CHALLENGE 7

ABSTRACT

Advanced age significantly increases the risk of developing chronic diseases such as cancer, diabetes, cardiovascular, immune and mental disease. Regarding the latter, advanced age is a necessary factor for the development of non-hereditary forms of neurodegenerative diseases such as Alzheimer's and Parkinson's. Despite years of intense research, we still do not know how these diseases occur, this being one of the main reasons for the lack of adequate interventions to prevent or cure these pathologies. To overcome the current limitations in the field, we plan to: 1) generate basic knowledge on the mechanisms responsible for cognitive, behavioral, motor, metabolic and sociability disorders that occur with age, 2) define the mechanisms that determine individual susceptibility to neurodegeneration, 3) design and develop strategies to improve brain aging, and 4) explore social and environmental conditions of the older population to know their influence in brain degeneration. Individual, social and policy interventions must be considered for future research.

KEYWORDS

genes | neurodegenerative diseases | Alzheimer's disease | diabetes | cardiovascular disease | immune system | microbiota | pharmacological interventions | nutrition | learning | memory | lifestyle | social support | environment | physical activity | public policies

CHALLENGE 7

AGING & BRAIN DEGENERATION

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1. INTRODUCTION AND GENERAL DESCRIPTION

Spain, with one of highest life expectancies, is expected to become the world's second oldest country by 2050. Although this fact can be a matter of national pride, representative of both good standards of life and a good health system, it is also a matter of social and political concern. In fact, aging is the main risk factor for disease and death (in the developed world) and the rise in longevity of the population dramatically increases the number of individuals with chronic diseases, many of them disabling, such as cancer, cardiovascular diseases, type 2 diabetes, and dementias like Alzheimer's disease. It is estimated that there are more than 10 million new cases of dementia each year worldwide, that is, one new case every 3 seconds. And in addition to the personal and family, emotional and financial costs, the total burden of dementia represents more than 1% of GDP worldwide.

In the last two decades, thanks to genetics studies we have come to the conclusion that non-Mendelian age-related disorders are consequence of the interaction between multiple genes (i.e., polygenic) and environmental factors. In this scenario, neither of these two factors is sufficient in itself to produce

disease; this will occur in those individuals who have the most "complete" portfolio of both, i.e. predisposing genes and a harmful environment (internal or external) (Timmers et al., 2019). Additionally, biochemical and cell biology studies in cell and animal models have taught us about the effect of different genetic variants and age-associated systemic and local alterations on the function of brain cells. Unfortunately, even with the current state of knowledge, we do not have precise clues to explain causation of neurodegenerative conditions and therefore we are still far from being able to know how to prevent the development of neurodegenerative diseases. On top of these limitations, several studies have shown that the same genetic-environmental variants could be associated with multiple age-related disorders (i.e. pleiotropy) (Martínez-Martínez et al., 2020). As consequence, our current repertoire of interventions is also insufficient to treat the disease or to satisfactorily improve the quality of life of sick individuals. Therefore, there is a dire need for research aimed at improving the impact of aging in our society.

An important venue of future research will necessarily focus on the continuous elucidation of the mechanisms that determine susceptibility or resistance to pathological brain aging (e.g. Alzheimer's disease, vascular dementia, fronto-temporal dementia, dementia with Lewy bodies). Multiple disciplines will contribute to this endeavour, from human genetics and epigenetics to basic cell biology and biochemistry research (not only of neurons, but of all the other brain cell types). These studies should be linked to research on the aging of sensory and peripheral organs and how the environment and social behaviors influence our genes, cells and the whole organism. Naturally, translational strategies will also be needed to foster ties between researchers and medical and social agents, as well as care providers, to improve the general well-being of the old.

2. IMPACT IN BASIC SCIENCE PANORAMA AND POTENTIAL APPLICATIONS

Scientific impact

Research has demonstrated that in laboratory animals such as mice and worms a number of age-associated diseases, including those neurodegenerative, can be prevented (or at least ameliorated) by natural, pharmaceutical and biotechnological interventions like low-calorie diets, fasting, physical and mental exercise, food supplements, medicines, antibodies, peptides, nucleic acids. The question now is: do we know enough about aging so to start an intensive,

multi-year search and clinical trials for ways to delay brain aging in people? The answer is, as expected, no. We do not know enough about how different predisposing genes can lead to disease (or protect against it) nor how they interact with different environmental milieux so to determine, by acting all together, the type of brain aging we will have, either normal or pathological (demented). Without knowing more on gene-gene and gene-environment interactions we will not be able to establish appropriate animal models that resemble different human situations, allowing to better test the efficacy of therapeutic approaches. We must generate basic knowledge that is as close as possible to the tremendous individual, genetic-environment, differences that exist between humans, in whom the genetic and environmental background is so diverse.

Social and economic impact

A second question we need to address is how societal bodies and organisations are going to face the increased aging of our population, and what strategies should be promoted to keep older people independent for a daily living. The current trend is to channel many social and political initiatives, as well as the older individuals' voices, into public policies and intervention programs, which poses a significant challenge to our social care system. Indeed, a third question is also emerging: what will be the cost for our societies of having a longer-lived population? A simulation in the United States of reducing the development of age-associated diseases such as cancer and heart disease by 2 years predicts that the costs to the social security will raise substantially. However, having a population with higher possibilities of a healthier aging may largely compensate its financial costs and, if successful, give substantial financial return.

What our research organization should do?

If we accept the premise that only bio-medical and social research will allow us to have a less onerous aging, both emotional and economic, we, as an institution, must unconditionally support this type of research. The question is therefore: how? All starts by identifying the key questions that we need to address (see below, Key Challenging points). Next, we need to identify and hire, irrespective of geographical origin, the most suited scientist to address such questions. Thirdly, these scientists need to be funded at a competitive, international level. And fourth, to be surrounded by the best critical mass and infrastructure is an essential condition to succeed. Even though we may require some decades until having solid results that reach the public, we have to

establish a solid aging research programme as quickly as possible if we do not want to be simply consumers of goods and services produced by others. As a matter of fact, once we do improve aging the benefits to the society will not be restricted to the emotional aspects but also will produce financial revenues from the tools we have had discovered, in new medicines, supplements and new technological tools. We need to remember that aging is already a "business", and one that has grown extensively over the past decade, with more services and products that help older adults live a better life today than ever before. And research and development will only boost even more this industry, so much that market specialists expect this industry will give the highest revenue through the supply of health and financial benefits to keep the aged population thriving.

3. KEY CHALLENGING POINTS

3.1. To characterize brain aging at the genetic, molecular and cellular level from an integrating individual-environment perspective

It is now well established that the brain aging phenotype, whether normal or pathological (dementias), is the result of multiple genetic variations (polygenic traits) combined to environmental influences, both internal (e.g. hypertension, diabetes) and external, of early and/or adult life. Therefore, we will need a global view of the molecular architecture of aging as a complex trait, which integrates intermediate phenotypes, such as transcript, protein or metabolite levels, in different populations of interest and different environmental conditions. This system biology approach is needed for the identification of genes, pathways and networks that underlie brain aging in conditions that are closer to the human scenarios. These are more elaborated strategies than currently used and that have only recently started to be addressed.

While studies based on gene expression and quantitative cell biology have taught us about the consequences of age on all and every single metabolic, signalling and gene expression event of brain cells (Ballabio and Bonifacino, 2020), we still do not know how age-related dysfunctions of intracellular mechanisms affect circuit organization and communication. Thus, it becomes evident that in the future cell biology approaches will need to be extended to the cell biology of circuits, to define how the changes in the cells' biochemistry affect the maintenance and function of circuits. These studies will naturally feed from the systems genetic approach, as genetic/epigenetic

peculiarities of susceptible/resistant-to-disease individuals will be translated to the cells' signalling pathways and from there to circuits. Additionally, and in accordance with the genetic discoveries that age-related pathologies are polygenic, we need to consider cell dysfunction during aging as a multi signalling/multi organelle problem. This will require a comprehensive approach to define relationships between interconnected signalling pathways in the compartmentalized intracellular milieu.

Importantly, these considerations do not only apply to neuronal cells. It is now well established that normal brain function involves complex interactions and rich signalling between neurons and different glial cell types, together with the vascular system (Araque et al., 2014). One important question that will require intense scrutiny in the future is how these interactions are altered by age. Several major research programs may be envisioned as necessary to get a better knowledge of cellular aging in the brain. First, we need a better characterization of the phenomenon of cellular aging across the different cell types in the brain. For example, how similar is the aging program in neurons and glial cells? Some differences are expected because of their distinct metabolic programs and characteristic cell activity responses. Nevertheless, some similarities may be revealed, and these would offer clues about fundamental mechanisms of cellular aging. Second, emerging evidence is revealing the existence of a large degree of heterogeneity among glial cell types and among subtypes within and in different brain areas. This heterogeneity is also reflected in the nature of neuron-glia communication, which is integrated at the level of neuronal circuits (Poskanzer and Yuste, 2016). Are glial cell subtypes differentially affected in aging? Are the alterations region-specific? These are fundamental questions that may contribute to understand the existence of brain regions with different vulnerability to neurodegeneration and aging. Importantly, some alterations may contribute to enhance the aging brain phenotype, while others may help protecting from it.

In addition to neurons and glial cells, it will be pertinent to better understand adult mother cell niches: their ability to generate new neurons and glial cells in an aged environment, the efficiency of the newly generated cells to provide trophic support and circuit integration, and also to define whether stem cell implantation strategies have therapeutic potential.

Finally, we need to establish the best strategies to make use of all the previous knowledge for a better understanding of typical diseases of the aging, especially the most devastating Alzheimer's disease (AD). On the one hand, this

will come from a better general understanding of brain aging: how different genetic backgrounds contribute to the type of aging we will develop, how this background is affected by different environmental conditions (and in turn affects our responses to the environment), and how these changes at the genetic/molecular level affect the different types of biochemical processes of our cells and these to the circuits involved in brain function. And on the other hand, progress will come through direct actions to answer specific disease questions, such as the relationships between the classical features of disease (e.g. intra and extracellular aggregates, synaptic dysfunction and neuronal loss) and systemic alterations (e.g. inflammation, metabolic disorders, and the aging of our senses). In this regard, strong emphasis should be put into the study of age-related hearing loss (presbycusis) which is now being recognised as an important factor in the type of brain deficits that we will have with age, so much so that it is estimated that the risk of Alzheimer's disease will decrease by a 9% by preventing mid-life hearing loss.

3.2. The influence of systemic aging in the brain: gut-brain axis, the cardiovascular system, the immune system

There is a growing knowledge of the fact that age-related systemic diseases affect the aging processes of the brain, although specific mechanisms are poorly understood. In addition to the need for healthy musculoskeletal system and metabolic organs, attention has recently been focused on the state of the gut microbiota, the immune system and the cardiovascular system (Cowan et al., 2018; Franceschi et al., 2018; Kalaria and Hase, 2019). In the near future we should be able of designing strategies to increase brain resilience to aging and neurodegeneration through improvement of peripheral signalling to the brain.

The interaction between gut microbiota and brain, known as the "microbiota-gut-brain-axis", is a well-established fact these days. Deleterious changes of diversity and composition of microbiota have been proposed to play key roles in age-related cognitive decline and neurodegenerative illnesses, mainly Alzheimer's and Parkinson's disease, but also in psychiatric illness frequent of the old age, such as anxiety and mood disorders.

The activity and composition of the peripheral immune system also actively participates in defining the way our brain ages. As a matter of fact, the peripheral immune system is remodelled at old age with thyme atrophy and increased senescent T cells, resulting in the reduced capacity of the aged immune system to cope with immune stressors and the concomitant progressive

increase of pro-inflammatory mediators resulting in a state known as "inflammaging". This state can be aggravated by a concomitant chronic inflammation caused by metabolic diseases, which defines a particular state known as "metflammation". This chronic inflammatory environment is likely to have a major impact on brain aging.

A third element of our internal milieu that exerts strong impact on our brain's well-being is the cardiovascular system. Heart and the main components of vessels, the vascular endothelium and media arterial wall, suffer structural and functional changes with aging, which together with increase of arterial stiffness and endothelial cells' senescence lead to hemodynamics dysfunction of the blood entering to cerebral vessels and consequently reduced oxygenation and provision of nutrients. On top, the reduced cardiovascular efficacy leads to increased arrival to the brain of pro-inflammatory factors and detrimental signalling molecules. Despite the abundant knowledge on this matter at the vascular level, we know very little about how the defects in cardiovascular system impact on brain function.

3.3. The influence of lifestyle and social environment on brain aging

The influence of lifestyle factors in relation to healthy brain aging are attracting great attention because they are amenable to modification and therefore feasible for implementation of effective gero-protective policies. Indeed, all preventive measures towards a healthy aging are nowadays based on lifestyle modifications such as physical exercise, diet and promotion of sociality. The latter deserves more careful attention. In social species such as humans, balanced relations, both familial and social, are critical for building social networks and social support, both contributing to proper brain development and brain health throughout the entire lifespan. Sadly, family and social support for the aged population is currently very much deteriorating in advanced countries, propitiating that old people become more and more socially isolated and living alone. Evidences demonstrate that lonely older adults are more prone to frailty, mental illness, and are exposed to greater risk of all-cause deaths, among other consequences (Rokach, 2019; NASEM, 2020; Kuiper et al., 2016). Therefore, we envision for the future to improve our understanding of the inner workings of the social brain, and how they impact on healthy brain aging (Fried, L. et al., 2020; Tan et al., 2020; Ong et al., 2016). This approach will include analyses of the genetic basis of loneliness in humans. In addition, circuit and behavioural studies on animal models will be required

to describe social areas in the brain and their molecular, structural and dynamic adaptations to aging. Finally, we should define targets for drug development, and microcircuitry mapping for non-invasive interventions, including current and new technological tools (transcraneal stimulation, artificial intelligence, virtual reality, etc) to improve their cognitive conditions through stimulating training. Moreover, social interventions are tested to be beneficial and supportive measures for general population, and specially for the older, to alleviate cognitive dysfunctions and to boost the cognitive functioning of healthy and cognitively impaired older adults. Particular attention should be paid to the use of computer-based training programs and video games (Ballesteros et al., 2018). Future research should be addressed to the design and validation of easing use of ICT products and software applications to maintain and/or improve the declining cognitive functions.

Finally, environmental factors influence the underlying biological mechanisms leading to the risk of cognitive dysfunction and of neurodegenerative diseases in older people. Environments could favor maladaptive behaviors and higher levels of environmental stress, linked to an increased risk of brain degeneration, disease and death (Leon and Woo, 2018), but also can stimulate brain plasticity in older (demented) subjects and enrich their lives. These environments, sometimes called 'therapeutic' (Calkins, 2018), can contribute to better cognitive and social interactions, sensory and functional skills, and benefits in learning and memory. Policies addressed for healthier environments can contribute to favour the older people' autonomy and motivation as essential drivers for a cognitive development as people age and to improve their quality of life, as evidences verify. Policies promoting age-friendly cities and communities will favour healthy lifestyles, as promoted by the World Health Organization (Fernández-Mayoralas et al., 2020).

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