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Review

# The companion dog as a unique translational model for aging

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ABSTRACT

The dog is a unique species due to its wide variation among breeds in terms of size, morphology, behaviour and lifespan, coupled with a genetic structure that facilitates the dissection of the genetic architecture that controls these traits. Dogs and humans co-evolved and share recent evolutionary selection processes, such as adaptation to digest starch-rich diets. Many diseases of the dog have a human counterpart, and notably Alzheimer's disease, which is otherwise difficult to model in other organisms. Unlike laboratory animals, companion dogs share the human environment and lifestyle, are exposed to the same pollutants, and are faced with pathogens and infections. Dogs represented a very useful model to understand the relationship between size, insulin-like growth factor-1 genetic variation and lifespan, and have been used to test the effects of dietary restriction and immunotherapy for Alzheimer's disease. Very recently, rapamycin was tested in companion dogs outside the laboratory, and this approach where citizens are involved in research aimed at the benefit of dog welfare might become a game changer in geroscience.


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## 1. Introduction

Aging is part of a continuous ontogenetic process from conception to death that includes growth and maturation. Aging has evolved as the consequence of primary selection for other life-history traits, and represents a prime example of how evolutionary changes are not directed towards what appears an obvious individual goal; i.e. the preservation of the individual itself [1].

A number of common cellular/molecular hallmarks of aging in mammals were identified recently: epigenetic alterations, genomic instability, stem-cell exhaustion, telomere attrition, mitochondrial dysfunction, cellular senescence, loss of proteostasis, and altered intercellular communication [2]. In addition, a number of theories have been proposed to explain the evolution of aging (see Reichard, this issue, for an updated review) and there is controversy over its underlying mechanisms and the respective roles of stochastic accumulation of molecular damage, as opposed to quasi-programmed system hyperfunction. These questions are relevant to understand the relationships between aging and increased disease risk [3,4], and to understand the biological mechanisms linked to successful aging in a selected population of extreme phenotypes, such as centenarians [5].

The diversity of individual life trajectories gives rise to another important aspect exemplified by the aging of the human olfactory system. This is not a continuous mechanism, but shows multiple discrete phenotypes (termed juvenile, mature, elder) where their frequencies change in the different age groups. However, the 'elder' olfactory phenotype can be detected in a subset of young subjects, which indicates early impairment of the system long before onset of degenerative processes, thus demonstrating early functional senescence that might have an impact on aging decades later [6].

Aging, as the age-dependent increase in mortality (often exponential), is caused by such senescence processes [7,8]. In this meaning, senescence is related to the deterioration of physiological functions (which is often linear) and can develop at different paces relative to the maximum lifespan [8]. Individuals exposed to risk factors, such as drug consumption, can accelerate the senescence of their physiological system (e.g., their chemoreception system), which consequently affects aging [9]. Thus, aging represents the biological mechanism, while senescence represents its subjective physiological expression.

The aim of the present review is to present the potential of the dog as a model organism for aging studies.

## 2. The comparative approach to aging

Within metazoans, there is at least a 10,000-fold range in lifespans, from the longest-lived species, such as an invertebrate sponge in the order of millennia (maximum reported, 15,000 years), through the ocean quahog in the order of centuries (507 years, see Blier in this issue) and the Greenland shark (390 years), and further reduced for other sea life, such as the bowhead whale (211 years), rockfish (205 years) and sea urchin (200 years) [10,11], (see also Dammann, this issue). Lifespan shows a strong positive correlation with body size and insight into the genetic control of aging can be gained from comparative studies across species where the longevity quotient is analysed (i.e., the residuals of the regression lifespan vs. body size) [12]. The availability of comprehensive databases makes it possible to probe the relationships between aging and a variety of other life-history traits [13,14]. These databases and their analysis become extremely relevant in light of the increasing availability of high-throughput technologies that allow genome-wide analysis of gene expression and positive selection in a large number of diverse species [e.g. 15–20].

## 3. Animal models of aging and the place of dogs

Given the large diversification of animal life spans, there can be no single model species for aging. For practical reasons, the vast majority of studies on aging animals are performed in nematodes (see Pires, in this issue). Invertebrate models, however, have some intrinsic biological limitations: their anatomical organisation is fundamentally different from that of mammals; they lack adaptive immunity and bones; they have limited stem cell populations; and they lack some genes that are highly relevant for human aging. Among these, for example, there are the Apolipo protein E (APOE) gene and the INK4 locus (coding for the cyclin kinase inhibitors CDKN2A and CDKN2B) that in genome-wide studies are associated with high reproducibility to exceptional longevity and age-related diseases [21,22]. In addition to these very general considerations, when the focus of an analysis is on age-related diseases and in a translational perspective, the size and the physiological and behavioural traits of the different species become highly relevant. Primates represent an ideal model for human, although aging studies in primates are exorbitantly and generally prohibitively expensive and last for decades [23].

The present-day companion dog represents a unique animal model that might provide a paradigm shift from laboratory research to 'citizen science'. The biology of the domestic dog has a number of unique aspects that are of relevance for aging studies:

(i) Due to selective breeding, there are almost 20-fold variations in body size and over two-fold differences in aging rates [24,25].
(ii) There are many strain-specific genetic diseases that became fixed, while the dog genome has been sequenced [26,27] and the high level of inbreeding facilitates the mapping of complex traits (e.g., [28]).
(iii) There is vast knowledge of dog diseases and many non-invasive procedures are available to assess health and function, accompanied by the vast development of drugs.
(iv) The dog shows specific adaptations for communication with humans and represents a unique model for human-like social skills [29,30], and the genetic basis of this behaviour is starting to be defined [31].
(v) The dog and human co-evolved and share recent evolutionary selection processes, such as adaptations to digestion of starch-rich diets, and there are clear signs of convergent evolution in the human and dog genome [32,33].
(vi) Unlike laboratory animals, companion dogs share the human environment and lifestyle, are exposed to the same pollutants, and are faced with pathogens and infections [34].

Most importantly, there are many millions of companion dogs in the world, with 80 million alone in the USA (estimate of the American Veterinary Medicine Association for 2012). The increasing quality of veterinary care leads to an increase in the elderly dog population that will show increasing senescence mechanism and consequent prevalence of age-associated diseases that need treatment. This can lead to a complete paradigm shift in translational research, where instead of inducing diseases in laboratory animals,