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Centenarians: An excellent example of resilience for successful ageing

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ABSTRACT

Centenarians are remarkable not only because of their prolonged life, but also because they compress morbidity until the very last moments of their lives, thus being proposed as a model of successful, extraordinary ageing. From the medical viewpoint, centenarians do not escape the physiological decline or the age-related diseases or syndromes (*i.e.* frailty), but the rate of such processes is slow enough to be counterbalanced by their increased intrinsic capacity to respond to minor stresses of daily life (*i.e.* resilience). These new concepts are reviewed in this paper. Allostatic stresses lead to a chronic low-grade inflammation that has led to the proposal of the "inflammaging" theory of ageing and frailty. The biology of centenarians, described in this review, provides us with clues for intervention to promote healthy ageing in the general population. One of the major reasons for this healthy ageing has to do with the genetic signature that is specific for centenarians and certainly different from octogenarians who do not enjoy the extraordinary qualities of centenarians.

1. Introduction

World's centenarian population has remarkably increased in the last decades (Collaborators, 2018). Indeed, in the nineties, centenarians in Europe occurred at a prevalence rate of about 1 per 10,000, and nowadays the prevalence rate is around 1 per 5000 (Teixeira et al., 2017). This makes centenarians one of the fastest growing segments of the population, although the limit in this demographic transition for women (i.e. compression of mortality) is uncertain. In this regard, although centenarian women outnumber centenarian men in all countries, the forecasted sex ratio is expected to decrease from 3.7 females for one male centenarian in 2015 to 1.9 females for one male centenarian in 2100 (Robine and Cubaynes, 2017). Fig. 1a and b shows the worldwide distribution of centenarians and the percentage of centenarian population by country, respectively.

The faster growth of the centenarian population is driven mainly by improved life expectancies among those aged 65 and older (Brown, 2015). Improved health care, hygiene, medical care, and healthier life styles have provided this advantage. However, this increase in life expectancy has not been accompanied by an increase in quality of life in the general population. Overall, increased life expectancy has increased the risk of disease, frailty, disability, dementia and advanced ageing prior to death (Brown, 2015). In contrast, centenarians exhibit medical histories with remarkably low incidence rates of common age-related disorders such as vascular-related diseases, diabetes mellitus, Parkinson's disease, and cancer (Andersen et al., 2012) and most remain independent in daily living until into their 90 s (Arai et al., 2017). Needless to say, like in all population segments, a heterogeneity in centenarians' physical and cognitive status exist, depending on their socioeconomic status, or their cultural/historical background (Franceschi et al., 2017b). Despite this fact, they are an example of living longer and better, and they have been proposed as a model of successful ageing (Franceschi et al., 1995). Centenarian-based studies may thus offer clues toward how to achieve healthy ageing. This review provides insights into these studies to better understand the mechanisms underlying healthy ageing.

2. Successful ageing paradigms

The reason by which centenarians constitute an example of successful ageing has been a matter of intense debate, and two major paradigms have emerged.

The most conservative of them was described as "compression of morbidity", in which the rate of disability decrease as morbidity is compressed into the shorter period between the increasing age at onset of disability and death (Fries, 1980). Postponement of chronic illnesses

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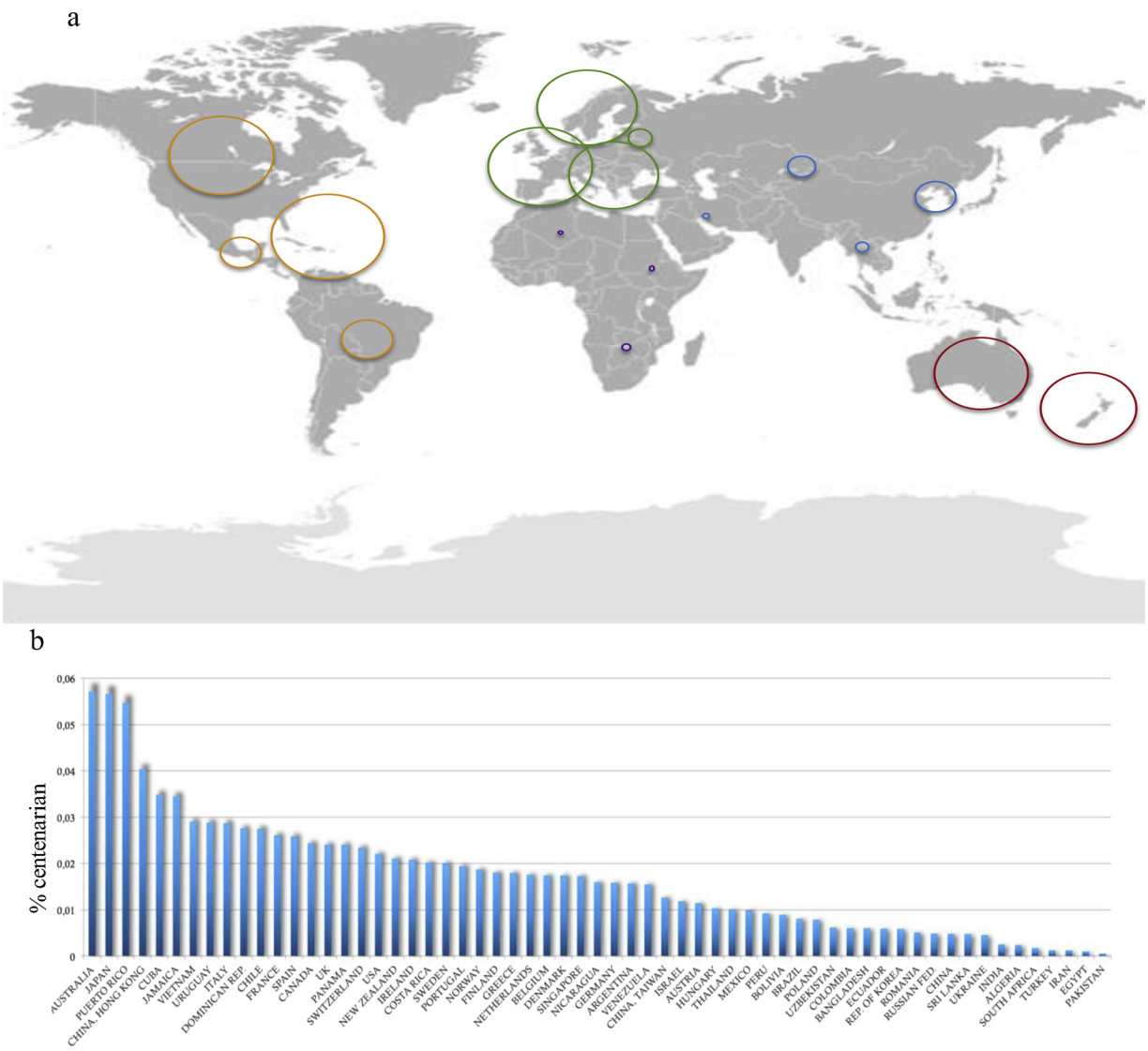

Fig. 1. Centenarian population in the world. a. Worldwide distribution of centenarians. b. Percentage of centenarian population by country. Data taken from Revision of World Urbanization Prospects (https://population.un.org/wpp/DataQuery/).

thus results in rectangularization of both the mortality and the morbidity curve (Fries, 1980). In this regard, a study of Massachussets centenarians thus far indicated that the centenarian cohort really fits Fries' rectangularized morbidity curve, where people live 96 % or more of their lives functionally independent and in good health. Given their extreme age, the period of time in which they experience morbidity is compressed into a small period at the end of their lives (Perls, 1997). According to the "compression of morbidity theory", there are several models of predicted morbidity proposed on the basis of extreme longevity (see Fig. 2a):

- In the first model, the age at initiation of morbidity is constant and life years gains are accompanied by increased morbidity.
- In a second model, both the initiation of morbidity and the accumulated life years are shifted to the right, with no gains or losses of morbidity.
- In a third model, the onset of morbidity is delayed and accompanied by accumulated life years, resulting in a compression of morbidity.

Fries' hypothesis sustained the possibility that chronic morbidity began later in life, and that the delay of onset of morbidity would exceed the increase in life expectancy. In essence, for such longer-living individuals, chronic diseases and associated disability duration is diminished, with the subsequent reduction in cumulative morbidity. Evidence that a reduction in disability occurs about 2 % per year, accompanied by a 1 % per year decline in mortality during the same period of time, supports this hypothesis (Pignolo, 2019).

A more ambitious paradigm is "deceleration ageing" (Fig. 2b). According to this point of view, there is a continuum between healthy and unhealthy ageing, and different age-trajectories can be depicted: accelerated, normal, and decelerated, depending on the age they display age-related diseases/ geriatric syndromes (Franceschi et al., 2018a). Since centenarians avoid or largely postpone the onset of age-related diseases or geriatric syndromes, they show a decelerated trajectory of ageing, in which the natural processes of ageing are slowed (Franceschi et al., 2018a). We believe this "deceleration ageing" may be due, at least in part, to their higher resilience/ intrinsic capacity, that can overcome chronic, low-grade inflammation (inflammageing), and accumulation of molecular garbage (garb-ageing) that accompanies ageing (Franceschi et al., 2018b, a). In other words, resilient centenarians are able to develop anti-inflammageing mechanisms to fight against age-related molecular damage.

It has been suggested that there may be multiple routes to achieving exceptional longevity and that there are sex differences depending on

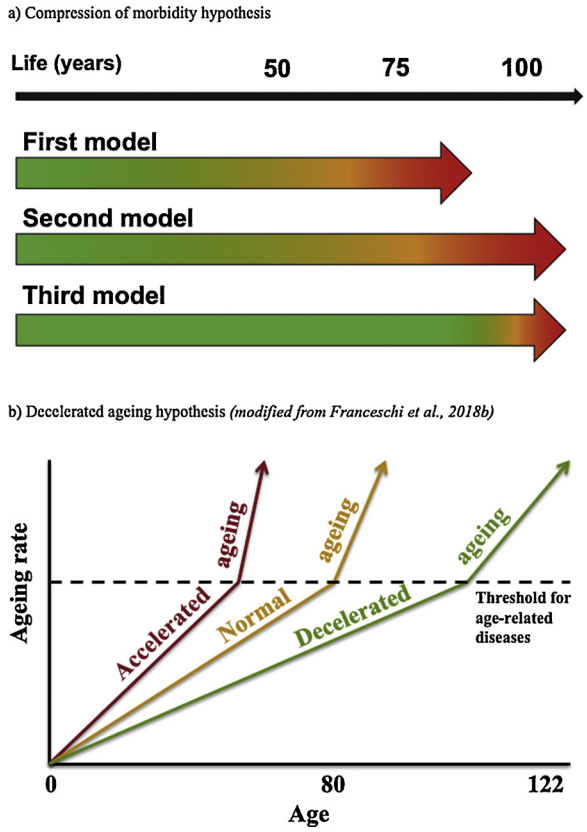

Fig. 2. Successful ageing paradigms.
a) Compression of morbidity hypothesis.
b) Decelerated ageing hypothesis *(modified from* Franceschi et al., 2018b).

which route is taken. These routes represent different phenotypes and thus likely different genotypes of centenarians (i.e. survivors, delayers, and escapers) (Evert et al., 2003).

The sex differences among centenarians regarding functional status are well documented. Centenarian men, although generally scarce in number, tend to have better cognitive and physical functional status than centenarian women. In fact, it has been reported that centenarian men have lower morbidity and fewer geriatric syndromes than women (Hazra et al., 2015). In this regard, whereas compression of both morbidity and disability seems to be an essential feature of survival to an old age for most centenarians, for others, particularly men, compression of disability and not necessarily morbidity, may be the key prerequisite (Terry et al., 2008).

The relationship between age of survival, morbidity, and disability among centenarians (age 100–104 years), semi supercentenarians (age 105–109 years), and supercentenarians (age 110–119 years) has been explored. In this regard, the older the person, generally, the later the onset of diseases, such as cancer, cardiovascular disease, dementia, and stroke, as well as of cognitive and functional decline (Andersen et al., 2012). More specifically, it has been suggested that survival at these high ages depends primarily on maintaining functional integrity rather than on preventing specific diseases (Nascimento et al., 2019).

Furthermore, centenarians display less comorbidities (average 3.3) and have a less steep rise of comorbidities over the final years before death, compared to nonagenarians or octogenarians, as demonstrated in a German cohort study (Gellert et al., 2018). Physical frailty and depression are two common comorbid conditions that have an important impact on older adults. A study performed on 91 centenarians found that from these, 5.5 % were classified as robust, 42.9 % as pre-frail, and 51.6 % as frail. The prevalence of depression was 35.2 % (51.1 % in frail centenarians; 21.1 % in pre-frail centenarians; 0 % in robust centenarians) in the whole sample. Frail centenarians presented higher risk of depression when compared to pre-frail centenarians, thus leading to the conclusion that depression is a comorbid clinical independent condition that is frequent in frail and pre-frail centenarians (Ribeiro et al., 2018).

3. The concepts of resilience and intrinsic capacity

Human ageing has traditionally been regarded as a negative and deleterious process. From this point of view, ageing has been associated with disease, frailty and care dependence. In the recent years, a more positive view of ageing has emerged, with the introduction of the concepts of “healthy ageing” or “successful ageing” (Bowling and Dieppe, 2005; Strawbridge et al., 2002). This has prompted to the need of new definitions of what “healthy ageing” is. Health is not merely defined by the absence of disease and we require positive concepts to assess which individual is ageing in a healthier way.

The concept of resilience was originally used to define the ability of elastic materials to regain its original shape after being bent (Tredgold, 1818). From there, the concept spread and has been used and studied from several viewpoints, such as physiological, psychological or economical (Karatsoreos et al., 2013; Tugade and Fredrickson, 2004; Whitson et al., 2016). Overall, it refers to the capacity to respond to or recover from relevant stresses.

In its classical definition (Bernard, 1957) homeostasis is regarded as the needed mechanisms to control the stability of the internal milieu, such as blood pressure, pH, or glucose level, which all are essential for every life form. When the internal mileu is disturbed, our different tissues and systems respond to maintain the homeostasis, the effectiveness and swiftness of this response reflects the resilience of an organism. Consequently, in a physiological context, resilience can be defined as the organism’s ability to recover from stressors that disturb the homeostasis of the system, such as surgery, infection or cancer (Kirkland et al., 2016).

Ageing is characterized by an accumulation of several types of damage, but also with a decrease in the ability to cope with this damage, hence resilience is diminished during ageing (Fontes and Neri, 2015).

Resilience is closely related to the concept “intrinsic capacity”, since the intrinsic capacity of an individual could be determined by the composite of all its physical and mental capacities, which is to say, the biological reserves of the organism (Cesari et al., 2018). These biological reserves make possible the recovery of the biological system after any stress may occur. Therefore, a higher intrinsic capacity would result in a more resilient individual. Although these two concepts may sound interchangeable, resilience considers not only the biological status of the individual, but also its sociocultural environment.

The World Health Organization (WHO) recently published the World Report on Ageing and Health (2015). In this report, the WHO encouraged to shift the focus from “disease” to “capacity” in the elderly. As the rate of physiological and functional declines are highly specific to the individual (Lauretani et al., 2003), we should not only diagnose diseases at a particular point in time, but also monitor trajectories across the life course, in order to develop interventions for the enhancement of the intrinsic capacity of the elderly, thus increasing the individual’s resilience (Beard et al., 2016). Furthermore, resilience may play an important role in the hormetic response of the individual against the low grade inflammation that accompanies ageing (inflammageing) (Franceschi et al., 2018b).

Frailty is defined as an increased vulnerability to external stressors resulting from ageing-associated decline in reserve and function across multiple physiologic systems (Fried et al., 2001). Consequently, one may consider resilience as the opposite of frailty. However, although they may be part of the same process, the loss of resilience occurs considerably earlier than the onset of frailty. For example, in Europe, less than 10 % of people below the age of 65 are frail (Santos-Eggimann et al., 2009), however, the walking speed begins to decrease at the age

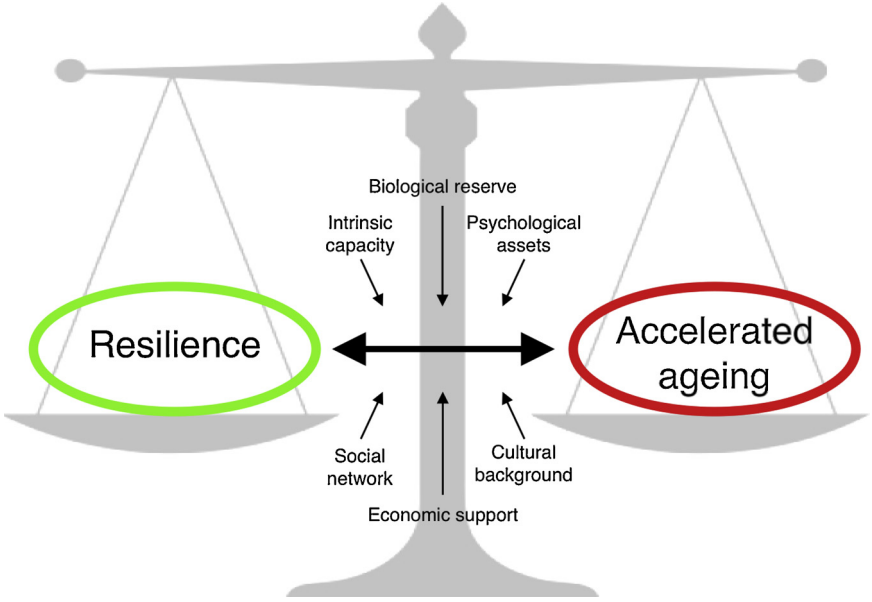

Fig. 3. Relationship between resilience and accelerated ageing and factors that may influence it.

of 40 (Ferrucci et al., 2016). Indeed, the frailty phenotype is a geriatric syndrome while the loss of resilience occurs much earlier than the geriatric age, as part of the lifelong continuum between healthy and unhealthy ageing (Franceschi et al., 2018a). Within this perspective, successful aged individuals (*i.e.* centenarians) do not scape the physiological decline or the age-related diseases or syndromes (*i.e.* frailty), but the rate of such processes is slow enough to be counterbalanced by their resilience/ intrinsic capacity. In this regard, resilience and intrinsic capacity may be considered as two measures of health that begin to decrease much earlier than the onset of age-related diseases/ syndromes or dependence in the elderly. Thus, monitoring and promoting them by means of biomarkers may have enable to delay age-associated functional decline. In the absence of reliable and valid biomarkers of resilience, some measurements of biological resilience may be informative of the biological age of the particular individual.

We propose centenarians as a good example of resilience, since they show a decelerated ageing, thus maintaining their functionality and overall health status well into an old age, when compared to people displaying normal or accelerated ageing (Fig. 3).

3.1. Measures of resilience in aged mice

The ability to survive or recover from a stressor is informative of the underlying health of the animal. The optimal outcome would be a fast and full recovery and return to homeostasis after the stress has finished. The ability to response to such stressors (*i.e.* starvation, water deprivation, exposure to chemicals and radiation) is known to be compromised with age, and may eventually lead to frailty. In contrast, adaptive recovery from such stressor fosters resilience (Kirkland et al., 2016). Importantly, when measuring resilience as an indicator of the overall individual's performance/function decrease and aging acceleration/ deceleration phenomena (Franceschi et al., 2018a), integrative responses involving multiple organs or tissues are desirable. Moreover, it is likely that a battery of tests, rather than a single one, will be most informative. The ideal battery of tests should have a wide dynamic range in the response that allows to classify the individual in robustly resilient, normal, and poorly or non-resilient. In this regard, interventions that improve resilience outcomes in mice may be extrapolated to humans, in order to enhance extraordinary ageing (i.e. centenariety) and delay ordinary ageing (that usually leads to frailty) or vice versa. For example, it has been proposed that long-lived individuals' exceptional phenotype is related to a specific nutritional habit complemented by an active everyday life. (Franceschi et al., 2018c). Thus, these interventions may be implemented in animal models, followed by a set of measurements of resilience, to gather information about the physiological mechanisms underlying decelerated ageing and resilience. Table 1 summarizes studies where outcome measures of resilience in ageing have been proposed in mice.

3.2. Measures of resilience in aged humans

A considerable amount of research has focused on psychological resilience influenced by social and behavioural stressors in humans. Nevertheless, limited research has been done on physiological or functional resilience, which is critical in the ageing process. Advanced age is accompanied by an increasing exposure to both external and internal stressors, such as the so-called inflammaging or Garb-aging, that fosters an accelerated ageing (Franceschi et al., 2018a,b). An optimal physiological/functional ability to recover from such stressors may result in a resilient individual. Thus, we propose that an optimal outcome in a set of measurements of resilience (summarized in Table 2) can result in desirable clinical or functional outcomes, and can thus serve as goals for health maintenance or therapeutic strategies.

Further studies to validate the measurement of resilience proposed both in mice and humans are needed. This may allow them to be implemented in the clinical setting as biomarkers of very successful ageing, in contrast to ordinary ageing.

4. Ordinary versus successful ageing

In the past decades new paradigms have emerged including the concept of "successful ageing" (Rowe and Kahn, 1997). Attention has been paid to quantify healthy ageing by measuring age-related changes in morbidity, physical function and cognitive status in order to avoid disability. In this regard, centenarians seem to delay or avoid major clinical diseases (i.e., heart disease, nonskin cancer, stroke) and disability, especially in their oldest age period (Evert et al., 2003). Indeed, they maintain such a remarkable health status until into their later years of life that their health span is similar to their lifespan, thus being considered as a model of "successful ageing", as first proposed by Franceschi C et al. (Franceschi et al., 1995). In this regard, the Tokyo centenarian study (TCS) found that most centenarians remained

Table 1
Summary of studies where resilience measures have been performed in mice.

Stressor	Function, organs and systems affected	Outcome measures	References
Starvation, water only-fasting	Metabolism, immune system, muscle and liver cells, and various organs	Body weight, glucose and ketone bodies levels, behaviour tests, muscle strength	(Kirkland et al., 2016)
Water deprivation or dehydration	Endocrine, renal and central nervous system components that control fluid and electrolyte balance	Physical and cognitive tests, renin-aldosterone system tests, blood urea nitrogen/creatinine ratio, blood and urine osmolality and blood and urine sodium	(Kirkland et al., 2016; Wilson and Morley, 2003)
Surgery with anaesthesia (partial hepatectomy)	Learning and memory abilities	Y-Maze test, IL-1β, HMGB1, S100B, NF-KB p56 and RAGE expression levels, glial fibrillary acidic protein (GFAP)-positive cells in the hippocampus	(Li et al., 2013)
Exposure to chemicals and radiation (paraquat, Cyclophosphamide, isoflurane and others)	Redox balance, DNA replication, apoptosis, immune system, cognitive function (*i.e.* memory and learning abilities), nervous system, inflammatory response (depending on the chemical agent)	Treadmill endurance, survival curves, cognitive tests (*i.e.* the Novel Object Recognition test, Fear Conditioning Test and Y-Maze test), rebound neutrophil count (depending on the chemical agent).	(Kirkland et al., 2016; Li et al., 2014; Schorr et al., 2018; Schosserer et al., 2018)
Cold stress	Thermoregulation, sympathetic nervous system, thyroid gland and muscle mass	Body temperature, VO_2, dry heat loss	(Kirkland et al., 2016; Schorr et al., 2018; Shefer et al., 1996)
Trauma: bone fracture	Bone metabolism, osteosynthesis	Gait analysis for bone fracture, sonic hedgehod protein expression	(Holstein et al., 2009; Kirkland et al., 2016; Matsumoto et al., 2016; Schosserer et al., 2018)
Trauma: Brain injury	Brain tissue, nervous system, behaviour, memory and learning abilities	Morris water maze, radial water trad maxe	(Carbonell et al., 1998; Cline et al., 2017; Drechsler et al., 2016; Kirkland et al., 2016; Schosserer et al., 2018)
Trauma: burn	Multiple organs and functions	Wound area or injury size, macrophage-derived mediators as IL-6, monocyte chemoattractant protein-1 (MCP-1) levels	(Drechsler et al., 2016; Kovacs et al., 2002; Schosserer et al., 2018; Shallo et al., 2003)
Sleep Deprivation	Memory and glucose metabolism	Radial water tread maze, radial maze test and blood glucose	(Naidoo et al., 2014; Schorr et al., 2018)
Sepsis	Immune system, inflammatory response	Hypothermia, serum IL-6 levels	(Saito et al., 2003)
Polypharmacy	Multiple organs and functions	Open field test, rotarod, grip strength and gait speed, locomotor activity, front paw wire holding impulse, rotarod latency and blood pressure	(Huizer-Pajkos et al., 2015; Schosserer et al., 2018)
Ischemic injury	Depending on the ischemic injury	Depending on the ischemic injury. For brain ischemia: bbehavioral and cognitive tests as radial-arm water maze, Y maze test, NOR paradigm	(Maki et al., 2011; Patel et al., 2017; Schosserer et al., 2018; Wolf et al., 2017)
Noise exposure	Redox balance, memory, inflammatory response	Auditory brainstem response, cytokine TNF-α and IL-1 α, NOR test and radial arm maze test, oxidative stress	(De Wazieres et al., 1998; Miller et al., 1998; Münzel et al., 2017; Schosserer et al., 2018; Sikandaner et al., 2017)
Light-dark cycles; Circadian rhythms alterations	Memory, general well-being, survival	Fear conditioned behaviour tests, survival curve	(Davidson et al., 2006; Loh et al., 2010; Schosserer et al., 2018)
Heat stress	Memory, cognitive function, survival,	Body temperature, cognitive tests as passive avoidance and NOR test	(Hoffman-Goetz and Keir, 1984; Lee et al., 2015; Schosserer et al., 2018)

NOR = novel object recognition test.

independent in daily living until into their 90 s. Interestingly, those centenarians who enjoyed physical and cognitive independence at the age of 100 years (20 %), were prone to become semi-supercentenarians (beyond 105 years) or even supercentenarians (over 110 years) (Arai et al., 2017).

Identifying the protective factors that enhance healthy ageing and longevity and translating such findings into evidence-based interventions is becoming a research priority. In this scenario, many studies have been carried out, in order to determine whether centenarians live longer and are healthier than their contemporaries due to genetic, epigenetic or environmental factors (Kirkwood, 2005).

Since centenarians are exposed to the same basic environmental conditions than their contemporaries experiencing an "ordinary ageing", it has been postulated that genetic factors may play a critical role in their longevity (Schoenmaker et al., 2006). Indeed, existing evidence suggests that the genetic contribution to a healthy life span in centenarians may be greater than in the general population (Abbott et al., 1978; Perls et al., 2002). We have determined the exome of centenarian families and provided an initial catalog of genes that may contribute to exceptional ageing (Cash et al., 2014).

In this regard, we previously reported that centenarians show a characteristic miRNA profile that differs from that of ordinary ageing (i.e. octogenarians) (Serna et al., 2012), and provided a possible explanation for this fact: miRNA biogenesis pathway is maintained in centenarians, when compared to octogenarians (Borras et al., 2017). We further demonstrated that the anti-apoptotic factors *BCL-xL, FAS and FAS-L* are overexpressed in centenarians when compared to septuagenarians, with *BCL-xL* playing a critical role in their mRNA profile (Borras et al., 2016). We also showed that centenarians maintain their stemness, this is, the ability to self-renew and replenish their damaged tissues better than octogenarians. Indeed, our results showing that centenarians upregulate pluripotency-related genes may indicate that they are better protected against cellular senescence (a hallmark of ageing), than octogenarians (Ingles et al., 2019).

However, there is growing evidence that non-genetic contributions may also play an important role in longevity. Studies in different animal models have revealed that environmental stimuli that alter lifespan and health span, such as nutrients, exercise, hormones and circadian cycles

Table 2
Summary of studies where resilience measures have been performed in humans.

Stressor	Function, organs and system affected	Outcome measures	References
Exposure to infectious agents	Immune, circulatory, genitourinary, pulmonary and dermatological systems	Avoidance of infection, time of recovery from infection	(Hadley et al., 2017)
Hip fracture	Musculoskeletal system	Recovery of ambulation, fracture union	
Exposure to anticholinergic drugs	Neurological, sensory and renal hepatic systems	Cognitive function	
Walking in uneven surface	Balance	Balance perturbation test, obstacle course performance, continuous postural sway measures on balance platform, step-to-step gait variability	
Bedrest	Muscle, cardiopulmonary capacity	Recovery of the physical function, dynamometry, muscle mass, perceived fatigability at a given physical task intensity, maximum or sub maximum VO_2	
Postsurgical MI	Thrombotic and thrombolytic mechanisms	Cardiac stress test, electrocardiogram, circulating inflammation markers, beat-to-beat sinus rhythm heart variability	
Surgical intervention	HPA Axis, and others	Neuropeptide Y, testosterone, dehydroepiandrosterone (DHEA), stress biomarkers: cortisol, IL-6, C-reactive protein, adrenaline, etc.	(Graham and Becerril-Martinez, 2014)
Physical exercise (treadmill test, Short-term maximum exercise)	Physical performance	Treadmill Test, heart rate by electrocardiogram, oxygen consumption, arterial blood pressure, Rated Perceived Exertion (RPE) Scale, models of heart rate kinetics and other fatigability tests, 12-point Short Physical Performance Battery (SPPB) and fast gait speed.	(Borg, 1982; Dipietro et al., 1993; Simonsick et al., 2014; Stirling et al., 2008)
Cognitive task (Stroop task)	Cognitive function	Cognitive fatigability tests such as the fatigue severity scale (FSS) and the multidimensional fatigue inventory (MFI)	(Krupp et al., 1989; Smets et al., 1995; Wang et al., 2014)
Driving (automated psychophysical test, ATP)	Coordination, cognitive and physical function	Cortisol and insulin levels, glucose tolerance	(Dipietro et al., 2012)
Cardiac surgery	NS	Short form survey, 36 items (SF-36) physical function, cerebral magnetic resonance imaging	(Mathisen et al., 2005)
Perturbations: lab-induced falls OR walk perturbation training/test/assay	NS	Induced falls, stability	(Pai et al., 2014)
Exercise (training and detraining) Long-term medium exercise	NS	Gait speed, rate of ascending and descending stairs and quality of life (Nottingham Health Profile)	(Teixeira-Salmela et al., 2005)

NS = non-specified.

might do so by inducing epigenetic changes (Benayoun et al., 2015). One of the most studied strategy to induce such changes is calorie restriction (CR). Indeed, a study carried out in flies showed that CR is able to delay the normal ageing-associated epigenetic changes (i.e. age-related loss of facultative heterochromatin) within 3 days and in a reversible way (Jiang et al., 2013). In this regard, centenarians are epigenetically younger than their chronological age and are similar to people who have followed calorie-restriction (CR) regimens. This may be due in part to their particular nutritional habits, which involve moderate food consumption (i.e. little meat and animal fat, reduced calorie diet), Mediterranean-type diet and regularity in meal timing, together with active life-styles, and a particular gut microbiota that adapts to age-related changes (Biagi et al., 2017). Interestingly, regularity in meal timing has been suggested to favor their maintenance of circadian rhythms, including their sleep cycle (Franceschi et al., 2018c).

Aside from epigenetics, other biological particularities have been documented. In this regard, it has been shown that centenarians are less prone to oxidative stress and have better antioxidant defenses than ordinary ageing (Borras et al., 2015; Paolisso et al., 1998). Furthermore, they have a particular immunological, endocrinological and metabolic profile, that have been proposed to exert an anti-inflammatory protection against inflammageing (Franceschi et al., 2017a, 1995; Monti et al., 2017). For example, it has been suggested that the hypothyroid state that characterizes centenarians may constitute a protective adaptation against an excessive catabolism, thus favoring longevity by reducing metabolism rate, oxidative stress and cell senescence (Garasto et al., 2017). The endocrine profile of centenarians has been also characterized by a well-maintained glucose handling and insulin sensitivity, while data concerning GH/IGF-I axis are controversial (Vitale et al., 2017). Other biological specific signatures of longevity and healthy ageing in humans have been related to centenarians' lipidomic (Jové et al., 2017; Pradas et al., 2019), glycomic (Monti et al., 2017), metagenomic (Biagi et al., 2017) and metabolomic (Martin et al., 2017) profiles, which may point out the anti-ageing molecular features that endow centenarians with a unique resilience to display a deceleration ageing.

Furthermore, other non-biological factors have been related to healthy ageing. Indeed, psychosocial studies have shown that education (Sebastiani and Perls, 2012), ability to cope with stress (Tafaro et al., 2009), adaptation to the challenges of ageing and social resources (Blazer, 2008) are also protective factors for healthy ageing and longevity among the oldest old people. Moreover, these studies have reported that centenarians display lower scores for anxiety and depression tan octogenarians (Dello Buono et al., 1998).

In the light of the above, it is likely that the prevalence of centenarians is increasing because the ability to survive to extreme old age is multifactorial. Thus, the key for achieving exceptional old age seems to result of a combination of genetics, environment, healthy lifestyle, and… luck.

5. Genetics of centenarians

In view of the foregoing, it is likely that centenarians reach a successful ageing because they display a low rate of ageing (the so-called decelerated ageing), which may be attributable to their extraordinary resilience maintenance. This, in turn, may be related to a unique genetic signature, which likely results from the interaction between the three genomes (mtDNA, microbiome, and nuclear DNA), the environment, and eventual somatic mutations occurring during the aging process (Giuliani et al., 2018).

Thus, the genetics of extreme-longevity has been mapped through

candidate gene analysis, linkage and linkage disequilibrium mapping, copy number variation and more recently, exome and whole genome sequencing. Indeed, whole-genome sequencing is to date the most informative approach for genetic analysis (Giuliani et al., 2018). Scandinavian twin studies and the Seventh-Day Adventist Health Study indicated that most of the variation in survival to mid to late octogenarian years could be explained by differences in environment and behaviors (Sebastiani et al., 2016).

In addition, a study of 2872 Danish twin pairs born between 1870 and 1900 found that the heritability of extreme longevity was 0.26 in men and 0.23 in women. Thus, based on these twin studies, various authors classically stated that the heritability of longevity is approximately 25 percent. However, as discussed by Sebastiani et al. in 2016, precisely these studies suggest that this heritability refers to survival average people may achieve in the absence of environmental factors that predispose to premature mortality and the presence of "health" behaviors (Puca et al., 2018). In this regard, it has been proposed that all factors contributing to the individual's ecological space (*i.e.* gender, individual (immuno) biography, population ancestry, socioeconomic status, family, and education—have to be consider as major variables for disentangling the complex genetics of longevity. Furthermore, these studies include a limited (or null) number of 90+ couples, so that the concept of missing heritability, in the study of complex traits, including longevity, has emerged (Giuliani et al., 2018).

Lifespan was heritable in Icelanders aged over 70 years (Gudmundsson et al., 2000). In line with these findings, the siblings of Okinawan centenarians showed increased probability to survive to old ages, that started at age 55 and increased with age (Willcox et al., 2006). Thus, there is growing evidence that genetic influence on longevity becomes higher with survival to ages beyond 90 years. Accordingly, the heritability of living to at least 100 has been estimated at 0.33 in women and 0.48 in men (Sebastiani and Perls, 2012). Thus centenarians (100 years of age), semi-super-centenarians (≥105 years of age), and super-centenarians (≥110 years of age) are the more informative subjects for investigating the genetics of human longevity (Giuliani et al., 2018). Whether centenarians maintain their reliance because of their extraordinary genetics of vice versa remains to be elucidated.

In this regard, centenarians have been studied extensively to identify the so-called "longevity genes", which might foster resilience. In this regard, a list between 300 to over 750 genes (without including rare copy number variants or alleles) are known to influence longevity in humans. Dato et al. and Shadyab and LaCroix (Dato et al., 2013; Shadyab and LaCroix, 2015) identified many genes including mitochondrial ones, that have been consistently shown to influence human lifespan: *IGF1, SOD1,2,3, P53, APOE1, ATM, BCL, CETP, eNOS, FOXO1A, FOXO3A, KLOTHO, LMNA, TERC, HSPA, NIOS1, 2, 3, RAGE* and others. As stated earlier, we found *APOB*, *PGC1α* and others as important in families of centenarians (Cash et al., 2014). Some of these genes are known to play an important role in cellular and metabolic functions, such as glucose metabolism (*IGF1*), oxidative stress (*SOD3; HSPA*), genome maintenance (*P53*), cognitive pathways (*APOE*), lipid metabolism (*APOE, CETP*), and development (*FOXO1*) (Govindaraju et al., 2015).

A comprehensive study reported that a variant close to APOE gene was found to be associated with survival beyond 90-year-old in the European Genetics of Healthy Aging study (GEHA). Apo E has three common alleles, E2, E3, and E4. Epidemiological studies have suggested that these alleles may affect age-related traits, with E4 and E2 playing a detrimental and a protective role in ageing, respectively. For instance, Schächter and colleagues showed that French centenarians had about half the proportion of E4 and twice the proportion of E2 of the population examined (Schächter et al., 1994).

This lower frequency of the *APOE*-ε4 allele in centenarians is consistent with its risk factor status for heart disease, whereas the increase in the *APOE*-ε2 allele frequency provides evidence for the long-term protective effect of this allele, when acting in later life. In addition, individuals carrying the *APOE*-ε4 allele are more prone to developing Alzheimer's disease (AD), whereas those carrying the *APOE*-ε2 allele display a decreased risk for AD. It has also been reported that a variant of Agiotensin Converting Enzyme (ACE), which predisposes to coronary heart disease, is surprisingly more frequent in centenarians, with a significant increase of the homozygous genotype. Another study in Italian centenarians has shown that the frequency of Apolipoprotein B with low tandem repeats (Apo B VNTR) is 50 % of that in young controls (De Benedictis et al., 1998), but this difference has been not found in French and Finnish centenarians (Gonos, 2000).

As stated before, our group has studied genetics and epigenetics of centenarians, and we found the miRNA and the mRNA profiles were more similar between centenarian and young individuals than compared with the octogenarian individuals (Borras et al., 2016; Serna et al., 2012). We identified three apoptosis-related genes which were involved in the extreme longevity of centenarians: *BCL-xL, FAS and FAS-L* (Borras et al., 2016).

The impact of single nucleotide polymorphisms (SNPs) on longevity is known. However, how genetic factors and their interactions with modifiable behavioral and environmental factors contribute to human extreme-longevity, and most importantly, to successful ageing remains unknown. In this regard, in the largest genome-wide association study (GWAS) ever performed on centenarians, including more than 2000 Han Chinese centenarians, a single nucleotide polymorphism (SNP) mapping in the IL6 gene locus (rs2069837) was ranked top among the genetic variants significantly correlated with longevity, contributing to 1.0 % of the variance of this complex trait (Zeng et al., 2016). Furthermore, the 20 most widely investigated SNPs identified in extreme-longevity are related to *FOXO3A*, *TP53*, *SIRT1* and interleukins (Santos-Lozano et al., 2016). We also performed a genome wide association study in centenarians and found, 5 genes (*DACH1, LOC91948, BTB16, NFIL3 y HDAC4*), based on the presence of at least 2 SNPs, as the most strongly associated with centenarity. Interestingly, these genes are involved in gene expression regulation to adapt to environmental changes (Gambini et al., 2016). In line with this findings, we also observed that frailty, as opposed to successful ageing, is related to SNPs involved in key biological processes, such as energy metabolism, biological processes regulation, cognition, and inflammation (Inglés et al., 2019). The studies regarding genetic variations, although all of them point out important processes in longevity, are not consistent, and more studies are needed to identify the genetic variations that are involved in extreme longevity.

Finally, we consider that resilience constitutes an innovative trait that should be included in the study of the contribution of genetic to extreme longevity (*i.e.* centenarians), in order to elucidate its real contribution to successful ageing.

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Declaration of Competing Interest

The authors declare no Potential Conflicts of Interest.

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