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Editorial

Impaired Proteasome as a Catalyst for cGAS-STING Activation in Alzheimer's Disease

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Alzheimer's disease (AD) is characterized by the buildup of amyloid-β (Aβ) outside neuronal cells in the form of senile plaques and intracellular neurofibrillary tau tangles. In addition, it is accompanied by synaptic loss, neuroinflammation, cognitive decline, and neuronal death. In a survey done in the United States, the long-term care costs for people with dementia are anticipated to reach 360 billion dollars in 2024 and almost 1 trillion dollars by 2050 [1]. However, no cure or treatment is available either to stop or reverse the disease progression. To develop effective therapy, it is necessary to understand the pathogenesis of AD.

Misfolded proteins and protein degradation systems have contributed significantly to the understanding of AD. For instance, the ubiquitin variant Ubiquitin-B+1 frameshift mutant (UBB+1) affects proteasome degradation and can be seen early in AD pathology. It has been shown to stimulate amyloid and tau pathology in cellular models [2]. A dysfunction in proteostasis not only leads to protein misfolding but also activates the innate immune system. This can be attributed to mitochondrial stress and the activation of the inflammation pathway triggered by the nucleic acid-sensing factors. In the case of proteasomal dysfunction, one consequence could be the leakage of mitochondrial DNA (mtDNA) from the damaged mitochondria into the cytosol. This leaked mtDNA acts as a danger-associated molecular pattern, thereby activating the cyclic GMP–AMP synthase (cGAS) and stimulator of interferon genes (STING) DNA-sensing pathway, to cause neuroinflammation [3–5] (Fig. 1).

1. Proteasome Dysfunction Links to Neurodegeneration and mtDNA Release

The ubiquitin-proteasome system, or ubiquitin-proteasome system (UPS), is vital for clearing abnormal proteins that could trigger inflammation if accumulated. Neurons are particularly vulnerable to UPS impairment due to their high reliance on precise protein homeostasis for function and survival. Findings from the studies of the 5×FAD and tau-P301S mice revealed that the synaptic proteasome function is impaired even in the early stages, a phase before overt plaque formation, correlating with early memory deficits [6]. Blocking proteasome function in healthy neurons causes AD-like effects, such as oxidative stress, synaptic loss, and cognitive decline. Conversely, boosting UPS activity can reverse these effects [6]. Deletion of a 26S proteasome subunit causes neurodegeneration and Lewy-like inclusions, accompanied by abnormal mitochondria, linking proteasome failure to mitochondrial dysfunction and neuronal damage that extends beyond protein aggregation [5]. Increased production of reactive oxygen species (ROS) can damage mitochondrial lipids and proteins, compromise membrane integrity, and ultimately cause membrane rupture. This occurs due to abnormal protein aggregation caused by proteasomal failure, which disrupts redox balance. Although UPS is involved in mitochondrial quality control, its impairment weakens the removal of damaged mitochondrial proteins, leading to oxidative stress that eventually causes mitochondrial membrane collapse. This collapse can then leak mitochondrial DNA into the cytosol. Also, it has been shown in a neuron-specific proteasome knockout mouse that the cGAS-STING pathway was activated, as evidenced by increased protein levels of cGAS and STING, and pro-inflammatory factors, such as STAT1, NF-κB, IL-1β, TNF-α, and IL-6, as well as signs of neurodegeneration, including decreased brain weight and necroptosis markers (phosphorylated mixed lineage kinase domain-like protein (MLKL) and receptor-interacting protein kinases (RIP) kinases). These results link proteasomal dysfunction to immune responses and cell death in the brain [4].

2. mtDNA Release and cGAS-STING Pathway Activation in AD

The cGAS-STING pathway drives chronic inflammation in aging and neurodegeneration [7]. cGAS detects double-stranded DNA in the cytosol and produces cyclic GMP, activating STING on the endoplasmic reticulum. STING then promotes the transcription of type I interferons and inflammatory genes, mainly protecting against infections. In AD, cytosolic mtDNA acts as a trigger [4,8,9]. Proteasome-deficient mouse brains exhibit increased pathway activity, linking proteostasis issues to immune responses [4,5,8]. In the 5×FAD mouse model, cytosolic

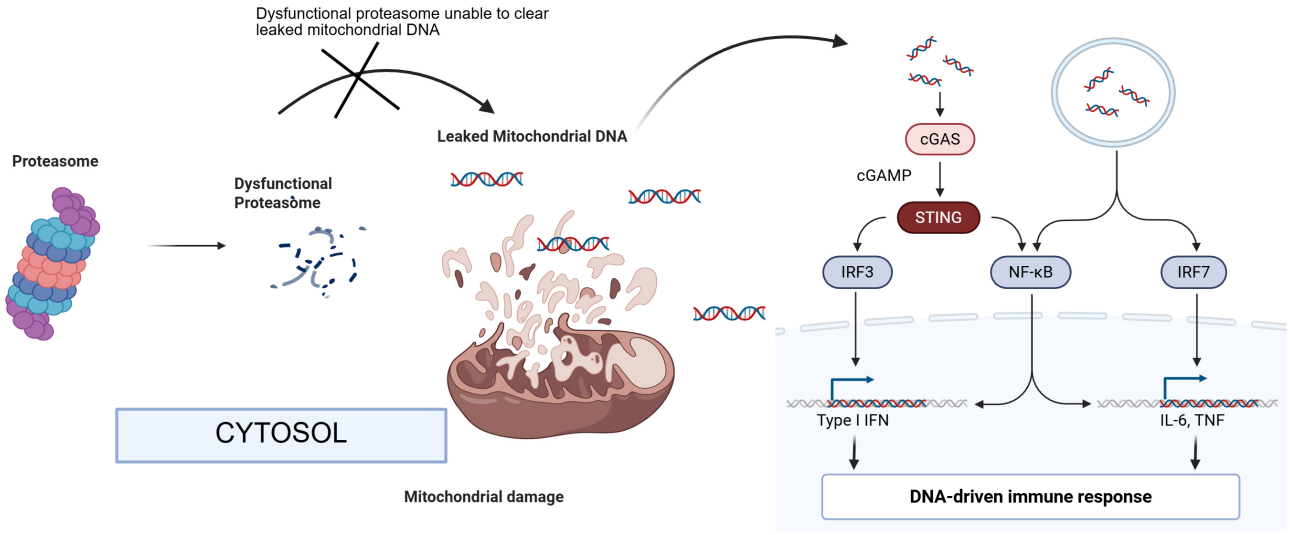

Fig. 1. Activation of the cGAS-STING pathway. Dysfunctional proteasome induces the alteration of mitochondrial structure and function, leading to the release of mtDNA into the cytosol, where mtDNA activates cGAS-STING and the downstream signaling pathways to cause neuroinflammation responses. cGAS, cyclic GMP–AMP synthase; STING, stimulator of interferon genes; cGMP, cyclic guanosine monophosphate; IRF3, interferon regulatory factor 3; IRF7, interferon regulatory factor 7. The figure was created in BioRender https://BioRender.com.

DNA triggers microglial cGAS production, whereas the deletion of cGAS reduces amyloid plaques and improves cognition [8]. Blocking STING with H151 reduces amyloid and inflammation in these mice [10]. While the main effector cells are microglia, neuronal activation can also occur under stressful conditions, particularly with aging or tau pathology [11]. Activation of cGAS-STING in microglia primarily enhances neuroinflammation by increasing the release of inflammatory mediators, including IL-1β, TNF-α, and IL-6, and alters microglial homeostasis, including phagocytosis. However, in neurons, cGAS-STING activation affects the cell intrinsically, leading to synaptic dysfunction and cell senescence, which directly contributes to neurodegeneration.

3. Therapeutic Implications

Recognizing that proteasomal dysfunction can trigger the cGAS-STING cascade in AD provides a new avenue for treatment. One approach is enhancing proteostasis at its root. In one study, activation of the proteasome through the cAMP/protein kinase A (PKA) signaling pathway, as with rolipram, restored protein turnover and rescued Aβ-induced synaptic failure [6]. Although proteasome-activating compounds are still being developed, other methods, such as activating proteasome subunits or enhancing autophagy, could also prevent the cascade [12]. Additionally, enhancing the removal of damaged mitochondria (mitophagy) is another strategy. Removal of defective mitochondria limits mtDNA leakage. Treating aged mice with mitophagy boosters, such as urolithin A, lowers cytosolic mtDNA, attenuates cGAS-STING activation, and supports neuronal health [9]. Similarly, the use of metabolic approaches to replenish intracellular NAD^+ has been shown to inhibit the inflammation triggered by the cGAS-STING pathway. Supplementing NAD^+ in a transgenic AD mouse model reduced the inflammation as well as the cellular senescence triggered by the cGAS-STING pathway, thereby improving neuronal resilience and function [13]. Again, inhibiting the cGAS-STING pathway itself is another approach [14,15]. The STING inhibitor H-151 is protective in AD models, and the drugs that inhibit cGAS are also being explored in inflammatory diseases [8,10,14]. However, these therapeutic strategies face several challenges and limitations. The broad suppression of the STING pathway by STING inhibitors such as H-151 can weaken antiviral defenses or cause off-target effects, raising safety concerns with long-term use. Also, approaches used to enhance proteasome activity or mitophagy are hard to confine to neurons, since the pathway is active in many tissues, and systemic activation can disrupt normal proteostasis elsewhere. These approaches also differ from traditional therapies targeting amyloid or tau, as they focus on upstream processes such as improving proteostasis, innate immune signaling, and mitochondrial function, rather than directly clearing misfolded proteins and protein aggregates. Since impairments in proteostasis can worsen Aβ and tau pathology, and cGAS-STING inhibition can lower amyloid levels in AD models, adapting combination therapy is a promising treatment strategy.

In conclusion, the discovery that proteasomal dysfunction activates the mtDNA-cGAS-STING pathway in the brain changes our understanding of AD, linking protein

aggregation and neuroinflammation. This reveals targets for therapy, such as enhancing mitophagy. Exploring these areas is vital, as restoring proteostasis and controlling innate immunity could break the cycle of protein buildup and inflammation, offering hope for new treatment strategies against AD and dementia. The role of the cGAS-STING pathway in neuroinflammation, compared with other innate immune drivers, such as those mediated by toll-like receptor (TLR) or NOD-like receptor pyrin domain containing 3 (NLRP3), has not been established, and such comparisons may represent an area of interest for potential future research.

Author Contributions

AD and HW made substantial contributions to the work. AD drafted the manuscript and HW reviewed and edited it. Both AD and HW were involved in searching literature and revised the work to ensure the accuracy of the cited work. HW was also responsible for acquisition of funding. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest. Hongmin Wang is serving as one of the Editorial Board members of this journal. We declare that Hongmin Wang had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

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