

Review

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Review

The cGAS–STING Pathway in Dementia: An Emerging Mechanism of Neuroinflammation

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Abstract

Dementia, characterized by a progressive decline in cognitive function, is a growing global health concern due to the aging population. It affects memory, executive function, language, and other cognitive capacities, significantly impairing daily life. Despite the growing burden, effective preventive and therapeutic strategies remain elusive, emphasizing the urgent need for novel interventions. Recent advances underscore the pivotal role of neuroinflammation in dementia pathogenesis, particularly in Alzheimer's disease (AD). Chronic activation of immune cells within the central nervous system, such as microglia transition from a homeostatic to a pro-inflammatory state called Disease-associated microglia status 1 and 2 (DAM1 or DAM2), exacerbates neurodegeneration, creating a self-perpetuating cycle of inflammation and cognitive decline. This review focuses on emerging research exploring the cGAS-STING pathway's role in dementia, examining its potential as a diagnostic and therapeutic target. The cGAS-STING pathway, integral to innate immune responses, may contribute to the chronic neuroinflammation seen in neurodegenerative diseases. By targeting this pathway, new strategies could mitigate the inflammatory processes that drive neuronal loss, offering a promising avenue for therapeutic development in dementia.

Keywords: neurodegeneration; dementia; Alzheimer's Disease; immune response; Disease Associated Microglia; cGAS-STING pathway

1. Introduction

Dementia is a syndrome characterized by the progressive decline in cognitive capacities such as memory, executive function, language, and visuospatial skills, ultimately impairing daily functioning without affecting alertness or consciousness. At its core, dementia is driven by the loss of neurons and synaptic connections within the brain, which disrupts neural circuits necessary for cognitive integrity (Spires-Jones and Hyman, 2014). The incidence of dementia has risen significantly due to global aging trends, with an increase in cases from 20.2 million in 1990 to 43.8 million in 2016

(Collaborators, 2019). Projections estimate that by 2050, the number of people living with dementia will escalate to over 152.8 million globally, reflecting both increased life expectancy and the persistent lack of effective preventive measures (2020, International, 2024).

Recent advances in our understanding of dementia pathogenesis have highlighted the significant contribution of neuroinflammation to disease progression, particularly in Alzheimer's disease (AD) and other neurodegenerative conditions (Heneka et al., 2015). Neuroinflammation is characterized by the activation of immune cells within the central nervous system (CNS), notably microglia and astrocytes, which can release pro-inflammatory cytokines, chemokines, and reactive oxygen species (ROS). While acute inflammation is necessary for CNS homeostasis and repair, chronic neuroinflammation is implicated in the exacerbation of neuronal damage, ultimately leading to cognitive decline (Ransohoff, 2016a). Microglia, the resident immune cells of the CNS, play a central role in this process. In response to pathogenic stimuli such as amyloid- β ($A\beta$) plaques or tau aggregates, microglia undergo a phenotypic transformation from a homeostatic to a pro-inflammatory state, releasing a cascade of inflammatory mediators (Salter and Stevens, 2017). Emerging evidence suggests that sustained activation of microglia in dementia can lead to a detrimental cycle, whereby neuroinflammation promotes further neurodegeneration, creating a self-amplifying loop (Heppner et al., 2015).

2. Dementia Classification and Neuroinflammation

Dementia is a complex disorder with various etiologies, often distinguished by the type of protein aggregation and its localization in the brain. However, the emerging role of neuroinflammation as a common thread across dementia types has garnered increasing attention. Inflammatory processes, including activation of microglia and astrocytes, have been implicated in the progression of these disorders, suggesting that targeting neuroinflammation could offer therapeutic potential (Heneka et al., 2015). The most prevalent forms of dementia - Alzheimer's Disease (AD), Vascular Dementia (VaD), Lewy Body Dementia (LBD), and Frontotemporal Dementia (FTD) - are associated with distinct pathophysiological mechanisms, yet all are linked to chronic neuroinflammatory processes, which exacerbate neuronal damage and cognitive (Moyse et al., 2022, Zhang et al., 2023).

2.1. Vascular Dementia and Neuroinflammation

Vascular Dementia (VaD) is the second most common type of dementia and is characterized by cognitive deficits resulting from cerebrovascular disease, such as cortical infarctions and white matter lesions. The subtypes of VaD include post-stroke dementia (PSD), multi-infarct dementia (MID), and subcortical ischemic vascular dementia (SIVD) (Venkat et al., 2015). While the primary mechanism of VaD is thought to be ischemia-induced neuronal damage, recent evidence suggests that neuroinflammation plays a pivotal role in VaD progression. In particular, pro-inflammatory cytokines such as IL-6 and TNF- α , as well as activated microglia, are known to disrupt the blood-brain barrier (BBB) exacerbate cerebral ischemia and contribute to the progressive loss of white matter integrity (Tian et al., 2022, Love and Miners, 2016). Agents targeting microglial activation such as colony-stimulating factor-1 receptor (CSF1R) inhibitor has shown promise in cerebrovascular disease model and postmortem brain tissue (Askew et al., 2024).

Moreover, advanced neuroimaging techniques, such as magnetic resonance imaging (MRI) have provided insights into the link between vascular pathology and neuroinflammation. For instance, MRI of VaD patients often reveals perivascular lesions and leukoaraiosis, which are closely associated with elevated levels of microglial activation and inflammatory marker expression (Custodero et al., 2022, Kalaria, 2016). Chronic neuroinflammation in VaD has also been associated with systemic risk factors such as hypertension and diabetes, further implicating the immune system in the progress of vascular brain damage (Kalaria, 2016). These findings underscore the potential of therapies targeting inflammatory pathways in VaD to prevent further cognitive impairment and brain atrophy.

2.2. Lewy Body Dementia and Neuroinflammation

Lewy body dementia (LBD) is characterized by the aggregation of α -synuclein into Lewy bodies, predominantly affecting the brainstem, cortex, and limbic regions. While α -synuclein aggregates are central to the pathology of LBD, mounting evidence suggests that neuroinflammation accelerates disease progression. Activated microglia have been observed surrounding Lewy bodies, where they release pro-inflammatory cytokines such as IL-1 β and TNF- α , which may contribute to neuronal death and synaptic dysfunction (Loveland et al., 2023). Moreover, clinical studies reveal a correlation between the elevated neuroinflammatory markers and the severity of cognitive and motor impairments in LBD patients (Surendranathan et al., 2018, Vrillon et al., 2024), suggesting that inflammation exacerbates the neurodegenerative progress. Therapeutic approaches targeting pathways that regulate innate immune response, for instance, cGAS-STING pathway may be considered as potential treatments for LBD as the correlation with cGAS-STING pathway and synuclein pathology has been reported (Hinkle et al., 2022, Stoll and Sortwell, 2022).

2.3. Frontotemporal Dementia and Neuroinflammation

Frontotemporal dementia (FTD) involves progressive degeneration of the frontal and temporal lobes, with marked neuronal atrophy linked to proteinopathies such as tau or TDP-43 aggregates. Inflammatory processes are implicated in the neurodegeneration observed in FTD. Studies using PET imaging have revealed that increased microglial activation in patients with FTD and correlates with disease progression and severity of symptoms (Bright et al., 2019, Bevan-Jones et al., 2020, Zhang, 2015).

Moreover, genetic evidence further supports the link between inflammation and FTD. For instance, mutations in the progranulin gene (GRN), a known risk factor for familial FTD, impair anti-inflammatory processes and lead to enhanced neuroinflammation (Baker et al., 2006). Similarly, C9orf72 gene disrupt autophagy and immune regulation, resulting in increased neuroinflammation and microglial activation in FTD (O'Rourke et al., 2016). Mutations in the microtubule-associated protein tau (MAPT) gene have been shown to drive neuroinflammation by promoting tau pathology and inducing a reactive microglial state (Leyns et al., 2017). A critical gene for microglial function, TREM2, triggering receptor expressed on myeloid cells 2 gene is known to exacerbate neurodegeneration by impairing the microglial response to inflammatory stimuli and phagocytosis (Ulland and Colonna, 2018). These findings have proved the exploration of therapeutic strategies aiming to mitigate neuroinflammatory responses by enhancing genes activity or modulating microglial states as potential interventions (Bright et al., 2019).

3. Distinctions Between Dementia and Alzheimer's Disease in Pathophysiology and Inflammation

Dementia is an umbrella term encompassing a range of cognitive impairments that significantly affect memory, thinking, and behavior. Alzheimer's disease (AD), the most common form of dementia, accounts for 60-80% of all dementia cases (Association, 2024). While all individuals with Alzheimer's have dementia, not all individuals with dementia have AD, as dementia can arise from various etiologies, including vascular causes, Lewy body formations, or frontotemporal degeneration (Jack et al., 2018).

3.1. Pathophysiology of Alzheimer's Disease versus Other Dementia

In the case of AD, the classical hallmark features include the accumulation of amyloid- β (A β) plaques and tau tangles. These aggregates primarily affect the medial temporal lobe and neocortical regions, leading to synaptic dysfunction, neuronal death, and eventual brain atrophy (Hardy and Selkoe, 2002, Jack et al., 2018). A β and tau accumulation is believed to trigger a neuroinflammatory cascade of events, including the activation of microglia, the resident immune cells of the central

nervous system, and the release of pro-inflammatory cytokines and chemokines, which further exacerbate neuronal damage (De Strooper and Karran, 2016, Heneka et al., 2015, Heppner et al., 2015).

In contrast, other forms of dementia have distinct etiological mechanisms. VaD is primarily caused by cerebrovascular damage, leading to ischemic events, small-vessel disease, and white matter lesions. This vascular damage disrupts blood-brain barrier integrity and function, triggering inflammatory responses and neuronal injury that contribute to cognitive decline (Gorelick et al., 2011). LBD, on the other hand, is marked by the aggregation of α -synuclein into Lewy bodies, which are often surrounded by activated microglia releasing pro-inflammatory mediators (Surendranathan et al., 2018). FTD involves the frontal and temporal lobes atrophy and shows tau or TDP-43 aggregates, which also stimulate neuroinflammatory pathway (Bright et al., 2019).

3.2. Neuroinflammation as a Shared Mechanism Across Dementias and Implications

Although these forms of dementia have distinct etiologies, neuroinflammation is increasingly recognized as a shared pathophysiological mechanism across various types of dementia. In each case, microglial activation contributes to the release of pro-inflammatory cytokines, oxidative stress and chronic neurodegeneration. Understanding these shared and distinct mechanisms is essential for developing targeted interventions. AD progresses through well-defined stages, beginning with a preclinical phase, during which mild cognitive impairment (MCI) is often noted, characterized by subtle memory loss. As the disease advances, moderate Alzheimer's results in significant impairments in reasoning, language, and recognition. The neuroinflammatory response, particularly through the activation of the cGAS-STING pathway, is implicated in driving this disease progression from early amyloid deposition to extensive tau pathology and brain atrophy (Mathur et al., 2017).

In the severe stages of AD, widespread neuroinflammation, sustained microglial activation, and the production of pro-inflammatory mediators contribute to a self-perpetuating cycle of neuronal death and cognitive decline (Cunningham, 2013, Tejera and Heneka, 2019). Interestingly, emerging evidence suggests that chronic systemic inflammation, stemming from infections, lifestyle factors, or aging itself, may influence microglial priming and exacerbate neurodegenerative processes (Ransohoff, 2016b, Bachiller et al., 2018).

Although no cure exists for AD or other forms of dementia, targeting neuroinflammatory pathways has emerged as a promising therapeutic strategy. Interventions aimed at modulating microglial activation, inhibiting pro-inflammatory cytokines, or suppressing the cGAS-STING pathway are under investigation for their potential to slow disease progression and preserve cognitive function (Huang et al., 2023, Paul et al., 2021).

4. Current Research and Findings in Dementia and Neuroinflammation

With an aging global population and the significant socio-economic burden dementia imposes on families and healthcare systems, research in dementia has expanded rapidly, especially in identifying early-stage risk factors and diagnostic methods. Among various pathological contributors, neuroinflammation has emerged as a central process in the pathogenesis of dementia. It is now recognized that chronic and excessive activation of the brain's immune system contributes to neuronal damage and cognitive decline (Zhang et al., 2023). Microglial dysfunction, coupled with the activation of inflammatory signaling pathways, exacerbates the progression of AD and other dementias. Additionally, the cGAS-STING pathway is increasingly seen as a major player in mediating these inflammatory responses, linking cytosolic DNA sensing to neuroinflammatory cascades (Huang et al., 2023, Guo et al., 2024, Liu et al., 2024, Sharma et al., 2024, Zhang et al., 2024).

4.1. Genetic Research and Inflammatory Pathways

Recent advances in genetic research have yielded significant insights into the genetic basis of dementia, highlighting the role of genetic variants in inflammatory pathways. Genome-wide association studies (GWAS) continue to identify novel loci associated with dementia subtypes,

highlighting the complex interplay between genetic predispositions, immune function and neuroinflammatory processes in dementia (Kunkle et al., 2019, Chia et al., 2021).

One of the most well-known genetic risk factors for AD is the apolipoprotein E ϵ 4 allele (APOE- ϵ 4), which not only influences amyloid- β deposition but also alters microglial reactivity. APOE- ϵ 4 carriers exhibit increased expression of pro-inflammatory cytokines in the presence of amyloid plaques, exacerbating neurodegeneration (Yin et al., 2023, Lee et al., 2023). Variants in the triggering receptor expressed on myeloid cells 2 (TREM2) gene, which modulates microglial activation, have been identified in populations with high dementia risk and associated with an increased risk for late-onset AD. TREM2 mutations impair the microglial response to amyloid- β , resulting in inefficient clearance of toxic aggregates and heightened neuroinflammation (Ulland and Colonna, 2018). The sialic acid-binding immunoglobulin-like lectins (CD33) gene and the membrane-spanning 4-domains subfamily A (MS4A) gene families suggest additional connections to microglial signaling. CD33 variants particularly regulate the immune inhibitory receptor functions of microglia, linking them to increased neuroinflammation (Siddiqui et al., 2019, Griciu et al., 2013). ATP-binding cassette transporter subfamily A member 7 (ABCA7) is also known to alter the response of inflammation, leading to amyloid accumulation (Dib et al., 2021). Variants in the MS4A gene cluster, which regulate immune signaling, are associated with AD risk (Kunkle et al., 2019, Naj et al., 2011). Furthermore, mutations in genes such as MAPT (tau protein) and GRN (progranulin) in frontotemporal dementia (FTD) have been shown to modulate microglial activation and the production of pro-inflammatory cytokines, amplifying neuroinflammatory responses (Baker et al., 2006, Bright et al., 2019). In LBD, genes involved in α -synuclein processing, such as SNCA, also have indirect ties to neuroinflammation through their effects on microglial activation (Chia et al., 2021) (Table 1).

Table 1. Genetic mutations associated with dementia that are also linked to microglial activation.

Gene	Chromosom Location	Role in Microglia Activation	Associated Dementia	References
CR1	1q32.2	Variants in CR1 impair complement regulation and enhance microglial activation via the complement cascade.	AD	(Karch and Goate, 2015)
BIN1	2q14.3	BIN1 variants may regulate microglial activity through interaction with the immune system, including modulation of pro-inflammatory responses.	AD	(Chapuis et al., 2013)
MEF2C	5q14.3	MEF2C regulates microglial homeostasis and suppresses pro-inflammatory gene expression, thereby protecting neurons from excessive neuroinflammation.	AD	(Zhang and Zhao, 2022)
TREM2	6p21.1	TREM2 mutations impair microglial phagocytic function and lead to chronic neuroinflammation, enhancing microglial activation.	AD, FTD	(Jonsson et al., 2013, Guerreiro et al., 2013)
MS4A	11q12.2	Modulates microglial inflammatory signaling by altering membrane protein interactions and intracellular communication pathways.	Alzheimer's Disease	(Naj et al., 2011, Kunkle et al., 2019)
SORL1	11q24.2	SORL1 mutations altered lysosome function of microglia, leading to amyloid β accumulation.	AD	(Mishra et al., 2022)
PS1	14q24.2	PS1 modulates microglial response to amyloid β and to maintain brain	AD	(Ledo et al., 2021)

		homeostasis by regulating lysosomal calcium signaling and autophagy.		
PLCG2	16q23.3	Activating mutations in PLCG2 promote microglial activation and phagocytosis, improving immune response in Alzheimer's disease.	AD	(Sierksma et al., 2020)
APOE ϵ 4	19q13.32	APOE ϵ 4 induces pro-inflammatory microglial activation through various pathways, including C1q complement activation.	AD	(Shi et al., 2017)
CD33	19q13.41	Loss of function of CD33 reduces microglial activation and enhances amyloid clearance, suggesting CD33 inhibits microglial activation in dementia.	AD	(Griciuc et al., 2013, Siddiqui et al., 2019)
ABCA7	19p13.3	ABCA7 regulates microglial activation by modulating cholesterol efflux and lipid metabolism, which influences the microglial inflammatory response and phagocytic activity.	AD	(Dib et al., 2021)
LILRB2	19q13.42	LILRB2 is co-expressed with TREM2 in microglia and associated with microglial activation by regulating the inflammatory response and the phagocytic activity of microglia.	AD	(Zhao et al., 2022)
TMEM106B	7p21.3	Loss of TMEM106B along with PGRN triggers the lysosomal dysfunction in microglia and exacerbates microglial activation, leading to neurodegeneration.	FTD	(Feng et al., 2020)
C9orf72	9p21.2	C9orf72 hexanucleotide repeat expansions lead to neuroinflammation and dysregulated microglial activation, contributing to neurodegeneration.	FTD, ALS	(O'Rourke et al., 2016)
GRN	17q21.31	GRN mutations reduce progranulin levels, leading to increased neuroinflammation and excessive microglial activation.	FTD	(Baker et al., 2006b)
SOD1	21q22.11	Mutant SOD1 increases oxidative stress and promotes neuroinflammation through enhanced microglial activation in ALS.	ALS	(Pasinelli and Brown, 2006)

4.2. Biomarkers of Neuroinflammation

The detection of biomarkers that reflect neuroinflammatory processes is an evolving area of research. While traditional biomarkers for dementia, such as amyloid- β and tau, remain pivotal, the recognition of inflammation-related markers in cerebrospinal fluid (CSF) and blood holds promise for identifying early-stage dementia and tracking disease progression. In AD, elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α), have been detected in both the CSF and plasma (Daniilidou et al., 2024). Additionally, soluble TREM2 (sTREM2) is being explored as a marker of microglial activation (Ewers et al., 2020). Elevated sTREM2 levels correlate with neuroinflammatory activity and may predict the progression of AD (Nabizadeh et al., 2024, Ewers et al., 2020). In FTD, increased levels of progranulin and inflammatory cytokines, such as IL-8, are being investigated as potential biomarkers of microglial dysfunction (Bright et al.,

2019). However, similar to traditional biomarkers, inflammatory biomarkers in the CSF remain difficult to utilize clinically due to the invasive nature of lumbar punctures. As a result, efforts are being made to identify reliable blood-based biomarkers. Plasma levels of sTREM2 and cytokines, as well as microRNA profiles, have shown potential in reflecting neuroinflammatory processes in both AD and FTD.

4.3. Neuroimaging and Neuroinflammation

Neuroimaging techniques have evolved beyond structural assessments and now allow the visualization of neuroinflammation in vivo. Positron Emission Tomography (PET) using ligands that target the translocator protein (TSPO), which is upregulated in activated microglia, has emerged as a powerful tool for mapping neuroinflammation in various forms of dementia (Pan et al., 2024). In AD, TSPO-PET imaging has shown increased microglial activation in regions corresponding to amyloid- β deposition, particularly in the hippocampus and frontal cortex (Pan et al., 2024, Gouilly et al., 2022). Similarly, in FTD, TSPO binding correlates with microglial activation in regions undergoing neurodegeneration, such as the frontal and temporal lobes (Zhang, 2015). This technique also holds promise in VaD, where chronic neuroinflammation in response to cerebrovascular damage has been observed using TSPO-PET. Furthermore, advanced MRI techniques such as diffusion tensor imaging (DTI) and arterial spin labeling (ASL) are being used to assess white matter integrity and cerebral blood flow, respectively, in the context of neuroinflammatory damage. In LBD, neuroinflammation visualized through these techniques may help differentiate the disease from other neurodegenerative disorders (Loveland et al., 2023).

5. Current Treatment Methods

Current therapeutic approaches for dementia primarily aim at symptom management, offering only transient relief without addressing the underlying pathophysiology. The predominant treatments, including cholinesterase inhibitors and NMDA receptor antagonists, provide modest symptomatic benefits but do little to alter the disease progression. This limitation stems from the complex etiology of dementia, wherein neuroinflammation plays a pivotal role in driving neurodegeneration (Frozza et al., 2018).

5.1. cGAS-STING Pathway and Neuroinflammation in Dementia: A Potential Therapeutic Target

The cGAS-STING pathway represents a crucial component of the body's innate immune system, functioning primarily as a sensor for cytosolic DNA. Cyclic GMP-AMP synthase (cGAS) detects aberrant DNA within the cytoplasm - whether of exogenous origin, such as viral or bacterial DNA, or endogenous, such as mitochondrial or nuclear DNA released during cellular stress or damage. Upon binding to this DNA, cGAS catalyzes the synthesis of cyclic GMP-AMP (cGAMP), a second messenger that subsequently binds to and activates STING (Stimulator of Interferon Genes) (Ablasser and Chen, 2019). This activation triggers downstream signaling through the TANK-binding kinase 1 (TBK1), leading to the phosphorylation of the transcription factor interferon regulatory factor 3 (IRF3) and the subsequent induction of Type I interferon (IFN) and other pro-inflammatory cytokines (Mathur et al., 2017) (Figure 1). In the context of neurodegenerative diseases, such as AD and other types of dementia, the activation of the cGAS-STING pathway has gained increasing attention as a key mediator of neuroinflammation (Huang et al., 2023, Paul et al., 2021). Mitochondrial dysfunction, which is well-established in neurodegenerative conditions, can lead to the release of mitochondrial DNA (mtDNA) into the cytoplasm, where it serves as a potent activator of cGAS (Mathur et al., 2017). This activation may exacerbate chronic neuroinflammation, a hallmark of neurodegenerative diseases. Additionally, nuclear DNA instability, which may occur during cellular senescence or in the presence of oxidative stress, can also trigger the cGAS-STING pathway, further promoting neuroinflammatory responses (Figure 1).

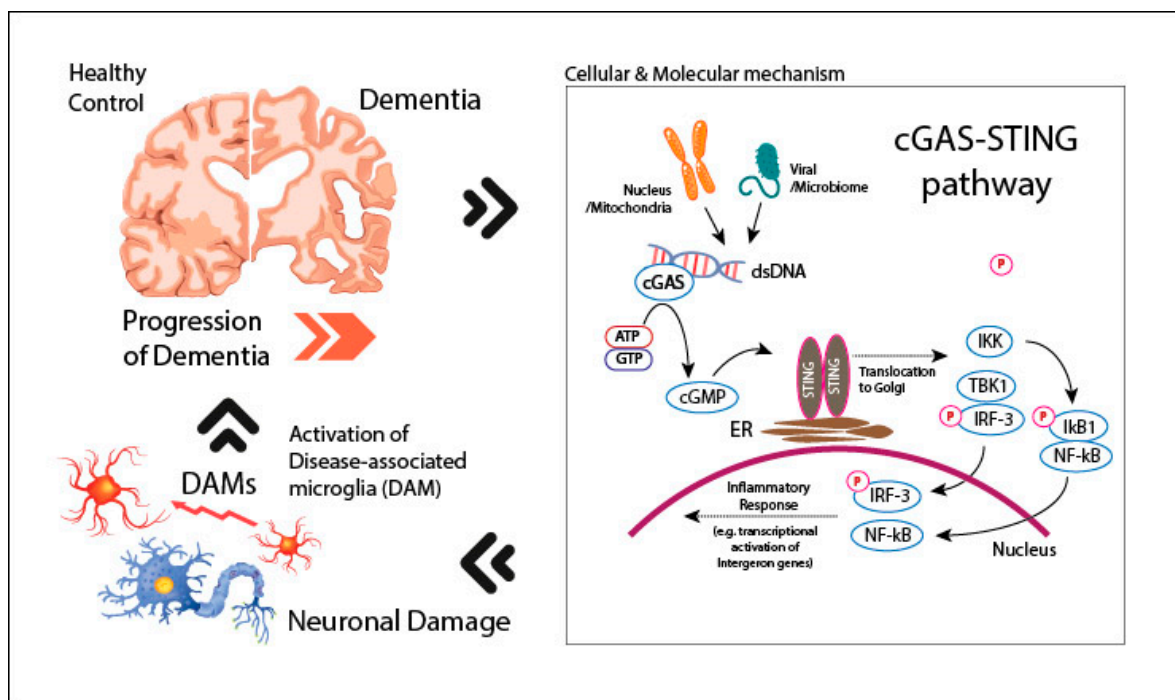


Figure 1. The cGAS-STING pathway in dementia progression and microglial activation.

Double-stranded DNA (dsDNA) from fragmented genome or mitochondria by DNA damage, or viral genomes activates the cytosolic sensor cGAS. This leads to the production of cyclic GMP-AMP (cGAMP), which binds to the ER membrane protein STING. Upon activation, STING translocates to the Golgi, where it triggers a signaling cascade involving TANK-binding kinase 1 (TBK1), leading to the phosphorylation of interferon regulatory factor 3 (IRF-3). Additionally, nuclear factor-kappa B (NF- κ B) signaling is activated through the phosphorylation and degradation of I κ B1. Both pathways induce the transcriptional activation of pro-inflammatory genes and interferons, amplifying the inflammatory response and contributing to neuronal damage in dementia by the activation of disease-associated microglia (DAMs). This feedback loop between DAMs and neuroinflammation potentially exacerbates the progression of dementia.

Emerging evidence further suggests that cGAS-STING activation is involved in the progression of several neurodegenerative diseases. In Parkinson's disease (PD), mutations in PINK1 and Parkin genes impair mitochondrial autophagy (mitophagy), leading to the accumulation of damaged mitochondria and the release of mtDNA, which activates the cGAS-STING pathway (Sliter et al., 2018). Mouse models of α -synucleinopathies, which mimic the neuropathology of PD, show specific activation of cGAS-STING in the nigrostriatal regions, accompanied by elevated cytokine levels and enhanced neuroinflammation (Hinkle et al., 2022). In amyotrophic lateral sclerosis (ALS), TDP-43 protein aggregates have been found to disrupt mitochondrial integrity, leading to mtDNA release and subsequent cGAS-STING activation (Bright et al., 2021). A similar phenomenon has been observed in Huntington's disease (HD), where cGAS upregulation has been identified in both murine models and human tissues (Jauhari et al., 2020, Paul et al., 2021).

Beyond these specific diseases, the cGAS-STING pathway also appears to play a significant role in broader neuroinflammatory processes. Elevated type I interferon levels, a downstream consequence of STING activation, have been documented in models of prion disease, promoting microglial activation and perpetuating neuroinflammatory cascades (Mathur et al., 2017). Post-mortem analyses of human CNS tissues from patients with AD, PD, ALS, and multiple sclerosis (MS) reveal increased STING protein levels in neurons and brain endothelial cells (Ferecskó et al., 2023, Marques et al., 2024, Govindarajulu et al., 2023). In vitro studies further demonstrate that mitochondrial stress induced by factors like palmitic acid leads to cytosolic DNA leakage and robust

activation of the cGAS-STING axis, suggesting that metabolic dysfunction may be a common trigger of neuroinflammation (Bryant et al., 2022, Picca et al., 2020).

5.2. Therapeutic Targeting of cGAS-STING in Neurodegeneration

Given its pivotal role in promoting neuroinflammation, the cGAS-STING pathway is a promising therapeutic target for neurodegenerative diseases. Current strategies to inhibit this pathway focus on both cGAS and STING proteins. cGAS inhibitors aim to block the synthesis of cGAMP, thereby reducing downstream interferon production (Decout et al., 2021). These inhibitors typically target the active site of cGAS or disrupt its interaction with dsDNA. Although several small-molecule inhibitors have shown promise in preclinical models, none have progressed to clinical trials yet (Yu et al., 2024).

STING inhibition has also attracted attention, particularly in the context of cancer immunotherapy; however, its potential in neurodegenerative diseases remains largely unexplored. Most STING inhibitors aim to block the ligand-binding domain or interfere with post-translational modifications that enhance STING activity (Decout et al., 2021). Despite the lack of clinically approved inhibitors, research in this area continues to evolve, offering hope for future therapies targeting neuroinflammation in dementia and related disorders.

6. Conclusion

In summary, the cGAS-STING pathway plays a crucial role in mediating neuroinflammation in various neurodegenerative diseases, including dementia. Activation of this pathway, often triggered by mitochondrial or nuclear DNA leakage, initiates a pro-inflammatory cascade that accelerates neuronal damage and disease progression. While much remains to be understood about the precise mechanisms by which cGAS-STING contributes to neurodegeneration, the development of inhibitors targeting this pathway holds significant promise and various genetic prepositions known to be involved in neuroinflammation and neurodegeneration are worthwhile to be considered in the future research.

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