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EDITORIAL

Special Issue: Protein Aggregation in Aging and Neurodegeneration

Aging and neurodegeneration: From molecular mechanisms to therapeutic interventions

Abstract

Protein aggregation is a common age-associated process and can be a pathological hallmark of various neurodegenerative conditions, possibly because of an age-associated decline in the activity of components of the proteostasis network. The specific molecular drivers of protein aggregation in certain cell types are not well understood, posing tremendous challenges to current research aimed at devising strategies to treat neurodegenerative diseases. This preface introduces the special issue "Aging and Neurodegeneration: from molecular mechanisms to therapeutic interventions," featuring articles that assess the drivers of pathology in the aging cell, including oxidative stress, protein glycation/aggregation, and mitochondrial impairment.

1 | PREFACE

Improvements in hygiene habits, the advent of antibiotics and other medications, and healthier lifestyle habits have significantly extended human lifespan. As a consequence, many more people are reaching advanced ages. Although the general life expectancy for the World is around 73 years, it is common for people in developed countries to live past their 80s, and well into their 90s. This poses novel challenges for modern societies, as we now deal with a tremendous burden of age-associated diseases that were not so frequent a few decades ago. Among these diseases, those affecting the brain have a significant impact, as they tend to be highly debilitating and last for several years. Together, Alzheimer's disease and Parkinson's disease affect over 50 million people worldwide, and this appalling number will continue to increase in the coming decades. Therefore, we need to act quickly and devise strategies that can interfere with disease onset and modify disease progression. To achieve this, we need to significantly increase our understanding of the molecular underpinnings of aging and neurodegeneration.

Protein aggregation is a common pathological hallmark among neurodegenerative diseases. Although this is considered an age-associated process, possibly because of a decline in the activity of the proteostasis network, it is still unclear what the molecular drivers of protein aggregation are in specific cell types and not in others. Importantly, under certain stress conditions, protein aggregation appears to function as a protective mechanism, enabling the cell to reorganize proteins and RNA molecules in specific compartments that can, once the source of stress is gone, be resolved and "release" proteins and RNAs without the need for now protein synthesis. How cells regulate the formation of such compartmentalized assemblies is still unclear.

Neuroplasticity is the ability of the nervous system to respond to intrinsic and extrinsic stimuli by reorganizing its structure, function, and connections. Neuroplastic changes in neurodegeneration and aging may represent pathogenic or compensatory responses. Several pathological molecules can directly influence neuroplasticity at the synaptic level. For example, amyloid-beta dimers can affect synaptic plasticity, thus establishing a possible cellular mechanism for pathology-induced plasticity in the brain circuits. Moreover, a decreased plasticity may further exacerbate pathology and, with increasing pathology over time, compensatory mechanisms may fail or become pathogenic.

Oxidative stress, protein glycation/aggregation, and mitochondrial impairment are considered major drivers of dysfunctional processes in the aging cell. Despite their contribution to both physiological and pathological changes associated with aging, neurodegenerative diseases affect only certain individuals, for reasons we still do not fully understand. In recent years, inflammatory signaling has gained increasing attention as a trigger of such processes at a cellular level and also in the context of the central nervous system.

This special issue on "Aging and Neurodegeneration: from molecular mechanisms to therapeutic interventions" was prepared on the occasion of the I FloripaNeuro meeting which took place in Florianopolis, Brazil, on February 8–10,2023. We include contributions of several participants and of other authors who took the opportunity to contribute to the topics of the special issue. Altogether, this special issue is composed of 16 articles: one editorial (preface), five reviews, one systematic review, and nine original articles, providing concrete examples of mechanisms involved in aging and neurodegeneration, and discussing open questions in the field.

Lippi and Krisko start by discussing an unanswered issue in the field of proteostasis: whether protein aggregation is detrimental or a cellular adaptation mechanism to deal with stressful conditions (Lippi & Krisko, 2023). Moreira-Gomes and Nóbrega introduce the concept

of functional protein/RNA aggregates and use the case of spinocerebellar ataxias to discuss how, in pathological situations, RNA may be disrupted and how targeting RNA-binding proteins might be used as a therapeutic strategy (Moreira-Gomes & Nóbrega, 2023). Next, Ma et al. (2024) present evidence for how the accumulation of extracellular elastin-derived peptides disturbs neuronal morphology and neuron–microglia cross-talk in the aged brain. Another topic bridging aging and neurodegeneration is introduced by Canever et al. (2023), who discuss how circadian rhythm alterations can affect the pathology of neurodegenerative diseases. Xiong et al. (2023) then discuss the association between genetic variations and morphology-based brain network changes in Alzheimer's disease. Next, Zanella et al. (2023) present their study demonstrating that guanosine increases the overall levels of sumoylation, an important posttranslational modification in neuronal function, and how this improves the short-term memory of young mice. Plácido et al., 2024 then provide evidence consistent with alterations in neurogenesis in Parkinson's disease by demonstrating altered expression of doublecortin in human hippocampal tissue. Along a similar topic, Saibro-Girardi et al. show how bexarotene drives the self-renewing proliferation of adult neural stem cells, promotes neuron–glial fate shift, and regulates late neuronal differentiation, suggesting it might be possible to interfere with neurogenesis in the adult brain (Saibro Girardi et al., 2023). Tullo et al. follow and present neuroanatomical and cognitive biomarkers of α-synuclein propagation in a mouse model of synucleinopathy prior to the onset of motor symptoms (Tullo et al., 2023). Next, two articles touch on neuroinflammation, which is relevant in aging and neurodegeneration. Scarpatto Rodrigues et al. (2023) present evidence that microglial cells contribute to cognitive decline in a mouse model of hypercholesterolemia. Peixoto et al. (2023) explore a possible role of the receptor for advanced glycation end products (RAGE) in the inflammatory-neurodegenerative axis in Parkinson's disease, a condition characterized by mitochondrial-associated oxidative stress and accumulation of toxic aggregates of α-synuclein. In fact, recent observations strongly suggest that glycation and α-synuclein/RAGE interactions may be crucial in the development of proteinopathy. Based on their findings, the same group Gasparotto et al. provides a critical discussion of the role of RAGE in Parkinson's disease (Gasparotto et al., 2023). Vieira et al. discuss how the prion protein, the culprit in prion diseases, can also play a role in Parkinson's disease by interacting with and acting as a sensor for α-synuclein, thereby leading to alterations in neuronal function (Vieira et al., 2023). Finally, two studies focus more directly on possible therapeutic interventions for neurodegeneration. Srivastava et al. provide evidence for the effect of a natural small molecule on inhibiting α-synuclein aggregation, thereby leading to neuroprotection in the versatile model *Caenorhabditis elegans* (Srivastava et al., 2023). Alves et al. end by presenting a systematic review of studies in animal models investigating the role of omega-3 polyunsaturated fatty acids in Parkinson's Disease (Alves et al., 2024).

In conclusion, we are confident the articles included in this special issue provide a broad overview of the field. We hope they inspire new studies and introduce new ideas to advance our understanding of the molecular mechanisms involved in aging and neurodegeneration and foster the development of future therapeutic strategies.

KEYWORDS

aging, neurodegeneration, neuronal plasticity, protein aggregation, therapeutics

AUTHOR CONTRIBUTIONS

Tiago Fleming Outeiro: Conceptualization; visualization; writing – original draft; writing – review and editing. **Patricia S. Brocardo:** Writing – review and editing. **Daniel P. Gelain:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Tiago Outeiro is a member of Journal of Neurochemistry's editorial board, but played no role in reviewing the articles where he is a coauthor. The authors have no other potential conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable since no new data were generated for this Preface.

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