Understanding why we age and how: Evolutionary biology meets different model organisms and multi-level omics

Meeting report on “Comparative Biology of Aging,” Roscoff, October 12–16, 2015

Eric Gilson1)2)*) and Thomas C. G. Bosch3)*)

Aging is ordinarily recognized as a process that results from the combined influence of genetic and epigenetic determinants, lifestyle-associated factors and external events. Studies using model organisms such as budding and fission yeasts, the nematode Caenorhabditis elegans, zebrafish, and mice have generated significant insight into (epi)genetic pathways involved in aging [1]. However, developing an integrated understanding of these diverse processes and, thereby, achieving insight into the causes and mechanisms of the aging process, remain a challenge.

Currently, more and more species of exceptional biogerontological interest are being discovered [2]. “Multi-level omics” has led to the publication of nearly complete genotypes, phenotypic descriptions, and accurate phylogenetic relationships for these species. To provide a discussion forum for the experts involved, an international 2015 meeting on the “Comparative Biology of Aging,” hosted by the Jacques Monod Conference in Roscoff (Brittany, France) and organized by the authors, included not only molecular cell biologists but also clinicians, evolutionary biologists, ecophysicologists, mathematicians, and demographers. Approximately 80 researchers from 15 countries gathered in Roscoff to share their work on aging. The participants left the meeting convinced that a “Comparative Biology of Aging 2.0” is on its way.

The molding of evolutionary theories of aging

The conference started by a keynote lecture by Tom Kirkwood (Newcastle), father of the disposable soma theory of aging [3]. Kirkwood is currently exploring life-history evolution (e.g. the evolution of menopause) and the optimal allocation of metabolic resources in varying environments (e.g. life extension through rodent calorie-restriction). Such models recently led to the first evidence for a trade-off between human longevity and fertility.

The demographer Annette Baudisch (Odense) addressed the questions of how and why the lifespans of closely related species vary, and the relevance of this phenomenon to human aging. Baudisch showed that recent developments in evolutionary biodemography offer new theories, methods, and data that have resulted in striking findings on the diversity of life histories (including, for some species, the ability to avoid aging) [4]. As human lives are rapidly changing owing to unimpeded population aging, the development of biodemographic theories, methods, and databases may prove useful and inspire sociological progress.

Advances in non-model organisms

There is a growing recognition of the importance of non-model organisms in aging research. These non-model creatures reveal the highly heterogeneous nature of the aging process, from the mandatory aging in bacteria and eukaryotes that divide by fission to slow-aging organisms such as the naked mole rat and those exhibiting seemingly unlimited lifespans (Hydra). How does Nature change the lifespan of species? Vadim Gladyshev (Boston) approaches the molecular basis for natural changes in longevity by identifying adaptations in long-lived mammals and examining longevity-associated processes across all mammals. His lab recently sequenced and analyzed the genomes of the naked mole rat and Brandt’s bat, as well as a number of other mammals with exceptional lifespans, and uncovered several underlying adaptations. The Gladyshev lab also identified general gene expression and metabolic changes—both common strategies such as nutrient sensing pathways and “private mechanisms,” i.e. lineage-specific pathways—that are associated with longer life, suggesting that these longevity patterns may allow lifespan to be increased in any mammal species. Naked mole rats are small, hairless, subterranean rodents that are not known to get cancer despite having a 30-year lifespan (see Fig. 1B). This lifespan is ~10-fold longer than that of the similarly-sized mouse. Along with its longevity, the naked mole rat boasts an array of characteristics that has made it, despite its unimpressive appearance, a darling of medical researchers. It can
survive in very low-oxygen conditions that cripple human brains. Furthermore, the species is immune to cancers—both natural and experimentally induced. Research carried out by Vera Gorbunova (Rochester) focuses on DNA repair and cancer-resistance in naked mole rats in order to understand more fully the mechanisms responsible for longevity. She identified high molecular weight hyaluronan as the chemical that triggers the anti-cancer response in the naked mole rat, and attributes the rodent’s longevity to a process that results in nearly-perfect protein synthesis.

David Miller (Townsville) presented an overview of aging in corals (Fig. 1E), an animal that can live for thousands of years. This, together with the fact that the coral and vertebrate gene repertoires are remarkably similar, makes the coral an attractive emerging model for aging studies.

The killifish *Nothobranchius furzeri* (Fig. 1D), which is the shortest living vertebrate known, was introduced to the conference participants by Karl Lenhardt Rudolph (Jena) and Anne Brunet (Stanford) [5, 6]. This fish is a particularly attractive model for aging research since short- and longer-lived strains can be crossed and produce viable offspring. Lifespan can be prolonged by environmental manipulations as well as pharmaceutical drugs and tools for genetic manipulation are available.

(Epi)genetic determinants of aging

To what extent does the incredible diversity of aging strategies result from adaptation to environmental changes? Helke Gruber (Plön) showed that pre-existing genetic diversity in a population of rotifers allows them to adopt different life-history strategies depending on the supplied energy level. Benjamin Barre (Gianni Liti lab, Nice) and Jerome Salignon (Gael Yvert lab, Lyon) are using the power of yeast genomics to understand how the environment impacts the complex genetic architecture of aging. Josh Mitteldorf (Cambridge, USA) regards aging as a programmed biological process that is selected at the communal level to accommodate environmental dynamics, reshaping the famous sentence of Dobzhansky: “Nothing in evolution makes sense except in the light of ecology.”

What determines the lifespan of *C. elegans*? Ivan Matic (Paris) reported that *C. elegans* exhibits high inter-individual variability in lifespan and that bacteria used as food may play a major role in affecting lifespan in isogenic nematode populations. Matic speculates that the developmental plasticity of *C. elegans* nematodes, which are self-fertilizing homozygous animals that produce offspring with negligible genetic variation, could increase the probability of survival in changing environments.

In the non-senescent freshwater polyp genus *Hydra*, one of the classical model systems for evolutionary
developmental biology and regeneration, the transcription factor FoxO modulates both stem cell proliferation and innate immunity [7]. This provides strong support for the role of FoxO as a critical rate-of-aging regulator. According to Thomas Bosch (Kiel), constructing a model of how FoxO responds to diverse environmental factors helps create a framework for how stem cell factors might contribute to aging.

**New findings in genome stability, chromatin, and telomeres**

DNA damage is recognized as a major contributing factor to aging. Among the stresses that trigger cellular senescence, telomere dysfunction plays a particularly critical role, since it behaves as an important clock that regulates lifespan [8]. Eric Gilson (Nice) presented very recent findings that have unmasked some of the circuits regulating telomere signaling, including DNA topology control and genome-wide outcomes of telomere dysfunction. Addressing the mechanism that maintains telomeres in non-dividing fission yeast cells, Vincent Géli (Marseille) revealed in quiescent cells bearing short telomeres new types of telomere rearrangements that are otherwise counter-selected when cells exit quiescence. Along with this interest on genome dynamics in post-mitotic cells, Benoit Arcangiolli (Paris) showed that in fission yeast genome size decreases during quiescence due to deletions and mutations increase. Jing Ye (Shanghai) revealed a specific role for telomeres in brain function, a tissue that is mostly post-mitotic, showing that the contribution of telomere changes to aging does not concern only dividing cells. Pat Monaghan demonstrated in zebra finches (see Fig. 1A) not only that environment greatly influences phenotype and life history but also that stress affects telomere attrition. Moreover, work on the Atlantic salmon has uncovered that telomere loss during growth varies with the environment and, even more interestingly, that social stress can alter telomere dynamics.

A permanent activation of the DNA damage response (DDR) leads to cellular senescence that may be involved in organismal aging. Björn Schumacher (Köln) used the nematode model to show that CEP-1/p53 plays a major role in regulating the DNA damage response in germ cells. His results also delineate a DAF-16/FoxO mediated DNA damage tolerance pathway that maintains the growth of somatic tissues despite genome instability. The longevity assurance mechanisms of DAF-16 activity might antagonize DNA damage-driven growth retardation and aging by elevating tolerance towards persistent or accumulating DNA damage, thus raising the threshold when the age-dependent accumulation of DNA damage leads to functional deterioration. DDR not only changes gene expression regulation but also various levels of chromatin organization. Along the same lines, the characteristic heterogeneity of the aging process is probably directly related to chromatin regulation mechanisms.

**Aging, stem cells, and regeneration**

Adult stem cells play a key role in tissue renewal. Their function declines during aging, suggesting that a functional reserve of stem cells extends lifespan. Exploring genetic and epigenetic instability in stem cell aging, Karl Lenhardt Rudolph (Jena) showed that there is a clonal selection of stem cells and shift in the stem cell pool during aging. Alternations in developmental pathways and key developmental regulators such as Hox genes in adult myogenesis lead to impaired satellite cell functioning. Focusing on recent discoveries in aging pathways that influence the function of human hematopoietic stem cells, Michelle Goodhardt (Paris) showed that aging is correlated with the formation of heterochromatin, reduced activity of stem cell genes and increased expression of lineage-restricted genes. Vincenzo Constanzzo (Milano) reported progress in identifying so-called Somatic to Embryonic Transfer Factors (SETRAFs) that are capable to resetting cellular age.

Interestingly, several marine invertebrates such as planarians and cnidarians (i.e. Hydra, sea anemones, corals) have extreme regenerative capacity and extreme longevity. Eric Röttinger (Nice) is studying the marine cnidian _Nematostella vectensis_ (see Fig. 1C), for which extreme regeneration ability appears linked to extreme longevity and non-senescence. Repetitive regeneration in _Nematostella_ adults is nutrition-independent.

Plants are special because of their indeterminate growth (some perennial plants are among the longest-living organisms, with lifespans of over 11,000 years), their modular development, and the fact that in plants there is no separation of germ line and soma. What keeps the genomes of plants stable for such a long time? Karel Riha (Vienna) proposed that the stratification of plant meristems might decrease mutations by protecting stem cells from excessive proliferation.

**Energy metabolism/proteostasis**

Metabolic signaling pathways, such as the IIS/TOR signaling network, play major roles in aging. Decreasing the activity of these signals reduces cellular metabolism while protecting against oxidative stress and aging. By expressing in the nematode _C. elegans_ a mitochondrial form of an antioxidant protein fused to a fluorescent moiety, Meng-Qiu Dong (Beijing) serendipitously discovered that the rate of fluorescent flashes in young animals is negatively correlated with its lifespan [9]. This highlights the view that aging is a programmed process and raises the question of how mitochondrial activity predicts its overall rate.

In his keynote address, Steven Austad (Birmingham USA) presented the observation that misfolded proteins tend to accumulate in aging cells, and are related to dysfunction and disease, most prominently Alzheimer’s. Long-lived species, therefore, need to keep proteins in the right conformation with “chaperone” molecules that are particularly effective. In his current research, Austad is isolating and transplanting some of these chaperone molecules from his menagerie of 500-year-old clams.

In the clinical sphere, Serge Adnot (Créteil) uncovered a link between telomere deficiency, the accumulation of senescent cells and pulmonary disease,
opening new avenues in the treatment of age-related pathologies. Loic Verlingue (A. Londono lab, Paris) showed post-translational regulation of molecular signaling for geroconversion, a special type of senescence that is increased in type 2 diabetes and can be decreased by rapamycin (see Fig. 1F).

Continued momentum in this field requires a careful analysis of both model and non-model organisms to achieve holistic insight into the mechanisms, physiology, and “raison d’être” of aging in the living world. If a comparative analysis of aging is to realize its full potential, it will be necessary to bridge the gap between biology and ecology-oriented research and to promote interdisciplinary collaboration. Through such collaborative work, we will achieve greater insight into underlying causes for variability in aging among closely related species, and thereby develop a deeper understanding of the aging process in humans.

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References