Brain, Behavior, & Immunity - Health 14 (2021) 100243

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Short Communication

Outside-in induction of the IFITM3 trafficking system by infections, including SARS-CoV-2, in the pathobiology of Alzheimer's disease

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ARTICLE INFO

Keywords:
Alzheimer's disease
IFITM3
Systems biology
Neuroimmunology
Epigenetics

ABSTRACT

Background: IFITM3 is a viral restriction protein that enables sequestration of viral particles and subsequent trafficking to lysosomes. Recently, IFITM3 upregulation was found to induce gamma – secretase activity and the production of amyloid beta. The purpose of this study was to determine whether dysregulation of IFITM3-dependent pathways was present in neurons and peripheral immune cells donated by AD patients. As a secondary aim, we sought to determine whether these perturbations could be induced by viruses, including SARS-CoV-2.

Methods: Gene set enrichment analyses (GSEA) previously performed on publicly available transcriptomic data from tissues donated by AD patients were screened for enriched pathways containing IFITM3. Subsequently, signature containing IFITM3, derived from entorhinal cortex (EC) neurons containing neurofibrillary tangles (NFT) was screened for overlap with curated, publicly available, viral infection-induced gene signatures (including SARS-CoV-2).

Results: GSEA determined that IFITM3 gene networks are significantly enriched both in CNS sites (entorhinal and hippocampal cortices) and in peripheral blood mononuclear cells (PBMCs) donated by AD patients. Overlap screening revealed that IFITM3 signatures are induced by several viruses, including SARS-CoV, MERS-CoV, SARS-CoV-2 and HIV-1 (adjusted p-value <0.001; Enrichr Database).

Discussion: A data-driven analysis of AD tissues revealed IFITM3 gene signatures both in the CNS and in peripheral immune cells. GSEA revealed that an IFITM3 derived gene signature extracted from EC/NFT neurons overlapped with those extracted from publicly available viral infection datasets, including SARS-CoV-2. Our results are in line with currently emerging evidence on IFITM3's role in AD, and SARS-CoV-2's potential contribution in the setting of an expanded antimicrobial protection hypothesis.

1. Background

The antimicrobial protection hypothesis of Alzheimer's disease (AD) describes a model of amyloidogenesis resulting from chronic activation of the innate immune cascades; this activation is not attributed to any single pathogen per se, but its progression to chronicity is considered the driver of beta-amyloid accumulation and its subsequent deposition (Moir et al., 2018).

Among potential crossroads between amyloidogenesis and immunity has been recently been found in interferon-induced transmembrane protein 3 (*IFITM3*) expression (Hur et al., 2020); Upregulation of *IFITM3*, a viral particle sequestration protein, was found to be a characteristic of neurons and astrocytes displaying higher γ-secretase, and consequently, increased amyloid beta (Aβ) generation (Hur et al., 2020).

In a recent study from our group, where we examined a data-driven, in silico model of tissue interaction in AD, several infection- and immune-

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https://doi.org/10.1016/j.bbih.2021.100243
Received 16 December 2020; Received in revised form 13 March 2021; Accepted 17 March 2021
Available online 26 March 2021

related gene networks were found to be overlapping between the central nervous system and the peripheral immune system (Vavougios et al., 2020). We hypothesize that (a) *IFITM3* is differentially expressed in both the CNS and the peripheral immune system in AD and that (b) viral infections, including SARS-CoV-2 can induce *IFITM3*'s expression.

2. Materials and methods

In a previous study, we had identified immune and infection-related pathways overlapping between the peripheral immune system and the CNS in a data driven manner (Vavougios et al., 2020). For the construction of our model, we had used gene expression data from peripheral blood mononuclear cells (PBMC), entorhinal cortex neurons containing neurofibrillary tangles (EC-NFT), and hippocampal cortex neurons, available from the National Institutes of Health (NIH) public repository, Gene Expression Omnibus (GEO). An overview of the datasets included in our analysis is presented on supplementary Table 1. Detailed descriptions of each study are found elsewhere (Blalock et al., 2004; Maes et al., 2007)(Dunckley et al., 2006).

For this study, we scrutinized these previously generated data for pathways containing *IFITM3*. Subsequently, we used an EC-NFT gene signature containing *IFITM3* in order to determine whether IFITM3's expression could be upregulated via viral infections, including SARS-CoV-2. For this purpose, we performed gene set enrichment analysis via the Enrichr web platform (Kuleshov et al., 2016), screening the "COVID-19 related gene sets", "Virus Perturbations Up" modules Additionally, the DisGeNET (Piñero et al., 2017) and KEGG (Kanehisa et al., 2017) pathways subsets were also scrutinized, in order to determine significant enrichments with other disease and specific pathways, respectively.

3. Results

In our original data, *IFITM3* which was part of several significantly enriched gene ontologies (GOs) in the PBMC dataset, the entorhinal cortex dataset and a hippocampal cortex dataset (Benjamini – Hochberg adjusted p-value <0.05; Table 1). These pathways were associated with interferon signaling and viral gene expression (Table 1); Several genes comprising these pathways overlapped between different tissues donated by AD patients (PBMC, HC, EC; See Venn Diagram (Khan and Mathelier, 2017), Fig. 1), as per the tissue interaction concept introduced by our study (Vavougios et al., 2020). In order to determine whether *IFITM3* dysregulation could arise secondary to viral infection, we used an AD NFT-EC gene signature to determine whether it overlaps with upregulated genes from viral perturbation experiments in Gene Expression Omnibus (GEO), available via the Enrichr web service (under the GEO Virus Perturbations UP module) (Kuleshov et al., 2016). Enrichment analyses revealed that several predominantly respiratory pathogens, including SARS-CoV-2, could significantly upregulate *IFITM3* (Table 2 – 5; See also Supplementary Materials 1). Aside from viral infections, DisGeNET enrichments included autoimmune diseases and neoplasms, with a notable enrichment of multiple sclerosis (Table 4 and Supplementary Materials 1) (see Fig. 2) (see Table 5).

Table 1
Gene signatures containing IFITM3 in the Vavougios et al. study, 2020.

Gene Ontology and corresponding dataset	Reference	Hits	Adjusted P-value
AD EC – NFT (GDS2795)			
response_to_type_I_interferon(5)	http://amigo.geneontology.org/amigo/term/GO:0034340	84	0.00200343
cellular_response_to_type_I_interferon(6)	http://amigo.geneontology.org/amigo/term/GO:0071357	82	0.00229691
type_I_interferon_signaling_pathway(7)	http://amigo.geneontology.org/amigo/term/GO:0060337	82	0.00229691
AD PMBC (GDS2601)			
multi_organism_metabolic_process(3)	http://amigo.geneontology.org/amigo/term/GO:0044033	144	0.000712085
viral_gene_expression(4)	http://amigo.geneontology.org/amigo/term/GO:0019080	139	0.000712085
viral_transcription(5)	http://amigo.geneontology.org/amigo/term/GO:0019083	130	0.0110638
AD HC (GDS810)			
viral_gene_expression(4)	http://amigo.geneontology.org/amigo/term/GO:0019080	184	0.0131733

GDSXXX or GDSXXXX format represents the Gene Expression Omnibus (GEO) dataset identifier used in these analyses. "Hits" refers to the number of genes comprising each signature.AD: Alzheimer's Disease; PBMC: Peripheral Blood Mononuclear Cells; NEC: Normal Elderly Controls; EC: Entorhinal Cortex; NFT: Neurofibrillary tangles; FDR: False Discovery Rate; GO: Gene Ontology.

4. Discussion

SARS-CoV-2 impact on the CNS is increasingly recognized in the literature, and its potential specific relationship with AD is the subject of ongoing studies (Lempriere, 2020). Within the conceptual framework of the antimicrobial protection hypothesis, SARS-CoV-2's interaction with *IFITM3* is even more relevant.

4.1. A proposed IFITM3-driven feed-forward loop in AD pathogenesis

The IFITM family of proteins have been previously recognized as important regulators of MERS-CoV-2 and SARS-CoV-2 virulence, either by physiological restriction of their entry, or as infection enhancers, following loss-of-function mutations (Zhao et al., 2018). *IFITM3* was found to be upregulated in SARS-CoV-2 -infected cells (Shi et al., 2020; Sardar et al., 2020); furthermore, specific polymorphisms, such as the rs12252-C have been identified as severity markers for COVID-19 (Zhang et al., 2020). A current concept for SARS-CoV-2's immunoevasion of *IFITM3* sequestration involves cleavage by TMPRSS2 (Zheng et al., 2020). Recently, yet another such host factor was identified in NRP1 (Cantuti-Castelvetri et al., 2020), indicating another CNS-specific interaction pathway. Interestingly, both IFITM3 and NRP1 have been identified as neuroinflammation-induced in a cellular model of AD (Correani et al., 2017).

As a viral restriction protein, endocytic vesicle *IFITM3* tags viral particles for lysosomal fusion (Spence et al., 2019). Viral particle restriction via *IFITM3* trafficking is a second line of defense active against a variety of pathogens including HIV-1, Dengue, Ebola, Influenza A (IAV) and CMV, among others (Wellington et al., 2019).

Several components of antiviral immunity have recently been recognized as per their potential contribution in the pathogenesis of AD and neuroinflammation. Type I interferon (IFNA) responses, while

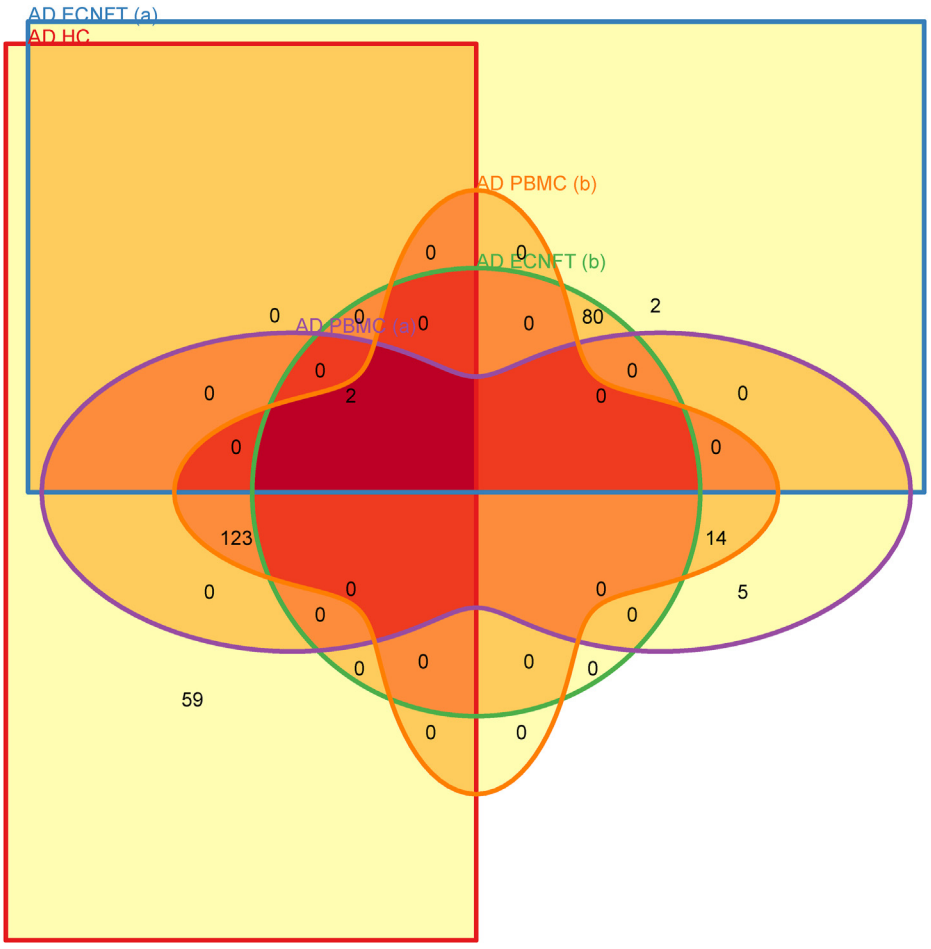

Fig. 1. Venn diagram displaying common genes between signatures. Each distinct colored shape corresponds to a gene signature, with the numbers in their intersection representing the number of overlapping genes in each signature. AD NFT – EC (a): response_to_type_I_interferon(5); AD NFT – EC (b): cellular_response_to_type_I_interferon(6); AD NFT – EC (c): type_I_interferon_signaling_pathway(7); AD PBMC (a): multi_-organism_metabolic_process(3); AD PBMC (b): viral_gene_expression(4) AD PBMC (c): viral_transcription(5); AD HC: viral_gene_expression(4). AD: Alzheimer's Disease; PBMC: Peripheral Blood Mononuclear Cells; NEC: Normal Elderly Controls; EC: Entorhinal Cortex; NFT: Neurofibrillary tangles; FDR: False Discovery Rate; GO: Gene Ontology.

pivotal in restricting viruses from propagating within the CNS (Roy et al., 2020), display dose-dependent neurotoxicity via both IFNAR- and NMDAR-initiated cascades (Kessing and Tyor, 2015). This paradigm has been studied in the HIV-associated neurocognitive disorder (HAND) spectrum, where cognitive impairment is considered to progress via accumulating exposure of the CNS to *IFNAR*-signaling (Thaney and Kaul, 2019).

In the setting of AD, IFN responses were recently shown to be elicited by Aβ-Nucleic Acid (NA) complexes, with *IFITM3* among the IFN-gene signatures detected (Roy et al., 2020). The immunogenicity and of these Aβ-NA complexes and the resulting microglial activation appears to be independent of the source of NA (i.e. whether or not they are xenobiotic). This concept, along with its close connection with IFN responses is another finding of both our current analyses (Cytosolic DNA-sensing pathway, adj. p-value = $3.755e^{-30}$; Table 3) and our previous study (Vavougios et al., 2020).

In this setting, Aβ-NA complexes may act as the immunogenic substrate of neuroinflammation propagating across the CNS in AD, a hypothesis supported by a correlation between IFN signaling upregulation (including *IFITM3*) and Braak staging in the study of Roy et al. (2020). This observation would further outline a positive feedback loop, where Aβ-NA induces *IFITM3* (Roy et al., 2020), and IFITM3 furthermore induces Aβ production[2]*. Notably, this model can readily account for the increased AD risk conferred by HSV-1 neuroinfection (Cairns et al., 2020), and may be further incorporate lysosomal/autophagosomal dysfunction noted in AD. Specifically, HSV-1 induced *IFITM3* upregulation (Nicholl et al., 2000) in the brain during neuroinfection (Cairns et al., 2020), would not lead to viral clearance in the case of perturbed *IFITM3*, i.e. unsuccessful lysosomal fusion (Orr and Oddo, 2013). In this sense, the discovery of HSV-1 genomes entangled in amyloid-β plaques in the CNS (Bearer, 2012) would reflect the debris of a defunct *IFITM3* shuttling system upregulated by the positive feedback of unresolved viral infection, and acting as an Aβ-NA immunogenic template, inducing neuroinflammation.

4.2. *A hypothesis on the potential consequences of SARS-CoV-2-mediated induction of IFITM3 signaling in the CNS*

SARS-CoV-2's modus operandi as a neuroinvasive pathogen provides further insight as to how viruses may trigger or sustain the proposed IFITM3 feedback loop. Even indirectly, SARS-CoV-2 may trigger IFITM3 by eliciting delayed and IFN responses (Meinhardt et al., 2021). In the scenario of transcribial neuroinvasion (Lei et al., 2020), SARS-CoV-2 would gain access to the entorhinal cortex. SARS-CoV-2 neuroinvasion has been shown to induce neurodegeneration in 3D brain organoids, pathologically associated with altered subcellular localization of hyperphosphorylated tau (Ramani et al., 2020). Interestingly, SARS-CoV-2 cellular entry and host-virus interactions further extent from IFITM3 to regulators of tau aggregation and phosphorylation, such as FYN (Briner et al., 2020; Glebov, 2020).

Direct and indirect induction of IFITM3 by neuroinvasion and IFN responses correspondingly, further contributed by Aβ oligomerization and Aβ-NA (both viral and i.e. fragments from neuronal apoptosis or genotoxic stress) would finally serve to evolve an in situ tauopathy to a distal Aβ-synaptopathy. Up to this point, our proposed model reiterates previously described mechanisms of HSV-1 modus operandi in β-amyloidogenesis (Bearer, 2012), with several important differences however.

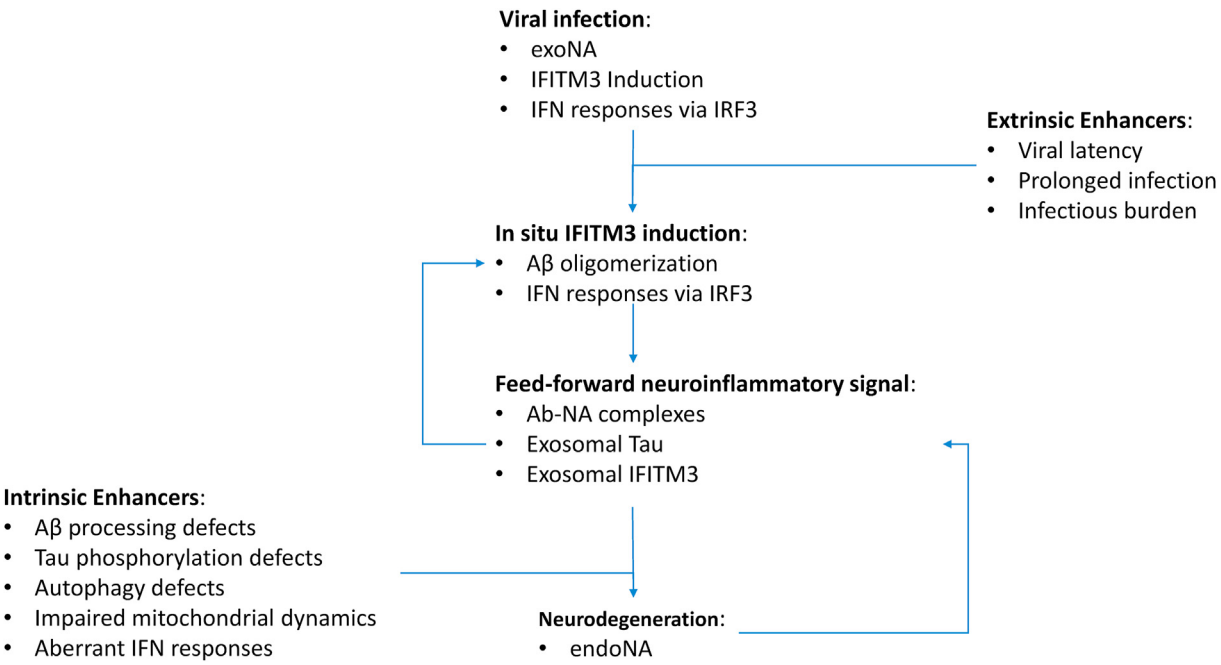

Fig. 2. Schematic representation of the proposed IFITM3 feed forward mechanism in AD pathogenesis. Within this concept, viral infection initially upregulates IFITM3 (a) directly, via physical interactions between IFITM3 and viral particles (b) via promoting IRF3-mediated IFN cascades. IFITM3 in turn modulates γ-secretase towards increased production of Aβ oligomers, while other interactors such as FYN, which are also implicated in antiviral responses, promote Tau hyperphosporylation and aggregation. IFITM3 and Tau containing exosomes, in conjunction with Aβ oligomers would then propagate a neuroinflammatory signal from the primary infection site to other distal, non-infected sites via transsynaptic uptake. Aβ and nucleic acid (NA) complexes (Aβ-NA) would serve to stimulate microglia and trigger further inflammation. Both viral (exoNA) and endogenous (endoNA) nucleic acids could contribute to this process, either as a result of the viral lifecycle or as apoptotic debris. Prolonged infections, lifelong latency (i.e. HSV-1) or accumulating infectious burden on the primary infection site (i.e. the entorhinal cortex) could provide feed-forward neuroinflammatory stimulus even in the absence of an active pathogen. In a similar manner, intrinsic defects (i.e. pathogenic variants of the amyloid processing machinery, autophagic cascades and so forth) in either the neuroinflammatory induction and response aspect, autophagy or cellular bioenergetics would serve as enhancers, reinforcing the noxious biological effects of e.g. IFITM3 uptake by non-infected neurons.

Table 2
Gene set enrichment analysis, scrutinizing the "COVID-19 related gene sets" subset of the Enrichr database.

Index	Name	P-value	Adjusted p-value
1	MERS-CoV Top 200 Predicted Genes from Geneshot GeneRIF via AutoRIF Co-Occurrence Gene Similarity	6.993e-67	1.434e-64
2	SARS-CoV perturbation Up Genes bronchial epithelial 2B4 from GSE17400:GPL570:6	3.746e-56	3.840e-54
3	Up-regulated by SARS-CoV-2 in Calu-3 24hr from GSE148729	1.243e-46	8.495e-45
4	Up-regulated by SARS-CoV-1 in Calu-3 from GSE148729	8.228e-42	4.217e-40
5	SARS perturbation Up Genes airway epithelium (HAE) from GSE47961:GPL6480:4	5.631e-38	2.309e-36
6	SARS perturbation Up Genes airway epithelium (HAE) from GSE47961:GPL6480:3	1.290e-37	4.407e-36
7	Up-regulated by SARS-CoV-2 2 MOI in Calu-3 from GSE147507	4.427e-37	1.134e-35
8	Up-regulated by SARS-COV-2 infection of Calu3 cells	4.427e-37	1.296e-35
9	SARS-CoV perturbation Up Genes bronchial epithelial 2B4 from GSE17400:GPL570:3	6.619e-37	1.508e-35
10	SARS perturbation Up Genes airway epithelium (HAE) from GSE47961:GPL6480:6	1.825e-36	3.740e-35

Results have been truncated to the first 10 entries. For this analysis, the AD Entorhinal cortex gene signature designated as "response_to_type_I_interferon(5)" was supplied to Enrichr.

Table 3
Gene set enrichment analysis, scrutinizing the "GEO Virus Perturbations UP" subset of the Enrichr database.

Index	Name	P-value	Adjusted p-value
1	A-CA-04-2009(H1N1) 12Hour GSE47960	1.345e-38	4.345e-36
2	SARS-BatSRBD 72Hour GSE47960	6.268e-37	1.012e-34
3	SARS-CoV 96Hour GSE47961	1.719e-30	1.388e-28
4	A-CA-04-2009(H1N1) 6Hour GSE47961	1.719e-30	1.851e-28
5	SARS-ddORF6 72Hour GSE47961	6.086e-29	2.457e-27
6	RSV 48Hour GSE32138	6.086e-29	2.808e-27
7	A-CA-04-2009(H1N1) 18Hour GSE37571	6.086e-29	3.276e-27
8	A-CA-04-2009(H1N1) 12Hour GSE47961	6.086e-29	3.932e-27
9	hMPV 24Hour GSE8961	2.035e-27	6.573e-26
10	SARS-dORF6 72Hour GSE47960	2.035e-27	7.304e-26

Results have been truncated to the first 10 entries. For this analysis, the AD Entorhinal cortex gene signature designated as "response_to_type_I_interferon(5)" was supplied to Enrichr.

On its own right, IFITM3 induction is not restricted to intracellular cascades. IFITM3 has been previously shown to be a mutant-tau exclusive cargo in AD exosomes (Podvin et al., 2020), whereas IFITM3-loaded exosome trafficking from infected to non-infected cells has been shown to confer resistance to DENV infection (Zhu et al., 2015). On these premises, IFITM3, exosomal hyperphosphorylated tau (Wang et al., 2017) and Aβ-NA may constitute a feed-forward signal expanding from a primary site of neuroinfection (i.e. the entorhinal cortex) via afferent

Table 4
Gene set enrichment analysis, scrutinizing the "DisGeNET" subset of the Enrichr database.

	Name	P-value	Adjusted p-value
1	Virus Diseases	6.209e-39	1.421e-35
2	Influenza	5.146e-33	5.890e-30
3	Hepatitis C	6.045e-30	4.612e-27
4	Infection	3.631e-23	2.078e-20
5	West Nile viral infection	5.699e-22	2.609e-19
6	Autoimmune Diseases	8.919e-21	3.403e-18
7	Hepatitis C, Chronic	1.657e-20	5.418e-18
8	Lupus Erythematosus, Systemic	3.981e-20	1.139e-17
9	Vesicular Stomatitis	2.520e-19	6.408e-17
10	Multiple Sclerosis	3.907e-18	8.943e-16

Results have been truncated to the first 10 entries. For this analysis, the AD Entorhinal cortex gene signature designated as "response_to_type_I_interferon(5)" was supplied to Enrichr.

Table 5
Gene set enrichment analysis, scrutinizing the "KEGG Pathways 2019" subset of the Enrichr database.

Index	Name	P-value	Adjusted p-value
1	Hepatitis C	1.047e-48	8.457e-47
2	Epstein-Barr virus infection	1.859e-48	8.457e-47
3	Influenza A	3.364e-45	1.020e-43
4	Measles	2.016e-44	4.587e-43
5	NOD-like receptor signaling pathway	1.105e-42	2.011e-41
6	Herpes simplex virus 1 infection	1.925e-40	2.919e-39
7	Kaposi sarcoma-associated herpesvirus infection	3.494e-40	4.543e-39
8	Human papillomavirus infection	7.803e-39	8.876e-38
9	JAK-STAT signaling pathway	7.715e-33	7.801e-32
10	Cytosolic DNA-sensing pathway	4.126e-31	3.755e-30

Results have been truncated to the first 10 entries. For this analysis, the AD Entorhinal cortex gene signature designated as "response_to_type_I_interferon(5)" was supplied to Enrichr.

projections (i.e. the hippocampi). Interestingly, while the primary site would be infected, the signal itself would propagate AD pathology even in the absence of infection: i. directly via Aβ oligomers, Aβ-NA and Tau and ii. indirectly, via IFITM3 uptake and the subsequent boosting in IFN and Aβ-oligomer production. The latter hypothesis could account for previously observed correlations between IFITM3 expression and Braak staging (Roy et al., 2020). In this setting, both the reactivation of a latent virus or de novo infection would reinforce the IFITM3 feed-forward loop.

4.3. Limitations and strengths

The proposed model of infection-induced, perturbed IFITM3 signaling in the pathogenesis of AD, as well as its specific iteration with SARS-CoV-2, should be interpreted within their respective limitations. Viral infection could have been a perturbator to any number of samples or studies included in our analyses. While the original studies report strict and stem from established brain banks (Supplementary Table 1), the possibility cannot be excluded and should be taken into consideration as a potential confounder on the results we report herein. Studying a significantly enriched signature that overlaps between different tissues (and by extent, studies) furthermore decreases but does not nullify this possibility. In a similar manner, as there is no detailed infection history on any of the original studies' participants, we cannot account for its impact on our findings.

Another important limitation of our study is that our results indicate overlapping mechanisms, rather than a mechanistic effect. In this sense, we detect pathways and gene signatures that are perturbed in a similar manner in both AD and viral infections; we do not however determine a causal relationship directly. While a possible explanation for this overlap in AD would be neuroinvasion, our study by design does not provide mechanistic evidence of such. Furthermore, The overlapping IFITM3 signatures we report on are significantly enriched both in neuropathologically determined AD and viral infections, including SARS-CoV-2. Using IFITM3 signatures from AD EC-NFT, we reconstruct multiple viral infection-induced signatures containing IFITM3, indicating both candidate targets and the potential pathways by which said infections may either induce or contribute to AD pathobiology. Notably, while IFITM3 was focused on due to its discovery as a γ-secretase modulator, our approach identifies IFN responses, viral latency and innate immunity as common mechanisms enriched by IFITM3 networks.

5. Concluding remarks

In the case of SARS-CoV-2, independent studies have shown that the novel coronavirus is capable of transcribial neuroinvasion and gain access to the entorhinal cortex (Meinhardt et al., 2021), is associated with AD-like dyscognitive phenotypes (Woo et al., 2020) correlated with hippocampal atrophy (Lu et al., 2020). Furthermore, SARS-CoV-2 both induces and evades IFN responses during its latency (Lei et al., 2020), indicating another plausible explanation for the transcriptomic overlap we outline. The latter finding may account for the noted deterioration of AD symptoms in patients during infection (Takeda et al., 2014), as well as post-infection risk of dementia(Muzambi et al., 2020). This hypothesis however, would require a singular experiment where all these independent observations, as well as our own findings, are replicated.

The interaction concept introduced in our study (Vavougios et al., 2020) with the global (PMBCs, Hippocampi, Entorhinal Cortex) presence of *IFITM3* networks furthermore supports an "outside – in" trigger for neurodegeneration. Finally, taking into account that multiple viruses could upregulate *IFITM3* based on overlap between our recent work (Vavougios et al., 2020), Hur et al.'s study (Hur et al., 2020) and GEO experimental data, the putative viral trigger for AD may not need to be any single viral pathogen, but rather a process of viral infection induced, positive/feed-forward feedback of the *IFITM3* trafficking system. Future experiments should explore a mechanistic model of IFITM3's perturbations introduced by viral infections, and their effects on β-amyloidogenesis and tau oligomerization.

Declaration of competing interest

None declared.

Acknowledgements

To Dr Athanasia Kefala, for her assistance with mathematical modeling and Edwards' Venn diagrams.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100243.

Author contributions

GDV conceived the study, performed the original analyses and wrote the first draft. GS oversaw the analyses and provided data quality assessments. CN, HSP and TD contributed with interpretations of the results in the clinical concept. KIG, SGZ contributed with interpretations

infection-related pathways. TD, HSP, KIG, GS and SGZ contributed equally in the paper.

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