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Opinions

Innate immunity in brain aging and neurodegeneration

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Inflammation has been linked to normal aging and gradual decline in various cellular processes [1]. However, the mechanism and the pathways responsible for inflammation-mediated aging, especially in the brain, remain elusive.

A new study by Gullen et al [2] shows that a molecular signaling pathway, consisting of two main proteins, cyclic GMP–AMP synthase (cGAS) and Stimulator of Interferon Genes (STING), plays a critical role in driving chronic inflammation and functional decline during aging. It was previously known that activation of the cGAS/STING pathway triggers an innate immune response in defense against viral and bacterial infections [3–6].

Now, by using the small molecule inhibitor H-151 [6] and RNA interference experiments in cultures and tissue samples, Gullen et al [2] demonstrate that the inflammatory response of senescent cells is suppressed after blockade of STING. These manipulations also protect against inflammation and activation of inflammatory genes [2].

Currently, the signaling pathway(s) involved in inflammation-mediated brain aging and associated cognitive decline is only poorly understood [7,8,9]. The work by Gullen et al [2] helps fill this gap in knowledge since it shows that STING inhibition not only reduces levels of immune-related signature genes in the brains of aged mice, but also improves both, spatial memory (assessed in the Morris water maze test) and associative memory (contextual-fear-conditioning test). Moreover, the authors report that STING inhibition protects against the loss of neurons in the CA1 region of the hippocampus and increases local levels of synaptophysin [10], a marker for synaptic activity. Further insight into the role of STING signaling was also provided in the work by Gullen et al [2] who found that the age-dependent increase of phosphorylated TBK1 (pTBK1), the major kinase responsible for signal transduction downstream of STING [11], is attenuated by inhibition of STING.

Microglial activation and microgliosis is widely implicated in age-related neurodegenerative diseases [12,13,14]. In their new study, the authors [2] observed that inhibition of STING activity results in an attenuation of the differential expression of genes in the hippocampi of young and aged mice, namely, those involved in innate immunity such as genes related to type I interferon (IFN) signaling and microglial function. They also found increased phosphorylated STING activity in hippocampal microglia from old mice, implying that a role for STING in orchestrating innate immune activation in the aging brain. Adding support to this, Gullen et al [2] found that blockade of STING mitigates microgliosis and immunoreactive astrocytes in the hippocampi of aged mice. This interpretation was supported by their finding that aged *Sting1*$^{-/-}$ mice simultaneously display reduced microglial accumulation and increased neuron density in the hippocampal area (Fig. 1).

At another level, the authors [2] used two mouse models to demonstrate that direct activation of cGAS is sufficient to generate transcriptional clusters that correspond to previously-identified subsets; these included disease-associated microglia (DAM), IFN-associated and neurodegenerative microglial states that are associated with ageing and neurodegenerative conditions [15,16]. Previous studies observed that cells in each of these states show strong upregulation of genes associated with IFN, DAM and neurodegenerative signatures [15,17,18].

To understand the link between cGAS and STING, it should be noted that earlier studies showed that mitochondrial DNA (mtDNA)

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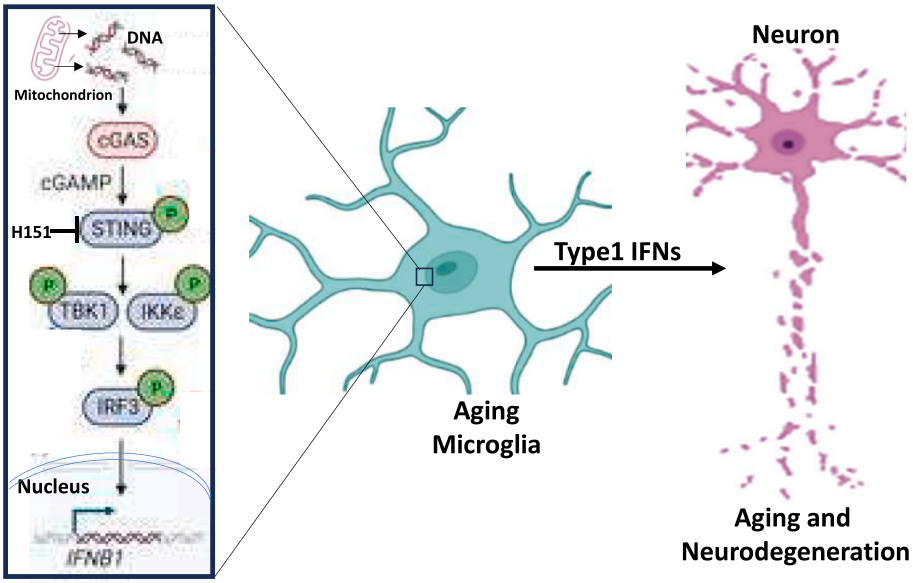

Fig. 1. Schematic of proposed new mechanism of age-related neurodegeneration. In aging microglia, loss of mitochondrial homeostasis leads to release of mtDNA which, after detection by cGAS leads to the activation of STING, followed by activation of inflammatory genes and release of type1 inflammatory molecules; the latter induce neuroinflammation and the loss of neurons.

is a central activator of cGAS–STING signaling, and that disrupted mitochondrial homeostasis is a hallmark of ageing and neurodegenerative disease [19,20]. In the new work, Gullen et al [2] observed an increase in the abundance of mtDNA, but not genomic DNA, in aged microglia. The release of mtDNA into the cytosol was previously shown [21] to be triggered by voltage-dependent ion channel (VDAC) 1/3 oligomers [21]; the latter work [21] also reported that treatment of aged microglia with VBIT-4, an inhibitor of VDAC oligomerization, suppresses several type I IFN and proinflammatory genes, thus confirming the role of mtDNA in activation of microglia.

While mitochondrial dysfunction, mtDNA release and STING-mediated inflammation has been implicated in several neurodegenerative diseases [22–27], it is still not clear if inmate immunity- mediated inflammation is a primary or secondary cause of neurodegeneration. Nevertheless, it is reasonable to argue that activation of the innate immune system may further exacerbate the clinical condition, thus making potential therapeutic interventions more complex. Involvement of innate immunity may also explain the variability of symptoms across patients. Lastly, it is worth noting that infectious agents have been widely implicated in neurodegenerative processes [28,29].

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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