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Aging: a New Perspective on an Old Issue

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Abstract: The world is undergoing a profound demographic change with a rapid increase in the prevalence of aged individuals. The finitude of life, the burden of senescence and the search for strategies to prolong human life span have troubled humanity since ancient times. However, only in the past few decades we started to understand how organisms age and how life span can be manipulated. Here I give an historical perspective of the aging field and conclude with the notion that aging is controlled by signals from the adipose tissue which are tightly controlled by small non-coding RNAs such as miRNAs.

Key words: aging, adipose tissue, miRNAs, longevity, DICER, diabetes.

THE REASONS TO STUDY AGING

The world's population is becoming older. Data from the World Health Organization (WHO) indicate that in 2020, for the first time in history, there will be more people aged 60 years or older in the world than children under 5 (www.who.int). In 2050, the prediction is that the elderly population will represent 22% of the world's population and 80% of the elderly will be concentrated in developing countries (www.who.int). These figures bring up a series of issues. With aging, there is a consequent increase in the risk of chronic diseases such as type 2 diabetes, cancer and hypertension, which diminish the individual's quality of life and increase the costs with health care. In developing countries like Brazil, where life expectancy increased by about 10 years between 1997 and 2017, the burden of an elderly population is even heavier, since public health policies, the economy and pension rules are not mature enough to deal with the increase in the number of individuals who need special and constant care. For reasons like those, the WHO proposes the widespread implementation of a "*Global strategy and action plan on ageing and health*", which recommends policies to promote healthy lifestyles, rehabilitation care and biomedical research focused on interventions capable of preventing not only diseases of aging, but delay aging itself (www.who.int).

Aging is characterized by the progressive deterioration of the body's physiological function, which leads to decreased health, increased incidence of degenerative diseases and, finally, a progressive increase in the risk of death (Austad 2005, Lopez-Otin et al. 2013). Aging is classically approached as an inevitable phenomenon whose problems are treated in a timely and palliative way, aiming only to minimize the suffering of the elderly or extend their life span. In addition, these illnesses, usually manifested by chronic diseases associated with aging, tend to be treated individually. That is, individuals with cancer will be treated to eliminate the tumor, while diabetics will be treated with drugs to lower blood glucose levels.

As much as it is obvious that these people should be treated, these treatments are still palliative, since even with the cure of one of these diseases, the elderly individual continues to be at an increased risk for other diseases that will inevitably kill them. That is why the main health agencies in the world, including the National Institute on Aging (NIA), started to approach aging itself as a clinical entity that deserves to be treated as such. Not by chance, the first clinical study that aims to delay aging itself has recently started (Barzilai et al. 2016).

The impact of having aging as a target for treatment is enormous, not only because aging is the main risk factor for death among humans (GBD 2017), but also because it tends to be one of the main expenses of elderly individuals and governments, and it is potentially a major cause of social inequality. According to Goldman and colleagues, if health systems maintain their current policy, public health costs are expected to double by 2050, creating a burden that many countries will not be able to sustain (Goldman et al. 2013). As proposals to reverse this trend, they consider 4 scenarios: 1) the maintenance of the status quo, 2) a 25% reduction in the incidence of cancer until 2030, remaining fixed after that date, 3) a 25% reduction in the incidence of heart diseases until 2030, remaining fixed after that date, and 4) a 20% reduction in mortality caused by factors related to aging until 2050. According to the authors, someone who is 51 years old in 2030 would have a life expectancy of 35.8 years in the first scenario (status quo), 36.9 years in the second (slowing cancer), 36.6 years in the third (slowing heart disease) or 38 years in the fourth (slowing aging). This represents a greater gain in health span when aging is delayed, even compared to a scenario of extraordinary reduction in the incidence of the two main groups of diseases that most kill human beings. In addition to health gains, intervening with aging would represent savings of approximately 7 trillion US dollars over 50 years in the US alone, while disease retardation scenarios would lead to minimal savings, since the risk of individuals acquiring other chronic disabling diseases remain. The economic revenue of targeting aging could be achieved, according to the authors, by a smaller number of disabled elderly people, which would bring benefits for the productive sector and consumption, in addition to reducing spending on health care. In time, targeting aging could reduce vulnerability of individual against infectious disease outbreaks such as COVID-19 (Zhou et al. 2020).

But is it even possible to delay the aging process itself, or even reverse it as some propose (de Grey 2019)? In 2016, Jan Vijg and collaborators suggested that there is a maximum limit to human life span, and that this limit is around 115 years old (Dong et al. 2016). This article, however, has been challenged in regard to the statistical analysis, and some are convinced that the limit on human longevity proposed by Vijg is not real (Dolgin 2018). In fact, in a more recent study of Italian centenarians, Elisabetta Barbi and collaborators showed that, surprisingly, the risk of death stops increasing with time when individuals reach the age of 105 years (Barbi et al. 2018). The progressive increase in the risk of death is what characterizes the aging process in living beings. Thus, eliminating this increase means, in practice, that aging stops happening after a certain age. According to the study, at 105 years of age, the chance of death remains fixed at around 50% per year. This leads to the conclusion that at a given moment the balance between damage and repair stabilizes, preserving vital functions as they are, ceasing, however without reversing, the aging process. Although the estimates are still up for debate (Beltran-Sanchez et al. 2018, Newman 2018), the question remains: if it is possible to stabilize

and mitigate the aging process at some point in life, why wouldn't it be possible to do it at a younger age?

Evidence that indicates this is possible is abundant in Nature. There are several species that show negligible aging, *i.e.* which do not present an increased risk of death (or hazard rate) with age. For example, some species of turtles live for decades and show no signs of senescence (de Magalhães 2006, Jones et al. 2014, Quesada et al. 2019). The Greenland shark is yet another vertebrate of extreme longevity and can live more than 400 years (Nielsen et al. 2016). Even among closer species and with similar habits, the lifespan can vary greatly. The naked mole-rat (*Heterocephalus glaber*) is a rodent that lives up to 30 years and practically does not develop cancer, unlike other rats and rodents that live a maximum of 5 years (Azpurua & Seluanov 2013). Some species, such as the hydra, are even considered "immortal", or "amortal", because they do not die from causes related to aging (Martinez 1998, Jones et al. 2014). Even in humans, there are cells that can be considered amortal, such as germline cells. In other words, Nature offers us examples of how aging and lifespan can be controlled. Looking at these examples, understanding how individual's senescence rate is determined, and proposing strategies to delay aging are the goals of a growing field called biogerontology.

THE EVOLUTION OF THOUGHT ABOUT AGING

The ability to rationalize the inevitability of death is something that has accompanied human beings since the beginnings, having guided decisions and history itself. This forced acceptance process made humanity appeal to abstract concepts of transcendence and seek to make peace with the fact that aging is inevitable, which has in some ways created barriers, even today, for some to accept evidence that shows how the aging process can be modified.

Even so, the idea (or the ideal) of extending human life is an old one and clearly seen as a noble goal. In his book "Immortality: The Quest to Live Forever and How It Drives Civilization", the British philosopher Stephen Cave writes that the obsession with immortality is at the origin of human conquests and achievements, it is the source of religions, the muse of philosophy, the architect of our cities and the impulse behind the arts (Cave 2012, Cordeiro & Wood 2019). The search for immortality follows myths, legends, rituals, literature, religions and scientific practice since its inception. In III BC, Aristotle already proposed a reason for the acceleration of aging. He suggested that the use of energy (or more precisely, heat) to maintain the vital functions of the human body is potentially destructive (Woodcox 2018). That is, as with objects in general, wear leads to tear. Aristotle also proposed that, although inevitable, aging can be influenced by the environment. The notion of "wear and tear" was reinforced by the famous physician Galen in the II AD (Burstein & Finch 2018), and later, in XVI AD, by the Italian aristocrat Cornaro (1770). Galeno proposed an "attenuated regimen" to his patients, while Cornaro, in his "Discourses on a Sober and Temperate Life", suggested a life without excess. Cornaro lived more than 90 years, which in his days represented more than twice the mean life expectancy of Europeans, serving as an important anecdotal reference for his followers.

The later emergence of Illuminism, Rationalism and the scientific method, as well as advances in Lavoisier's chemistry and the evolutionary theories proposed by Darwin (1859) and Wallace (1858) allowed the establishment of a conceptual basis for the study of aging and its

relationship with reproduction, the availability of nutrients and the ecological balance between species. Among the evolutionary theories that sought to explain the aging process and how it differed between species, Peter Medawar's (a British naturalized Brazilian) on the "Accumulation of Mutations" (Medawar 1952), George Williams' on the "Antagonistic Pleiotropism" (Williams 1957) and Tom Kirkwood's on the "Disposable Soma" (Kirkwood 2005) deserve particular attention. The theory on the "Accumulation of Mutations" suggests that, as the aging process initially takes place in a post-reproductive phase, it undergoes little or no selective pressure. Thus, aging is manifested by the accumulation of low-frequency and late-acting mutations, which do not have a negative impact during the reproductive phase, but, when accumulated, can lead to progressive degeneration characteristic of aging. The "Antagonistic Pleiotropism" theory, on the other hand, says that genes that promote an increase in reproductive and growth capacity, despite being beneficial for the maintenance of species under conditions of high selective pressure, are harmful to individual's longevity, explaining the inverse relationship between life span and reproductive capacity. Similarly, to explain such a dichotomy, the "Disposable Soma" theory states that the organism uses energy to maintain its vital functions (metabolism, reproduction and repair) and that, under conditions of nutritional stress, it allocates most of the resources to the maintenance of the soma in detriment of the germline. This results in a decrease in fertility and an increase in life span, which keeps the individual alive for a longer period so that it increases its chances of resuming reproduction when the period of nutritional scarcity ceases.

In addition to the evolutionary theories, at the end of the 19th century and the beginning of the 20th century, ideas surged to propose explanations for factors that seemed to determine the rate of aging, among them the correlation between the metabolic rate and life expectancy. When observing the differences in the life span of some species, the German physiologist Max Rubner suggested that the life span of each organism should be determined by its metabolic rate. This hypothesis gained strength years later in Raymond Pearl's publication "The Rate of Living", where when expanding Rubner's analysis to other species, Pearl stated that the life span of an organism is inversely proportional to its rate of living, that is, to the rate of energy expended by each organism during its life time (Pearl 1928).

These observations, combined with the evidence obtained in the following decades that free radicals produced in response to radiation or by cellular metabolism itself caused damage to macromolecules, including DNA, causing mutations and premature aging (Hempelmann & Hoffman 1953, Stein & Weiss 1948, Commoner et al. 1954, Michealis 1951), led the physician Denham Harman to propose his theory of aging based on free radicals. In "Aging: A Theory Based on Free Radicals and Radiation Chemistry", Harman speculates that both aging and degenerative diseases are caused by attacks by free radicals to basic cellular components (Harman 1956). Because they are generated largely in the mitochondria in response to increased energy demand, free radicals derived from reactive oxygen species (ROS) are the major culprits in this process. This theory elicited the idea of using antioxidants against aging. However, numerous reports have shown that the elimination of oxidizing agents is not enough to delay aging. In part, this is because these molecules also serve as signals for a more efficient cellular response against endogenous and exogenous damage – a mechanism often

named mitohormesis (Ristow & Schmeisser 2014).

The first theories that tried to explain aging through a biochemical perspective could not remove the stigma of aging being a passive, entropic, non-reversible and, above all, inevitable process. Between the 80s and 90s, however, studies with the nematode *Caenorhabditis elegans* began to challenge this notion. The laboratories of Tom Johnson and Cynthia Kenyon, in a pair of seminal articles (Friedman & Johnson 1988, Kenyon et al. 1993), discovered two genes whose mutations could lead to a considerable increase (up to 2x) in the nematode life span. These were the first direct evidence to show that genes can control life span. It was later discovered that these genes participated in the same pathway, conserved in humans, that is, the insulin and IGF-1 signaling pathway (Kimura et al. 1997). These data brought a clear demonstration that aging is influenced by metabolism, giving molecular basis to the classical theories. Furthermore, given the evolutionary conservation, these studies revolutionized the way scientists started to think about human aging, since for the first time in history scientific evidence suggested that aging could potentially be genetically manipulated. This enthusiasm was fueled by subsequent discoveries that showed the role of several other genes in controlling longevity (Kenyon 2010), in addition to showing that reduced insulin/IGF-1 signaling increases life span of other animal models (Bluher et al. 2003, Broughton et al. 2005, Taguchi et al. 2007, Selman et al. 2009) and were correlated with the very low incidence of cancer and the absence of type 2 diabetes in certain human populations (Guevara-Aguirre et al. 2011).

More recently, in an initiative to compile the main finding in the field of the past couple of decades, López-Otin and collaborators listed 9 hallmarks of aging: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication (Lopez-Otin et al. 2013). The authors also propose interventions that, by acting on these marks, could extend the health span in humans. Some of them, such as senolytics, which selectively eliminate senescent cells, are so promising that they are being envisioned as a strategy for rejuvenation (Xu et al. 2018). As of today, their effects in humans are being explored in several clinical trials.

THE RELATIONSHIP BETWEEN GENES AND THE ENVIRONMENT DETERMINES LIFE AND HEALTH SPAN

Of all interventions capable of delaying aging, dietary (or caloric) restriction is undoubtedly the best known and well-studied. In 1935, McCay and colleagues showed that decreasing food intake without malnourishment increases the longevity of rats (McCay et al. 1935). More recently, studies have shown that eukaryotes from yeasts to primates benefit from health span extension when subjected to dietary restriction (Fontana & Partridge 2015). In general, dietary restriction results in a delay of the aging process and decreases the incidence of age-related diseases (Genaro et al. 2009, Merry 2000). On the other hand, increased calorie intake and obesity accelerate the manifestation of age-related symptoms (Burton & Faragher 2018).

The synthesis of the findings of McCay, Johnson, Kenyon and many others aroused the interest of the scientific community, as it revealed a relationship between metabolism and genes, which in turn could be controlled to determine the individual's rate of aging. The strategy to understand the relationship between

metabolism and aging has relied largely upon genetic studies performed in model organisms which unveiled the mechanisms of action of dietary restriction and identified conserved pathways capable of influencing life span in different species. Among the best characterized pathways in this context are: 1) nutrient-sensing pathways (mediated by mTOR, GCN2 and AMPK kinases); 2) hormonal and growth pathways (e.g., insulin, IGF-1 and GH); 3) pathways that control redox balance and mitochondrial function (e.g., antioxidant or pro-oxidant molecules, stress response pathways such as the unfolding protein response or autophagy); 4) pathways controlling cell cycle, cell death and senescence (e.g., those mediated by telomerase, p53, p16 or by the senescence-associated secretory phenotype); and 5) epigenetic changes (e.g., histone modifications, methylation or silencing by non-coding RNA) (Gallinetti et al. 2013, Masoro 2005, Taormina & Mirisola 2014, Wang et al. 2010, Yun & Finkel 2014, Fontana & Partridge 2015).

ADIPOSE TISSUE: A METABOLIC "THERMOSTAT" THAT PARTICIPATES IN DETERMINING THE RATE OF AGING

The strong link between metabolism and aging is reinforced by the special relationship between adiposity and longevity, health span and age-related diseases. Obesity, which is characterized by the excessive accumulation of adipose tissue, is one of the main risk factors, along with aging, for the development of type 2 diabetes, cardiovascular diseases and cancer (Hruby et al. 2016). In addition, at least part of the beneficial effects of dietary restriction in mammals is known to be mediated by adipose tissue (Buemann & Tremblay 1996, Huffman & Barzilai 2009, Liao et al. 2011, Mitchell et al. 2016). In fact, the reduction or expansion of adipose mass using surgical or genetic techniques has an impact on the risk of chronic diseases and affects the mean and maximum life span in rodents (Huffman and Barzilai 2009). On the other hand, excessive energy consumption leads to fat accumulation and increases the risk of mortality and chronic diseases that normally appear with aging (Baur et al. 2006, Huffman & Barzilai 2009). Obesity can also increase the expression of markers associated with senescence in adipocytes (Minamino et al. 2009, Schafer et al. 2016, Burton & Faragher 2018). Interestingly, inhibition of p53 protein activity in adipose tissue reverses these senescence-related changes, decreases the expression of pro-inflammatory cytokines and improves insulin resistance in type 2 diabetic mice (Minamino et al. 2009). In contrast, an increase in p53 activity in adipose tissue causes an inflammatory response that leads to insulin resistance. The elimination of senescent cells also protects against obesity-induced adipose tissue dysfunction (Palmer et al. 2019). Together, these data suggest that changes that occur in adipose tissue can modulate aging and the risk of age-related diseases. In fact, the fat-specific insulin receptor knockout mice (FIRKO mice) (Bluher et al. 2003) or mice in which C/EBPα was replaced by C/EBPβ (β/β mice) (Chiu et al. 2004) are long-lived and have a reduction in adiposity. Beyond longevity, the FIRKO mice also exhibit extended health span, which includes improved mitochondrial function and increased whole-body glucose tolerance (Bluher et al. 2003, Katic et al. 2007). This points out to the important role of adipose tissue in controlling whole-body metabolism, thus affecting organ function at a broad spectrum.

Adipose tissue is an extremely plastic tissue, constituted by a variety of cells, such as pre-adipocytes, macrophages, fibroblasts, mesenchymal stem cells and adipocytes, the latter being the main cells of our organism

capable of storing fat (Wisse 2004). The primary role of the adipocyte is to store energy in the form of triglycerides during periods when calorie supply exceeds energy expenditure, and to mobilize fatty acids for oxidation in periods of food shortage or physical activity (Fruhbeck et al. 2001). There are different types of adipocytes, including the white adipocyte, which plays a major role in energy storing; the brown adipocyte, which is highly thermogenic; and the beige adipocyte, which is also thermogenic but is recruited in deposits of white fat in response to stimuli such as cold exposure or physical exercise (Rosen & Spiegelman 2014).

Adipose tissue also plays an important endocrine role and responds efficiently to nutritional changes to maintain the body's energy homeostasis, which mainly includes maintaining the balance between energy availability, growth, repair and reproduction. Several types of molecules and more complex structures such as extracellular vesicles are secreted by adipose tissue to control satiety, energy expenditure, insulin signaling, inflammation, senescence, bone and muscle growth and fertility (Sales et al. 2019, Mori et al. 2019, Deng & Scherer 2010, Holloway et al. 2002, Reverchon et al. 2014, Waki & Tontonoz 2007, Charles et al. 2017, Yoshida et al. 2019). These signals act in the periphery and also in the central nervous system, where they may affect behavior, cognition and neurogenesis (Forny-Germano et al. 2018). An example is adiponectin, an adipokine that is involved in energy metabolism, cardiovascular function and inflammation (Wang & Scherer 2016), while also acts in the brain to induce neurogenesis and antidepression-like behavior in mice (Yau et al. 2014, Zhang et al. 2016). It is interesting to note that these parameters represent important determinants of the rate of aging in multicellular organisms, which again attributes to adipose tissue a key role in longevity and healthspan (Figure 1).

THE RNA INTERFERENCE PATHWAY AND THE CONTROL OF CELLULAR ROBUSTNESS AND AGING

Small RNAs are a class of non-coding RNAs whose existence and function had been underestimated until the early 1990s, when discoveries in the nematode *C. elegans* showed the importance of these molecules for the regulation of gene expression in eukaryotes. Andrew Fire and Craig Mello (Fire et al. 1998) discovered, in 1998, that the injection of double-stranded RNA (dsRNA) in *C. elegans* causes potent and specific gene silencing. Remarkably, the effect of this silencing is transmitted to

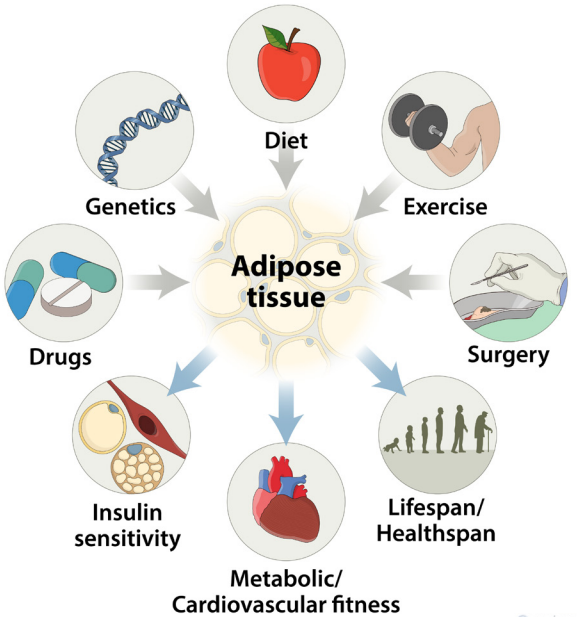

Figure 1. An adipocentric view of aging. The adipose tissue responds to interventions such as diet (e.g., dietary restriction), exercise (e.g., aerobic exercise training), drugs (e.g., thiazolidinediones) and surgeries (e.g., bariatric surgery) and controls whole-body metabolism leading to changes in insulin sensitivity, metabolic/cardiovascular fitness and lifespan/ healthspan.

the germline, spreads through the cells of the organism and causes intergenerational changes (Fire et al. 1998). This discovery led to the identification of a new biological process of epigenetic nature called RNA interference (RNAi). A few years earlier, the laboratories of Victor Ambros and Gary Ruvkun had identified a 21-nt RNA called *lin-4* which controls the nematode's developmental timing (Lee et al. 1993, Wightman et al. 1993). Complementary sequences to *lin-4* were present in the 3' untranslated region of the messenger RNA of *lin-14*, a protein coding gene that interacted genetically with *lin-4* and whose product appeared to be downregulated by this small RNA (Lee et al. 1993, Wightman et al. 1993). These were the molecular bases that supported the description of mechanisms of RNA-based gene regulation and that culminated in the discovery, in the early 2000s, of molecules similar to *lin-4*, called microRNAs (or miRNAs). Very quickly it was found that miRNAs were part of a class of numerous and conserved small non-coding RNAs (Lagos-Quintana et al. 2001, Lau et al. 2001, Lee and Ambros 2001, Reinhart et al. 2000). In addition to miRNAs, other small non-coding RNA species with regulatory role have been described since then, including rasiRNAs (repeated associated small interference RNAs), snoRNAs (small nucleolar RNAs), snRNAs (small nuclear RNAs), piRNAs (piwi-interacting RNAs) and siRNAs (small interference RNAs) (Dogini et al. 2014).

Mechanisms of RNAi are present in the vast majority of species; rudimentary in yeast, but highly complex in plants and metazoans (Geley & Muller 2004). RNA interference is triggered by dsRNAs that can be introduced exogenously and give rise to small interference RNAs (siRNAs), or expressed endogenously and give rise to miRNAs or endo-siRNAs (Elbashir et al. 2001, Rana 2007). In most species, RNAi serves as a fundamental process for gene expression regulation. RNAi also appears to protect organisms against mobile genetic elements, such as RNA viruses or transposons, preventing these sequences from being expressed (Elbashir et al. 2001, Rana 2007, Maillard et al. 2013).

The production of siRNAs and miRNAs requires endonucleolytic processing of long dsRNA molecules. DICER - a type III endoribonuclease - converts long dsRNAs into smaller, functional dsRNAs, with 21-23 base pairs and 2 nucleotides overhanging at the 3'end and a phosphate group at the 5' end. In addition to showing RNase III activity and binding to dsRNAs, DICER has a helicase domain in the amino-terminal DEAD-box, followed by a DUF283 domain and a PAZ domain, which specifically binds to the 3' end of single-stranded RNAs (Jinek & Doudna 2009, Rana 2007).

In metazoans and plants, the main effectors of the RNAi pathway in somatic cells are miRNAs. In general, miRNAs recognize complementary sequences in the 3'-untranslated region of mRNAs and induce destabilization of the transcript or inhibit their translation. Thus, each miRNA can fine-tune the expression of hundreds of mRNAs. As a consequence, the prediction is that at least 30% of the human genome is regulated by miRNAs, thus constituting one of the main processes for gene expression regulation of the cell (Bartel 2009, Guo et al. 2010, Stark et al. 2005). In general, miRNAs are expressed in a temporal or tissue-specific manner, which further suggests a regulatory role for these molecules in maintaining cellular identity and robustness (Kosik 2010). miRNAs are synthesized through the pathway depicted in Figure 2.

The regulation of miRNA expression, as well as that of some components of its processing pathway, has already been described in some physiological processes, such as during development, and in various pathological processes. For example, reduced expression of

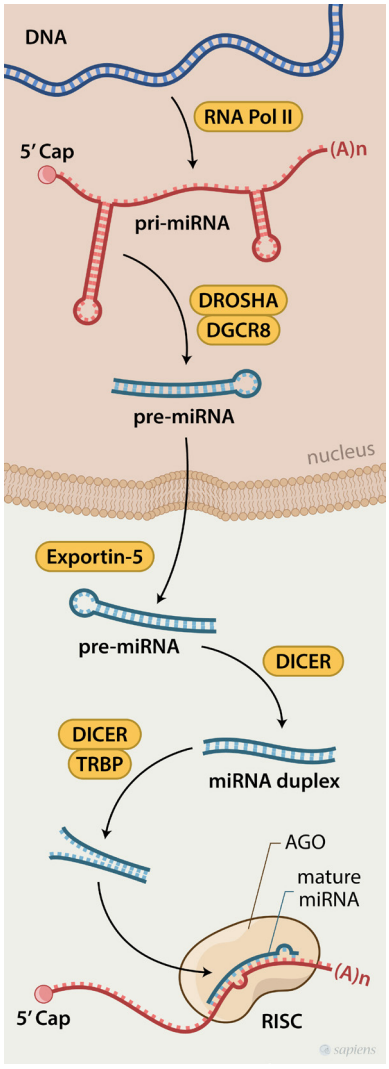

Figure 2. The miRNA processing pathway. Schematic representation of the mechanism of synthesis and processing of miRNAs in mammalian cells. Primary miRNA transcripts (pri-miRNA) are synthesized by RNA polymerase II, many of them corresponding to intronic regions or clusters of miRNAs. Pri-miRNAs are processed in the nucleus by the microprocessor complex (containing DROSHA and DGCR8), or by components of the splicing machinery (not depicted in the figure), for the generation of miRNA precursors (pre-miRNAs). These molecules are then exported to the cytoplasm by Exportin-5 and recognized there by DICER. DICER cleaves the pre-miRNAs and with the help of TRBP gives rise to mature miRNA molecules, which then recognize their target mRNAs and recruit the RNA-induced silencing complex (RISC) to mediate the silencing process (i.e., inhibition of translation and/or mRNA decay) through the action of Argonaute proteins (AGO) such as AGO2.

miRNAs as well as *DROSHA* and *DICER*, has been observed in several cancers and correlated with the poor prognosis of the disease (Lu et al. 2005, Merritt et al. 2008, Lai & Chen 2018). Changes in miRNA expression have also been associated with senescence and different metabolic, cardiovascular and neurodegenerative diseases in mammals (Couzin 2008, Hackl et al. 2010, Krutzfeldt & Stoffel 2006, Munk et al. 2017).

My group has been particularly interested in understanding how miRNAs and the miRNA processing pathway participates in the aging process. We found that miRNA biogenesis is reduced in adipose tissue of mice with aging or obesity due to a reduction in DICER levels (Mori et al. 2012, Oliverio et al. 2016). Interestingly, this phenomenon appears to be conserved in species from *C. elegans* to humans (Mori et al. 2012). Dietary restriction reverses this pattern in worms and mice (Mori et al. 2012, Guerra et al. 2019). Consistent with a role of DICER in delaying aging and increasing health span, fat-specific DICER knockout mice exhibit insulin resistance, dyslipidemia, impaired mitochondrial function and a significant proportion of these animals die prematurely (Mori et al. 2014), while worms that overexpress DICER in the intestine (the closest analog to mammalian adipose tissue) are stress resistant and live slightly longer (Mori et al. 2012). Moreover, dietary restriction requires DICER to induce adipose tissue browning in mice and prolong life span in worms (Guerra et al. 2019, Reis et al. 2016). Finally, pharmacological stimulation of the miRNA processing pathway with enoxacin promotes longevity (Pinto et al. 2018). We also found that adipose tissue is a major source of circulating exosomal miRNAs in mice and potentially humans, and that these miRNAs mediate intertissue communication (Thomou et al. 2017). In turn, when adipose tissue miRNA biogenesis is defective, gene expression in other tissues such as liver becomes dysregulated. A

review on the role of small non-coding RNAs in adipose tissue and their impact on aging and metabolism has been recently published and it could be used as a comprehensive or specific source of information on the topic (Brandao et al. 2017).

In conclusion, aging is accelerated when miRNA biogenesis becomes impaired in adipose tissue or in analog tissues. Under this circumstance, stress response, which requires rapid and efficient upregulation of specific miRNAs, is limited and cells become exposed to more damage. Given the role of adipose tissue and miRNAs in endocrine regulation, these changes eventually contribute to "altered intercellular communication" as observed in aged individuals. In contrast, interventions that promote miRNA biogenesis, such as dietary restriction and enoxacin, prolong life and health span. Hence, I envision strategies to sustain miRNA production in adipocytes and other cell types as potential therapies to treat age-related diseases and to potentially reverse a trend that is leading the world to a profound demographic and socioeconomic change, *i.e.* aging.

CONCLUSIONS

The world's population is undergoing a drastic demographic change, leaving societies to wonder how to deal with the overwhelming increase in the number of elderly individuals which depend on health care and social assistance. Recent advances in the field of biogerontology have helped scientists to understand what happens when we age and what can be done about it. Experiments using animal models have demonstrated that life and health span can be extended through changes in lifestyle and potentially by drug or nutritional interventions. In principle, if translated to humans, these interventions could render us several additional healthy and productive years. The next important step is to understand whether the same interventions can be applied to human beings and if they exert the same benefits observed in animal models. This will require time, investment, commitment and a strategical plan that involves professionals from different areas. I hope this article provided sufficient arguments to justify the urge for it.

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