NEURODEGENERATIVE DISEASES: A SYSTEMIC OVERVIEW OF THE UNDERLYING MECHANISMS

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Abstract

Neurodegenerative diseases affect an ever-increasing number of the human population, especially the elderly, the immune-compromised or both. Studies show that more than 55 million people have Alzheimer's disease and more than 10 million are afflicted with Parkinson's disease worldwide. Even though complex by nature, these diseases all share one key feature, their lack or miscommunication between neurons and other cells. They are also aided by a number of other factors, ranging from age, diet, lack of exercise up to aberrant cell signal, abnormal protein production or degradation and formation of aggregates. The loss of neurons in both the central and peripheral nervous system, making them unable to regenerate leads to loss of motor function, impaired speech, compromised memory, inflammation, aberrant proteostasis and neuron death. Aberrant signaling of several signaling pathways have been shown to play a crucial role in the development and progression of neurodegenerative diseases. Apart from abnormal signals, the immune system has been found to be a factor involved in the progression of neural degeneration and death. These findings in correlation with the fact that clinical approaches do not always reflect base research, make it a priority to further understand the underlying mechanisms affecting these diseases in order to treat them. Our study focuses on summarizing recent advances in neural pathology research to accurately diagnose them and finding novel treatments based on the mechanism of action.

Key words: *neurodegenerative, disease, aggregates, signaling, toxicity.*

Përmbledhje

Sëmundjet neurodegjenerative prekin një numër përherë dhe në rritje të popullatës njerëzore, sidomos të moshuarit, të imunokompromentuarit ose të dy. Studimet tregojnë se më shumë se 55 milion njerëz janë të prekur nga sëmundja e Alzheimer-it dhe mbi 10 milion vuajnë nga sëmundja e Parkinson-it në mbarë botën. Edhe pse komplekse nga natyra, këto sëmundje kanë të gjitha një veçori të përbashkët, mungesa ose komunikimi jo i saktë midis neuroneve dhe qelizave të tjera. Ato ndihmohen dhe nga faktorë të tjerë duke filluar prej moshës, dieta, mungesa e stërvitjes deri në sinjalizim qelizor të gabuar, prodhim dhe degradim jo normal të proteinave e të agregatëve. Humbja e neuroneve në sistemin nervor qendror dhe atë periferik, duke e bërë të paaftë për rigjenerimin e tyre çon në humbjen e funksioneve motore, të folur me probleme, kujtesë të kompromentuar, inflamacion, proteostazë të gabuar dhe vdekjen e neuroneve. Sinjalizimi i gabuar i disa rrugëvë sinjalizuese ka shfaqur një rol kyç në zhvillimin dhe përhapjen e sëmundjeve neurodegjenerative. Përveç sinjaleve jo normale, sistemi imunitar është gjetur si faktor në përhapjen e degjenerimit neural dhe vdekjen e tyre. Këto zbulime në korrelim me faktin që përqasjet klinike nuk reflektojnë përherë kërkimin bazë, e bëjnë një përparësi për të kuptuar dhe më tej mekanzimat veprues që prekin këto sëmundje në mënyrë për t'i trajtuar ato. Studimi ynë fokusohet në përmbledhjen e kërkimeve të reja në zbulimet e patologjive neurale për t'i diagnostikuar ato në mënyrë të saktë dhe gjetjen e trajtimeve noveliste bazuar në mekanizmin e veprimit.

Fjalë kyçe: *Neurodegjenerative, Sëmundje, Agregatë, Sinjalizim, Toksicitet*

Introduction

Neurodegenerative diseases are firstly connected with older ages and this is due to the impairment of the internal cell mechanisms to maintain homeostasis. Under non-physiological conditions, cells tend to explore new mechanisms of living thus altering themselves more often than not, including the surrounding neighboring cells. Diseases affecting the nervous system are very complex with one common key feature; the lack of communication between neurons or neurons and other type of cells. They can differentiate according to the neuronal regions that shows malfunctioning characteristics. Over the years, studies have shown an increased involvement of the peripheral nervous system as well as the immune system in the development of neurodegenerative diseases. However, there are still many unanswered questions about the underlying mechanisms that trigger the onset of the disease or promote its development.

There is a lack of knowledge about the type of cell/s responsible for initiating or sustaining the degeneration of the nervous system and even fewer information about the possible repair mechanisms that might take place to either inhibit or stop the development of this type of disease. Under these circumstances, researchers and neuroscientists in particular, have created a list of common factors that influence the development of neurodegenerative diseases. Amongst them listed include aging, dietary customs and nutritional customs, physical activity and environmental toxins (Wareham et al., 2022).

One of the inevitable phases of life is aging process which has been associated with many different diseases with the passage of the years with special attention in neurodegenerative diseases (Hou et al., 2019). Studies have shown that the Alzheimer disease for example, has been diagnosed in more than 5 million people only in the United States of America in 2018 ("2021 Alzheimer's disease facts and figures," 2021). In 2017, up to 3% of the population worldwide over the age of 65 years old have developed Parkinson's disease (Wareham et al., 2022). These numbers will increase in the coming years as longevity of humans rises. The molecular mechanisms of aging are associated with multiple key processes within the cell. The most prominent mechanisms are DNA-related as several physical alterations of the DNA (strand breaks, deletions, and telomere shortening and epigenetic events) can enhance degeneration of nervous cells (Lopez-Otin et al., 2013). Further studies on aging demonstrated that the quality of proteostasis plays a focal role and is another aspect that can disrupt and lead to different protein abnormalities affecting structure, activity and degradation (Lopez-Otin et al., 2013) (Fang et al., 2017).

Multiple studies have shown that a correct nutritional diet can help in decreasing the risk of developing age-related diseases. Better results were obtained on individuals suffering from cognitive impairment and especially in their early stages. Indirectly, food supplements did help with depression as one of the concomitant diseases (Businaro et al., 2021).

Regular and continuous physical activity has been suggested as an alternative therapy for a healthy brain. Researchers have hypothesized on at least two separate mechanisms on how exercising can help treating neurodegenerative disorders. Shortly summarizing, physical activity is believed to rapidly increase the amount of IL6 able to enter the brain and act as neuroprotectors. In addition, lower levels of apoptosis and ROS formation have been associated with exercising resulting in healthier mitochondria and less mitophagy

(Marques-Aleixo et al., 2021).

- Inflammation within the central nervous system

Inflammation is a defense mechanism of the organism against internal and/or external damaging stressors through the activation of white blood cells, in particular monocytes. Inflammation occurring in the central nervous system is mainly driven by astrocytes and microglial cells (Wareham et al., 2022). In Alzheimer disease it has been shown that apart from neuronal-derived damages, immune cells either residing in the CNS or in PNS can play a critical role in the progression of the disease (Guzman-Martinez et al., 2019). In 2018, Cortes et al demonstrated that neuroinflammation can induce incorrect folding of *tau* protein. The majority of the *tau* protein structure in neurons is localized in the axons and a much lesser amount in the dendrites. In the beginning, the role of *tau* was only associated with the integrity of the microtubules (Weingarten et al., 1975) (Drechsel et al., 1992), but in 2010 Citron proved another function in the nucleus (Citron, 2010). Under normal physiological conditions, *tau* is lost leading to the formation of different epitopes (Guzman-Martinez et al., 2019). *Tau* hyperactivation creates a favorable environment for auto-accumulation inside the cells that lead to toxicity (Braak & Braak, 1991). This pathology, in the majority of cases with AD is as a result of the amyloid plaques (Pontecorvo et al., 2017).

The latter is able to bind at least 3 different types of receptors like TLR, RAGE and NLR that activate microglia. A cytokine and chemokine storm leads to a higher recruitment of more microglia and astrocytes at the site (Heneka et al., 2014). Their purpose is to remove the amyloid β plaques. In case amyloid β plaques phagocytosis is not complete, neuroinflammation persists and toxicity can happen (Hansen et al., 2018). It is hypothesized that higher levels of amyloid β segments induced from the microglia themselves might upregulate IFITM3 expression that leads to higher levels of beta amyloid (Hur et al., 2020). Researchers believe that the link between the amyloid β and tau aggregation is precisely because of the activation of glial cells (Nisbet et al., 2015) (Yoshiyama et al., 2007). Loss of function and apoptosis in neurons induced from tau hyperphosphorylation is probably due to the disruption of the cell membrane (Guo et al., 2017) (Meng et al., 2022).

In postmortem brain cells analysis from individual who suffered from PD demonstrated, for the first time in 1998, the presence of activated glial cells emphasizing the potential role of neuroinflammation in the development of PD (McGeer et al., 1988). Other follow up studies confirmed that aggregation

of α-synuclein, which until then was considered as the primary cause of neuronal loss, was not always leading to neurotoxicity (Milber et al., 2012). In fact, it was shown that α-synuclein plaques exhibited a toxic effect in neurons only if microglia cells were present (Zhang et al., 2005) (Acuña et al., 2019). Over time, several contradictory papers were published where sometimes α-synuclein aggregation induced mitochondrial abnormalities and cell death (Ludtmann et al., 2018) (Di Maio et al., 2016).

Other in vivo investigations and samples from PD patients reported dysfunctional nervous cells releasing damaged α-synuclein in the surrounding microenvironment (Gundersen, 2020) (Kim et al., 2013) (Choi et al., 2020). Once outside the cell, α-synuclein can in turn stimulate other glial cells by acting as a ligand for either different receptors expressed in the cell membrane or intracellular ones (Tansey et al., 2022) (Grozdanov et al., 2019) (Chavarría et al., 2022). The high phosphorylation level found in aggregated α-synuclein was firstly considered as a pathological feature. Latter investigations showed that it might in fact be a protective mechanism (Kawahata et al., 2022) (Ghanem et al., 2022). Moreover, there is ample evidence that microglia cells can cooperate to faster degrade α-synuclein aggregates through the formation of intercellular bridges for α-synuclein transportation (Scheiblich et al., 2021). After deeper analysis, Banati et al hypothesized that α-synuclein transfer between adjacent microglia cell and other glial cells occurred in an attempt to recruit a higher number of glial cells (Banati et al., 1993). Theoretically they would be able to degrade all of the insoluble plaques, but instead they enabled microglia-neuron interaction due to the constant activation of the glial cells (Xia et al., 2021). Nowadays, the critical role of the immune system in the onset and development of Parkinson disease is documented.

Signaling pathway potentially leading to neuroinflammation

-TLR signaling

Toll-like receptors are key players of the innate immune response and are found throughout the organism without a specific localization. In humans there are 10 different TLRs, but three of them are strictly connected with neurodegenerative diseases, TLR2, TLR4 and TLR9 (Kumar, 2019). They are abundantly found in normal neurons and other neural cells and overexpressed in patients with NDD (Adhikarla et al., 2021) (Fiebich et al., 2018). Even though TLR2 is the most investigated type among TLRs, there are still contradictory results. Some studies have demonstrated that TLR2 mediate microglia activation from amyloid β aggregates and vice versa where the

ablation of TRL2 induced inactivation of microglia and prevention of memory loss (Liu et al., 2012) (McDonald et al., 2016) (Rangasamy et al., 2018). On the other hand, other research groups have shown the opposite where TLR2 activity increases amyloid β aggregations and induced-brain damage upon TLR2 knockout (Chen et al., 2006) (Zhou et al., 2019). In PD patients, expression of TLR2 induced accumulation of α-synuclein, while knocking it out gave the opposite effect (Fig.1) (Xia et al., 2021) (Dutta et al., 2021; Guo et al., 2020).

TLR4, shows a similar contradictory activity profile in AD patients. Inhibition or deletion of its activity neutralizes the toxic effect of amyloid β (Balducci et al., 2017). On the other hand, in vivo experiments showed that mild constant TLR4 activation enhanced memory improvement (Qin et al., 2016). Conflicting outcomes were obtained from PD mouse models also. Less neuroinflammation was achieved in the lack of TLR4 activity (Campolo et al., 2019) as well as in hyperactivation of the receptors (Venezia et al., 2017).

TLR9 differs from all other TLRs because is the only one that can identify DNA with unmet-CpG region (Yan et al., 1996). Studies have demonstrated that TLR9-mediated microglia activation were present in PD samples. AD models instead showed that TLR9 signaling pathway enhanced the regression of amyloid β aggregates (Patel et al., 2021; Scholtzova et al., 2009).

Despite the enormous work done so far in understanding the TLR molecular mechanism underlying the triggering factors and the development of the neurodegenerative disease there are still a lot of gaps. As described earlier, the many contradictory outcomes present a very complicated pathological condition, making its treatment even more difficult to establish.

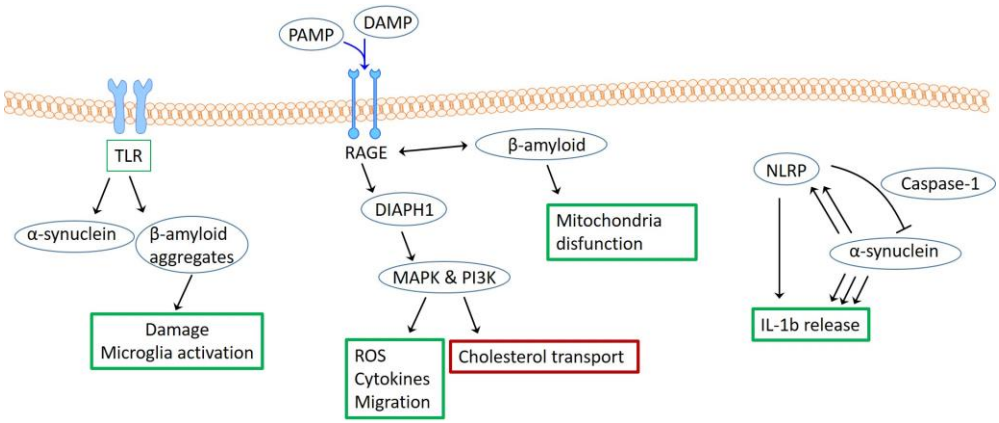

Figure 1. Illustration of altered signaling pathways in neurodegenerative diseases.

RAGE signaling pathway

Similarly, to TLR, RAGE signaling can be activated by pathogen- and damage- associated molecular patterns, PAMP and DAMP respectively. Both patterns promote activation of the immune system (Juranek et al., 2022). The direct downstream effect of RAFE receptors is DIAPH1 (diaphanous 1) that in turn stimulates the mitogen-activating protein kinases (MAPK) and phosphoinositide 3 kinase (PI3K) cascades. The formation of the RAGE-DIAPH1 complex shows multiple effects within the neural cells: accumulation of reactive oxygen species, release of cytokines, increased migration and lower levels of cholesterol transporters. Altogether, they promote alteration of the normal cell functions (Derk et al., 2018).

Advanced glycoxidation end (AGE) products are another ligand for RAGE receptors. High concentration of AGEs is mainly produced from glycation and diets (Scheijen et al., 2016; Vlassara & Uribarri, 2014). A combination of elevated AGEs and ROS in cells strongly promotes systemic inflammation and maybe degeneration of the nervous system. A very similar profile was demonstrated for aging and diabetes, suggesting that this communication can be the linking bridge between three critical physiological conditions, diabetes, neurodegeneration and aging (Fig.1) (Derk et al., 2018).

RAGE induced inflammation was demonstrated also in AD because amyloid β aggregates can act as a ligand for this type of receptor and ultimately activate microglia and other neural cells in the CNS (Yan et al., 1996). In addition, many studies proved that amyloid β interaction with RAGE receptors induced the translocation of amyloid β itself to the mitochondria and dysfunction of the latter (Sbai et al., 2022). PD in vivo models also exhibited a significant increase in RAGE expression. In a total knock-out RAGE mouse model the survival of neurons was higher (Guerrero et al., 2013; Sathe et al., 2012; Teismann et al., 2012).

The important role of RAGE signaling has been testified, however most of the performed research have made use of total knock-out conditions. Therefore, it is of great importance to investigate the function of this specific cascade under several strength-dependent activation.

Inflammasomes

Inflammasomes are complex proteinic structures localized in the cytosol that

are activated by a number of structurally different stimuli patterns including viruses, bacteria, ARN, ATP, etc, (Lamkanfi & Kanneganti, 2010). Over the years, an increasing number of inflammasomes have been discovered, but NLRP3 showed the most consistent association with neurodegeneration. Up to date, NLRP3 is believed to require two different signals to be fully functional. For the first time NLRP3 was discovered in Alzheimer's disease, where NLRP3- dependent IL-1b release was promoted from amyloid β (Halle et al., 2008; Parajuli et al., 2013). Total ablation of this inflammasome stimulated the phagocytosis of the amyloid β aggregates (Heneka et al., 2013) as well as an anti-inflammatory behavior of microglia (Dempsey et al., 2017). Based on these results, testing of NLRP3 inhibitors serves as a potential therapeutic agent for AD patients (Gordon et al., 2018).

In Parkinson's disease the situation is more complicated because the precise role of inflammasome NLRP3 is not fully clear. Some studies reported an activation of NLRP3 specifically by α-synuclein polymers, while higher activity of IL-1b was also detected from monomeric α-synuclein (Codolo et al., 2013). Moreover, partial or total inhibition of NLRP3 diminished neuroinflammation and degeneration in PD in vivo experiments (Lee et al., 2019; Zhou et al., 2016). The opposite was demonstrated from Wang et al which showed that NLRP3-dependent caspase-1 promoted α-synuclein aggregation (Wang et al., 2016). In this case, inflammasome activity stimulates longer maintenance of inflammation that probably led to neurotoxicity (Fig.1).

cGAS (cyclic GMP-AMP synthase) -STING (stimulator of interferon genes) signaling pathway

The human immune system has the ability to identify damaged or exogenous DNA material and to consequently trigger an immune response. The cGAS-STING signaling pathway is responsible for recognizing cytosolic DNA and secrete type-1 INF and other cytokines (Decout et al., 2021; Wan et al., 2020). This pathway starts with the production of cGAMP upon detection of circulating DNA from cGAS. Once cGAMP binds to STING in the endoplasmic reticulum, they move to the Golgi apparatus where activation of IRF3 and NF-κB signalization occurs promoting the release of interferons and cytokines (Zhang et al., 2023). In parallel, activated cGAS-STING cascade is able to induce cell death through the destruction of lysosomes and also autophagy (Guijarro-Muñoz et al., 2014; Stark et al., 2013). There are many unanswered questions about the mechanisms involved or triggered by the

cGAS-STING pathway under healthy and pathological conditions. In this context, in AD, the cGAS-STING pathway could help in the inactivation of microglia (Fang et al., 2017). Some studies reported that the lack of cGAS diminished cognitive impairment and aggregation of amyloid β (Xie et al., 2023), whiles others showed the same result but through the activation of STING (Fig. 2) (Xu et al., 2019).

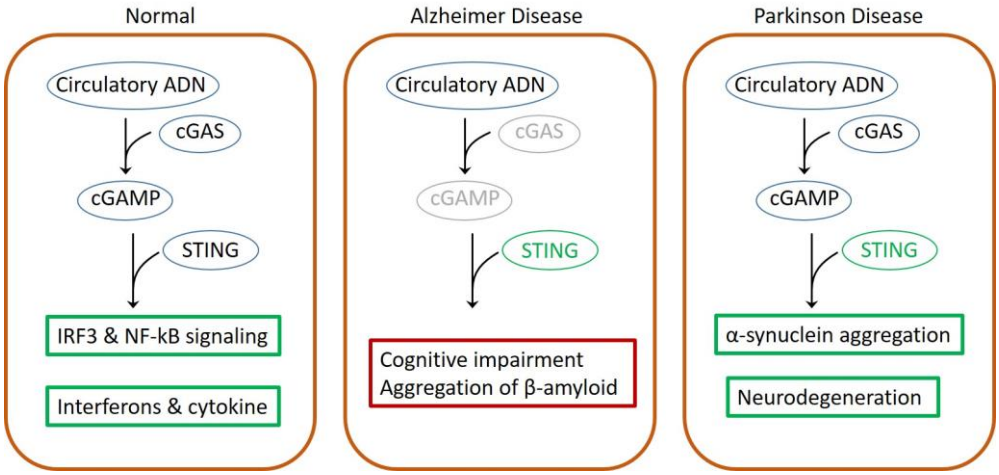

Figure 2. cGAS-STING signaling under normal and abnormal conditions.

The role of active cGAS-STING was investigated also in the pathology of Parkinson's disease. Researchers elucidated a promotion of neuroinflammation and degeneration in a STING-dependent manner (Hinkle et al., 2022; Standaert & Childers, 2022). In PD animal models, motoric function was restored upon deletion of STING protein (Sliter et al., 2018). A more recent publication reported that STING hyperactivation could all by itself increase aggregation of α-synuclein and neurodegeneration (Szego et al., 2022). Even in the case where all studies fully agree with each other, it is still important to understand the effects of this pathway in different types of cells in order to facilitate the development of efficient therapy strategies.

Conclusions

For many years, protein aggregation was considered as the only pathological characteristic of neurodegenerative disorders and all therapy approaches focused in degrading these aggregations. However, several studies demonstrated that fewer aggregates did not correlate with disease regression. In the last years, alteration of the immune response in the nervous system has gained a lot of attention by acting as a critical player not only in the

development of neurodegenerative diseases but also on their onset. There is now enough evidence that demonstrates that neuroinflammation occurs even prior to protein degradation. This discovery definitely increases the chances of developing a much more efficient therapy, even though this approach is not that simple. As previously described, there are many contradictory results on the role of different inflammatory cascades emphasizing the high complexity of this pathology. All data taken into account together suggest the need of a specific requirement of the immune response depending on the stage of the disease, timing, strength of the stimuli, cell type and the target protein in every signaling pathway. In conclusion, there is a great amount of knowledge about the role of neuroinflammation in neurodegenerative pathologies gathered over the last decades. However, the exact and precise underlying molecular mechanisms is still not completely understood and requires further detailed investigation.

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