knowledge of the pathology

survival against infectious agents and the negative effects of inflamm-aging, among others.

Concluding remarks

In our perspective the take home message of the this paper can be summarized in the Table 1 where we list the major advantages and disadvantages of invertebrate model systems in comparison to humans, within a "balanced" view which appreciate what and how the different models, including humans can contribute for a better understanding of the highly complex phenotype of aged soma.

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