Supplementary material

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Beyond genetics

Complexity behind aging

Together with the complex network of genetic components discussed in the main text, environmental factors, including diet, exercise, stress, pollution and socio-economic environment also make a fundamental impact on human aging. Actually, the heritability of individual differences in aging phenotypes and average lifespan did not exceed 35% in many studies (Crimmins and Finch, 2012; Finch and Tanzi, 1997). (However, the heritability of extreme longevity was found to be higher – see e.g. Perls et al. (1998) and Sebastiani and Perls (2012)). Revealing the key environmental elements that modify expected lifespan and untangling their complex interactions with the genetic background should be an important step to develop effective interventions. In this regard, experimental models may have severe limitations, because many of the factors that affect natural human populations are challenging to be mimicked under laboratory conditions, or are simply not relevant in model animals because of their limited social capacities. In this aspect the dog has unmatched potentials, because its social and physiological needs closely resemble those of humans. There are empirical and also scientific indications that training and socialization level can affect the well-being and health status of companion dogs (Arhant et al., 2010; Blackwell et al., 2008; Hiby et al., 2004).

Exercise

In modern societies both humans and their pets are affected by a so called “westernized” lifestyle, which is characterized by dramatically reduced physical activity, an increase in psychological stress and high calorie intake. These factors are considered responsible for an elevated rate of obesity and increased incidence of cardiovascular disease and cancer, which are known to share molecular mechanisms with aging. Therefore, it seems a valid assumption that such lifestyle changes would decrease average lifespan, However, it is likely that the concurrent developments in medical care systems may have actually confounded these effects in humans - and companion animals (Bonnett and Egenvall, 2010). Yet, an increasing body of evidence suggests that health parameters can be severely hindered by the lack of exercise. Physical exercise was shown to reduce anxiety and depression, improve cognitive function and decrease the occurrence and severity of certain diseases and neurodegeneration, both in humans and mice (Churchill et al., 2002; Eriksson and Gard, 2011; Hillman et al., 2008; Kronenberg et al., 2006; Larson et al., 2006; Salmon, 2001). It was also shown to slow down the progression of Alzheimer’s disease or other forms of cognitive decline and muscular atrophy (Adlard et al., 2005; Ahlskog et al., 2011; Heyn et al., 2004) (Cartee et al., 2016).

The negative behavioral and health consequences of reduced exercise in dogs are likely to be similar, although not many studies have investigated this question so far (Kobelt et al., 2007). In the future, systematic exercise interventions, together with diet changes and behavioral enrichment may yield positive results in dogs as well.

Diet

The composition of one's diet has long been considered a key element in health and disease. In modern human societies obesity is one of the main health concerns (Williams et al., 2015) which – in addition to low levels of daily exercise - is mainly caused by consuming high-fat, high-calorie diet, often called "westernized" diet (Cordain et al., 2005). Obesity is also prevalent in pet animals (German, 2006). Physiological changes in obese dogs show similar patterns as in humans, proposing the species as a large animal model of obesity (Kleinert et al., 2018; Osto and Lutz, 2015; Stachowiak et al., 2016). Importantly, obesity was reported to shorten healthspan and lifespan in laboratory dogs and in pet dogs (German, 2006; Salt et al., 2018). Also, laboratory dogs kept on a restricted diet lived longer and healthier than paired animals kept on a normal diet (Larson et al., 2003). These findings were in concordance with the vast evidence that supported the longevity effects of restricted diet regimens in several other species. The most comprehensively investigated dietary intervention, called caloric restriction (CR), consists of a low calorie diet, which still contains the optimal amount of essential biomolecules, minerals and vitamins. It was first shown to extend lifespan of rats and mice (McCay et al., 1935; Weindruch and Walford, 1982) and later the same beneficial effects were reported from other examples, including yeast (Lin et al., 2000) worms (Klass, 1977) and even non-human primates (Colman et al., 2009, 2014), suggesting an evolutionary conserved physiological basis for this effect. Importantly, CR was also reported to be effective even when implemented in old animals (Cao et al., 2001). Although it is still a fundamental question, whether the increase in healthspan and lifespan would reach the same extent in humans, case reports have already confirmed a potential longevity effect for various forms of diet restrictions in isolated human populations (Willcox et al., 2006). Furthermore, voluntary participants who followed a strict diet for years were reported to have lower activity of the insulin signaling pathway and their gene expression profiles changed towards a pattern typical for younger people (Mercken et al., 2013). Another study reported improved muscular mitochondrial function in response to CR in young adult humans (Civitarese et al., 2007). Importantly, both CR and intermittent fasting were shown to be an effective intervention to delay or even reverse cognitive decline and slow down the progression of Alzheimer's disease (Luchsinger et al., 2002; Patel et al., 2005; Witte et al., 2009). All these effect can result from the concordant modulation of several age-related pathways by CR. IGF1 signaling (Kari et al., 1999), the activation of sirtuins (Cohen et al., 2004) and the epigenetic inhibition of somatic transposon activity (De Cecco et al., 2013) were all shown to be affected by nutritional status. On the other hand, the universality of CR as a powerful tool to increase life- and healthspan has been questioned by several studies that showed no effect or even negative effects of restricted food intake in rodents, depending on their genetic background (Barrows and Roeder, 1965; Fernandes et al., 1976; Forster et al., 2003). A more comprehensive study further supported these findings by screening heterogeneous populations of mice for the effects of caloric restriction (Liao et al., 2010). Later, Schleit et al. (2013) pinpointed various possible molecular pathways that may be at the bottom of such differences. Nevertheless, it is important to note, that the type of dietary restriction may vary among studies, and thus not all conditions of restricted diet may correspond with the exact definition of caloric restriction. Yet, these findings clearly demonstrated the need for more research on the applicability of CR in highly variable natural populations. Studies on human populations, however, are not easy to be conducted, especially when the effects of lifelong CR are to be evaluated. In this regard, the dog can again become a favorable model system, as a species with high genetic variability, coupled with lifestyle and diet variation between individuals. Longitudinal studies on laboratory Beagle and Labrador retriever dogs have already shown promising results regarding the applicability of dietary interventions (Kealy et al., 2002; Larson et al., 2003; Wang et al., 2007), yet it is important to note, that physiological responses to caloric restriction may vary among breeds, similarly as it was reported in mice. For this reason, further studies should be designed to investigate the effects of CR on family dogs, which represent a much wider range of breeds.

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