Estudos em Biociências e Biotecnologia:

Desafios, Avanços e Possibilidades

Manuel Simões
(organizador)

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PREFÁCIO

O volume IV da edição “Estudos em Biociências e Biotecnologia: Desafios, Avanços e Possibilidades” disponibiliza ao leitor informação científica avançada de caráter fundamentalmente aplicado. O livro está organizado em sete capítulos que focam essencialmente em conhecimento avançado em ciências biomédicas, neurociências, parasitologia, saúde animal e em processos avançados e sustentáveis de produção alimentar.

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CAPÍTULO 2

DEVELOPMENTAL HETEROCHRONY AND ITS RELATIONSHIP WITH THE CELLULAR SENESCENCE: A NEW PERSPECTIVE ON THE ETIOLOGY OF NEURODEGENERATION[1]

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ABSTRACT: The prevailing neurodegeneration model proposes neuronal death as the origin of behavioral and cognitive dysfunctions. Nevertheless, some studies have shown that patients with Parkinson's and Alzheimer's disease exhibit cognitive impairment in the absence of neuronal death. These data suggest that during the initial and intermediate phases of neurodegeneration, neuronal death may not be the origin of the symptoms. An alternative mechanism to explain the dysfunction observed in the early stages of neurodegeneration, in neuronal death absence, is cellular senescence. A cell in a senescent state is characterized by being resistant to apoptosis, secreting pro-inflammatory factors, and favoring the decline of regenerative potential. Therefore, the accumulation of senescent cells within neuronal circuits could favor a malfunction of neighboring cells, promoting a generalized dysfunction in the central nervous system. It's known that the neurodegenerative process occurs heterochronically in the cerebral cortex, the entorhinal and motor cortices being the most affected during the early stages of this process. Interestingly, the cells that make up both cortices during adulthood are those cells that originated early during embryonic development. On the contrary, the somatosensory cortex, which isn't very sensitive to damage by neurodegeneration, is mainly made up of cells that originated in the last embryonic days. In this review, we explore the limitations of the cell death model to explain the onset of neurodegenerative processes and propose that the neurons of early embryonic origin express the senescent phenotype in advance in adulthood. In this way, the asynchronous neurodegeneration pattern of the cerebral cortex could be explained by the cellular chronoarchitecture that's established from the embryonic period to the adulthood.

KEYWORDS: Neurodegeneration. Neuronal death. Cellular senescence. Heterochrony. Chronoarchitecture.

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LA HETEROCRONÍA DEL DESARROLLO Y SU RELACIÓN CON LA SENESCENCIA CELULAR: UNA NUEVA PERSPECTIVA DE LA ETIOLOGÍA DE LA NEURODEGENERACIÓN

RESUMEN: El modelo actual de la neurodegeneración propone a la muerte neuronal como el origen de las disfunciones conductuales y cognitivas. Sin embargo, algunos estudios muestran, que pacientes con enfermedad de Parkinson o Alzheimer presentan deterioro cognitivo en ausencia de muerte neuronal. Estos datos sugieren que, durante las fases iniciales e intermedias de la neurodegeneración, la muerte neuronal podría no ser el origen de la sintomatología. Un mecanismo alterno para explicar la disfunción observada en etapas tempranas de la neurodegeneración, en ausencia de muerte neuronal, es la senescencia celular. Una célula en estado senescente se caracteriza por ser resistente a apoptosis, secretar factores proinflamatorios y favorecer el decline del potencial regenerativo. Por lo tanto, la acumulación de células senescentes en los circuitos neuronales podría favorecer un mal funcionamiento de las células vecinas, promoviendo así una disfunción generalizada en el sistema nervioso central. Es conocido que el proceso neurodegenerativo ocurre de manera heterocrónica en la corteza cerebral, siendo las cortezas entorrinal y motora las más afectadas durante las etapas tempranas de este proceso. De manera interesante, las células que integran ambas cortezas durante la etapa adulta son aquellas que se originaron de forma más temprana durante el desarrollo embrionario. Por el contrario, la corteza somatosensorial, la cual es poco sensible a daño por neurodegeneración, está integrada por células que se originaron en los últimos días embrionarios. En esta revisión, exploramos las limitaciones del modelo de muerte celular para explicar el inicio de los procesos neurodegenerativos y proponemos que las neuronas de origen embrionario temprano pueden expresar de manera anticipada el fenotipo senescente en la etapa adulta. De esta forma, el patrón de neurodegeneración asincrónico característico de las enfermedades neurodegenerativas, podría explicarse por la cronoarquitectura celular que se establece desde el periodo embrionario y hasta la etapa adulta.

PALABRAS CLAVE: Neurodegeneración. Muerte neuronal. Senescencia celular. Heterocronía. Cronoarquitectura.

1 INTRODUCTION

Neurodegeneration is characterized by a progressive deterioration of neuronal function, presumably caused by the degeneration of synapses, axons, and ultimately the death of nerve cells (Andreone et al., 2020). The loss of neuronal populations occurs in the central and peripheral nervous system, is characteristic of diseases such as Parkinson's and Alzheimer's, and leads to cognitive decline and dementia (Braak et al., 2003a; Braak et al., 2006).

Neuronal death is a process that occurs normally during development, it is highly regulated and allows to maintain the tissue homeostasis, eliminating cells that serve as transient targets, supernumerary, error-prone or defective (Buss et al., 2006; Miura, 2012;

Yamaguchi & Miura, 2015). However, it has been proposed that neuronal death in adulthood leads to functional decline, and that it is this death that underlies the progression of neurodegenerative disease (Andreone et al., 2020).

Neuronal loss, a characteristic of the neurodegenerative process, is preceded by a number of initiating mechanisms including mitochondrial dysfunction, oxidative stress, neuroinflammation, protein aggregation and failures in the proteosomal degradation system (Andreone et al., 2020). These mechanisms, which are the basis of functional and cognitive impairment associated with neurodegeneration, can occur in parallel and are presumed to lead to neuronal death.

2 LIMITATIONS OF CELL DEATH TO EXPLAIN THE NEURODEGENERATIVE PROCESS

The predominant focus in research has been on describing a series of mechanisms that lead to cell death, which has been raised to explain the etiology and progression of neurodegenerative disease. However, even though the model points to neuronal death as the final manifestation of the neurodegenerative process, there is a disconnect between the initiating mechanisms and the subsequent activation of cell death (Andreone et al., 2020). While it is true that neurons face a wide variety of stimuli that can lead to death, experimental evidence suggests that the initial and intermediate stages of neurodegeneration progress in the absence of neuronal death. Here we will briefly review some of the limitations that the model of neuronal death has to explain the origin of neurodegenerative diseases and propose an alternative mechanism of the etiology of neurodegeneration.

2.1 NEURON LOSS DOES NOT PREDICT COGNITIVE DECLINE

Neurodegenerative diseases such as Parkinson's and Alzheimer's are characterized by progressive impairment of cognitive function, allegedly caused by loss and widespread dysfunction of neural cells. However, the first flaw that emanates from the cell death approach is that, in fact, the loss of neuronal populations does not predict the presence of cognitive decline and dementia. This was shown by the results obtained by West et al. (1994). When estimating the number of neurons in the hippocampus, it is observed that the subregions CA2, CA3 and dentate spin do not show a significant loss of neurons in patients with Alzheimer's, when compared with individuals of the same age without cognitive impairment or neurological disease. This evidence points out that the number of hippocampal neurons does not predict the level of cognitive impairment.

2.2 NEURONS OF PATIENTS WITH ADVANCED NEURODEGENERATIVE DISEASE EXPRESS ANTI-APOPTOTIC MARKERS

One of the main limitations of using cell death as a support to explain neurodegeneration is that the proposed mechanisms require short lead times for cells to die. This makes them incompatible with the slow progression of neuronal degeneration and the long clinical latency of different neurodegenerative diseases (Zhu et al., 2006) This temporal disjunction, coupled with the experimental evidence showing the expression of antiapoptotic markers in neurons of patients with neurodegenerative disease, raises doubts that cell death gives rise to the neurodegenerative process.

Jellinger & Stadelmann (2001) evaluated postmortem, hippocampal and *substantia nigra* neurons of patients with Alzheimer's and Parkinson's, respectively. In both cases, less than 1% of the cells counted were positive for active caspase 3. In contrast, almost all neurons expressed the anti-apoptotic markers Bcl-2 and Bcl-X. In agreement with these observations, Zhu et al. (2004) reported that the Bcl-w protein acts as a promoter of cellular survival in neurodegeneration. This was revealed by a series of experiments in which a significant increase in the expression of Bcl-w in pyramidal neurons of the hippocampus in patients with Alzheimer's was reported. This increase occurred in association with the formation of neurofibrillary twists and neuritic plaques.

Taken together, these results suggest that neurons affected by protein accumulation try to survive by mobilizing a protective mechanism mediated by anti-apoptotic proteins (Zhu et al., 2004). This fact would decrease the possibility of observing neuronal death during the early and intermediate stages of the neurodegenerative process.

2.3 THE ACCUMULATION OF TOXIC PROTEIN AGGREGATES IS NOT ASSOCIATED WITH COGNITIVE IMPAIRMENT OR CELL DEATH MARKERS

Abnormal accumulation of toxic protein aggregates and neuronal death are the main histopathological markers of neurodegenerative diseases. However, in the case of Alzheimer's disease, it has been documented that some individuals retain cognitive function despite the presence of neurofibrillary tangles (Zolochevska et al., 2018). This evidence exposes another limitation of the current model of neurodegeneration: the main histopathological biomarker of neurodegenerative disease does not predict in all cases the presence or development of cognitive impairment. The above could be explained by evidence that most neurons containing neurofibrillary tangles are not positive for cell death markers. This was shown by the data published by de Calignon et al. (2009),

in which using a murine model of Alzheimer's it was revealed that, out of all cells with neurofibrillary tangles, only 6% die.

We can conclude that the predominant model that proposes cell death as the cause of neurodegeneration has three fundamental limitations: 1) cell death does not predict the presence of cognitive deterioration and dementia; 2) neurons with b-amyloid plaques express anti-apoptotic proteins that seem to promote cell survival; and 3) the presence of protein aggregates does not lead to cell death. In addition to these model prediction deficiencies, we must consider that the therapeutic measures proposed to date have not succeeded in solving the progression of neurodegenerative diseases. The body of evidence therefore suggests that these explanations are insufficient to provide satisfactory clarification of the scientific problem they seek to model.

3 CELLULAR SENESCENCE

An alternative biological process that would unify the evidence that contradicts the mechanism of neuronal death in the neurodegeneration model is cellular senescence. Cellular senescence was described by Hayflick & Moorhead in 1961. The experiments carried out by these researchers showed that fibroblasts have a finite capacity to divide into cultures. Currently, cell senescence can be defined as a homeostatic process that reduces proliferation and helps prevent the spread of damaged cells. (Martínez-Cué & Rueda, 2020).

Different types of cells in the CNS can acquire senescent phenotype: astrocytes, oligodendrocytes, neurons and neural stem cells (Martínez-Cué & Rueda, 2020). Senescent cells are often resistant to cell death signals (Campisi & d'Adda di Fagagna, 2007), by expressing numerous anti-apoptotic proteins such as Bcl-2, Bcl-w and Bcl-xL (Si et al., 2021). Senescent cells express a distinctive phenotype that includes persistent DNA damage, senescence associated secretory phenotype (SASP) and changes in cellular metabolism.

4 THE ROLE OF CELLULAR SENESCENCE IN NEURODEGENERATIVE PROCESSES

According to the characteristics described as part of the senescent phenotype, cells in this state could contribute to the neurodegenerative process, mainly in three ways: 1) Because senescent cells are resistant to apoptosis, senescence could promote the retention of aging neurons and/or promote the conservation of larger numbers of neurons than required in neural circuits. 2) Senescent cells are a source of pro-inflammatory and pro-oxidant stimuli, which could modify the microenvironment of the brain as well

as its structure and function. 3) Cells in senescent state could affect other cells in their environment, inducing a senescent phenotype in surrounding cells.

5 DEVELOPMENTAL HETEROCHRONY OF THE CEREBRAL CORTEX AND ITS CONTRIBUTION TO NEURODEGENERATION

Considering that cellular senescence has been linked to aging and neurodegeneration, and that sustained damage to DNA has been proposed as the origin of this phenotype, senescence is likely to operate as a cellular aging mechanism associated with the chronological age of cells. That is, older cells that have been subjected for longer time to different intrinsic and extrinsic environmental stress factors will be more likely to accumulate damage in their DNA, which will favor the establishment of senescent phenotype.

Bayer (1980) and Bayer & Altman (1991) studied the cytoarchitecture of murine cerebral cortex. According to their day of origin, the cells were classified into: old, cells born between embryonic day 13 and 15; intermediate age, born between embryonic days 16 and 17; and young, those cells that originated between the embryonic days 18 and 20. Analysis of neurogenic gradients indicates that somatosensory, entorhinal and motor cortices show an asynchronous organization pattern that provides a different cellular age to each cortex.

The entorhinal and motor cortices are mostly composed of old cells (40% and 51%, respectively). However, the motor cortex has twice as many new cells (12%) as the entorhinal cortex (6%). In contrast, somatosensory cortex is constituted by a low percentage of old cells (14%), and a higher percentage of new cells than observed in the entorhinal and motor cortices (29%). Therefore, the organization of cells according to their day of origin, indicate that the entorhinal cortex is older than the somatosensory and motor cortices. The motor cortex is intermediate in age and the somatosensory cortex is younger. More interesting is the fact that this differential chronoarchitecture correlates with the previously described asynchronous neurodegenerative process (Braak et al., 2003a, 2003b).

Based on neuropathological analyses performed in postmortem tissue of patients with Parkinson's and Alzheimer's disease, Braak et al. (2003a, 2003b & 2006) identified stereotyped patterns of neuronal degeneration that develop sequentially in the central and peripheral nervous systems and are consistent with clinical severity of disease. According to the progression of the same, these patterns have been classified into six stages. Speaking specifically of the cerebral cortex, neuronal degeneration begins in stage 4 with

the entorhinal cortex. In stage 6, the pathological process extends to the motor cortex and is rarely seen in the somatosensory cortex. In short, the entorhinal cortex in which neurodegenerative pathology occurs earlier is formed by chronologically older cells. On the contrary, the somatosensory cortex which rarely suffers from neuronal degeneration is formed preferably by young cells.

If we consider that old cells are more susceptible to expressing senescent phenotype due to the accumulation of damage in their DNA, those cortices formed by a greater number of old cells, will accumulate senescent cells before those cellularly younger. Therefore, the entorhinal cortex is likely to accumulate a greater number of senescent cells than motor and somatosensory cortices. Based on the evidence that the somatosensory cortex is a region not susceptible to neurodegeneration damage, and conforming with a low percentage of old cells, we propose that this region will accumulate a small number of senescent cells. Thus, the asynchronous pattern of neurodegeneration in the cerebral cortex could be explained by the cellular chronoarchitecture that is established from the embryonic period to early adulthood.

Taken to the neurodegenerative process, this fact could explain the syntomatology characteristic of the initial and intermediate stages in the absence of neuronal death, and the temporal progression of neurodegenerative processes. Cellular senescence could explain why patients with cognitive impairment and dementia do not show, in all cases, loss of neuronal populations. Cells may be present in senescent state, and not function properly in neural circuits. Cell senescence can also explain why cell death is not observable in all cases. A cell in senescent state can be counted, even if it is in a dysfunctional state. Thus, the dysfunction observed in early and intermediate stages of neurodegeneration could be explained as the result of the accumulation of dysfunctional cells in senescent state, rather than as a consequence of cell death.

6 CONCLUSION

Studies in patients with Parkinson's and Alzheimer's disease show that during the initial and intermediate stages of neurodegeneration, neuronal death may not be the cause of symptomatology. We alternately proposed cell senescence as a unifying mechanism that would explain the onset of neurodegenerative process in the absence of neuronal death. It is known that neurodegeneration occurs asynchronously in the cerebral cortex, with the entorhinal and motor cortices being most affected during the early stages of this process. Interestingly, the cells that make up both cortices during adulthood are those that originated earlier during embryonic development.

Taking this into account, the present review evaluated the possibility that cortical regions composed of chronologically older cell populations accumulate a greater number of senescent cells. Thus the pattern of heterocronic neurodegeneration characteristic of the cerebral cortex could be explained by the cellular chronoarchitecture that is established from the embryonic period to adulthood. Thus, this work is an approach to evaluate the possibility that the initial and intermediate stages of neurodegenerative disease are the result of the accumulation of cells in senescent state, and not a consequence of the massive loss of neuronal populations. In the future, it will be important evaluate alternative proposals that allow us to elucidate the mechanisms regulating the origin and progression of neurodegenerative processes.

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Manuel Simões é licenciado em Engenharia Biológica e doutorado em Engenharia Química e Biológica. Atualmente é Professor Associado com Agregação e Pró-Diretor da Faculdade de Engenharia da Universidade do Porto (FEUP), e investigador sénior do Laboratório de Engenharia de Processos, Ambiente, Biotecnologia e Energia (LEPABE) do Departamento de Engenharia Química da FEUP. Nos últimos anos esteve envolvido em 10 projetos nacionais (5 como investigador principal) e 6 projetos europeus. Foi membro do comité de gestão da ação COST BACFOODNET (Rede Europeia para Mitigação da Colonização e Persistência Bacteriana em Alimentos e Ambientes de Processamento de Alimentos) e esteve envolvido em outras 2 ações: iPROMEDAI e MUTALIG. Manuel Simões tem mais de 190 artigos publicados em revistas indexadas no Journal of Citation Reports, 4 livros (1 como autor e 3 como editor) e mais de 40 capítulos em livros. Ele é Editor Associado para o jornal Biofouling - The Journal of Bioadhesion and Biofilm Research (o periódico mais antigo sobre pesquisa em biofilme), Editor Associado para o jornal Frontiers in Microbiology e Section Editor-in-Chief para o jornal Antibiotics. Seus principais interesses de pesquisa estão focados nos mecanismos de formação de biofilme e seu controlo com agentes antimicrobianos, particularmente usando novas moléculas antimicrobianas, e no uso de microalgas para tratamento de efluentes. É um dos investigadores mais citados do mundo (top 1%), tendo sido distinguido nos últimos dois anos no índice Essential Science Indicators, um dos mais prestigiados indicadores da qualidade de investigação.

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