

Preview

Burned by experience: Epigenetic inflammatory memory in neurons drives synaptopathy after infection

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Shammas et al.¹ report that LCMV infection epigenetically primes hippocampal neurons for heightened responses to viral rechallenge, driving synaptopathy. These findings suggest epigenetic inflammatory memory in neurons, resembling previous observations in other CNS non-immune cells, and may guide therapeutic interventions.

Epigenetic inflammatory memory is a phenomenon by which inflammatory signals imprint epigenetic programs in immune and non-immune cells, shaping their responses to subsequent challenges.^{2–4} In recent years, epigenetic inflammatory memory has also been described in central nervous system (CNS) cells, for example, in microglia² and astrocytes.^{4–6} The potential for epigenetic inflammatory memory appears to exist in other CNS non-immune cells as well, including neurons. Indeed, neurons exposed to transient hypoxia have been shown to acquire neuroprotective phenotypes that increase resistance to subsequent insults. Neurons exposed to tumor necrosis factor α (TNF- α) and inflammatory environments in experimental autoimmune encephalomyelitis (EAE) have also been described to develop alterations in glutamate transmission,⁷ which may modulate existing neural circuitry and lead to long-term changes in the neuron epigenetic landscape. Retinal ganglion cells in EAE mice also acquire chromatin marks associated with inflammation and senescence.⁸ However, up to this point, evidence of epigenetic inflammatory memory in neurons has only been indirect.

In a new study, Shammas et al.¹ provide, for the first time, evidence of epigenetic inflammatory memory in mouse neurons, resulting in a stronger response to interferon γ (IFN- γ) and increased synapse loss in viral-exposed neurons upon sys-

temic rechallenge with the same virus. To perform these experiments, Shammas et al. used an elegant experimental system termed viral déjà vu, in which neonatal mice were infected intracerebrally at P0 with a non-cytopathic, attenuated strain of lymphocytic choriomeningitis virus (LCMV), displaying no symptoms and normal development, then rechallenged peripherally with intravenous wild-type LCMV at 5 weeks of age, after which they developed weakness and paralysis. The authors combined this model with two Cre-lox strategies to irreversibly label neurons initially infected by LCMV during neonatal exposure with red fluorescence protein (RFP) or nuclear translating ribosome affinity purification (NuTRAP)-green fluorescence protein (GFP), enabling the use of immunofluorescence (IF) and RNA sequencing (RNA-seq) to investigate differences in the recall response of neurons that had been previously infected with LCMV (viral-exposed) vs. those that had not been directly infected (bystanders). Specifically, they show that viral-exposed neurons have greater phosphorylation of STAT1 and a greater number of disease-induced differentially expressed genes (DEGs) upon viral rechallenge. These findings are pathologically relevant because after viral rechallenge, viral-exposed neurons display a greater loss of synapses than bystanders do, a phenomenon dependent on IFN- γ signaling and microglial activity, as the authors previously described (Figure 1).⁹

Following their demonstration of inflammatory memory in neurons, the authors delved into the epigenetic changes underlying the differences in the response of viral-exposed vs. bystander neurons to LCMV rechallenge, performing bulk transposase-accessible chromatin sequencing (ATAC-seq) in viral-exposed and bystander neurons and bulk chromatin immunoprecipitation sequencing (ChIP-seq) for H3K4me3, H3K27ac, and H3K27me3 in all hippocampal neurons at various time points after viral rechallenge. Shammas et al. established that, consistent with their RNA-seq results, after rechallenge, viral-exposed neurons undergo epigenetic remodeling at more loci than bystander neurons do, with a major fraction of new loci showing late chromatin opening (module 2) and other genes showing an early transient opening (module 1) and transient or persistent closing (modules 3 and 4).

To define the epigenetic status of these genes, they quantified H3K27ac, H3K27me, H3K4me, and H3K4me3 marks to identify genes marked with H3K27ac \pm H3K4me (active genes), H3K4me (poised genes), or H3K27me \pm H3K4me3 (silenced genes), as well as the transcription factor motifs enriched in open loci. Notably, while both viral-exposed and bystander neurons exhibit opening of loci associated with the IFN response, including those driven by STAT1, viral-exposed neurons display a more pronounced closing of loci enriched in motifs for transcription factors



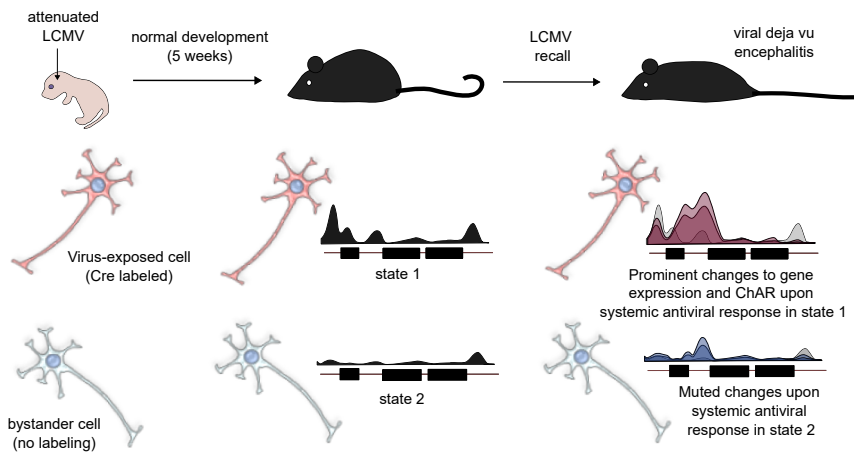


Figure 1. Epigenetic changes in neonatal viral-exposed neurons vs. bystander neurons affect their epigenetic landscape and subsequent behavior after viral rechallenge

In the model of viral déjà vu used by Shammas et al. (top), neurons infected with attenuated virus in the neonatal period are labeled with a Cre-lox mechanism and followed into adulthood, at which point the mice are rechallenged with wild-type virus. Various properties, including the epigenetic profile, of previously viral-exposed neurons (red) are compared against bystander neurons (blue) before and during rechallenge. LCMV, lymphocytic choriomeningitis virus.

governing synaptic regulation and plasticity, some of which are not seen in loci closed in bystander neurons. In addition, late opening genes in viral-exposed neurons are enriched in FOS, JUNB, ATF3, and BATF transcription factor motifs, while in bystander neurons, these binding motifs are enriched in closed genes (module 4), suggesting a qualitatively different epigenetic landscape in viral-exposed vs. bystander neurons. A significant portion of the changes in loci availability are dependent on IFN- γ receptor signaling, and the downregulated loci are durably closed after rechallenge. Based on these data, the authors conclude that the anti-viral immune response induces profound epigenetic changes in neurons that result in a durable decrease in the expression of synaptic genes and that promote synaptopathy, resembling changes seen in human CD8⁺ T cell driven Rasmussen's encephalitis—a human neuroinflammatory disease of unknown etiology possibly triggered by viral infection.

These findings align with the growing picture that immune and non-immune cells in the CNS acquire and retain memories of prior inflammatory experiences through epigenetic changes, which affect subsequent responses to stimulation. These findings also suggest how epigenetic inflammatory memory is shaped by

the specific stimulus involved. Finally, although in this model, epigenetic inflammatory memory results in a pathological decrease in synaptic connections, it is conceivable that in other situations, it may be beneficial, for instance, in supporting antiviral immunity.

Future directions and outlook

The characterization of neuronal epigenetic memory in this study raises a number of interesting questions, opening new research avenues. One foremost question is the following: how cell intrinsic is the phenomenon of neuronal epigenetic memory described in this model? With the *in vivo* model used in the study, it is difficult to completely isolate the effect of priming and rechallenge in viral déjà vu on neurons. Namely, while the neonatal infection with attenuated LCMV mainly targets neurons and does not cause a significant amount of cell death, it could also impact astrocytes, oligodendrocytes, microglia, and other cells indirectly as a result of their modulation by infected neurons. Indeed, neuron activity has been shown to alter the epigenetic status of astrocytes.¹⁰ Viral rechallenge may also directly affect the behavior of astrocytes and other CNS cells, which may then synergize with cell-intrinsic responses in viral-exposed neurons. In addition, viral-exposed and bystander neurons may be

exposed to different levels of IFN- γ in their local microenvironments. Further investigations using *in vitro* infection or cytokine stimulation models of neurons alone or co-cultured with glial and/or immune cells, rechallenge with cytokines instead of LCMV, would further delineate the cell-intrinsic mechanisms that control epigenetic inflammatory memory in neurons. A direct comparison of the epigenetic changes induced in viral-exposed vs. bystander neurons at baseline, before rechallenge, may also shed additional light on additional specific epigenetic changes involved.

Additional questions arise from the detection of distinct epigenetic responses of neurons in the hippocampus vs. brain stem of mice subjected to viral déjà vu. While hippocampal viral-exposed neurons display significant changes in chromatin availability on rechallenge, brainstem viral-exposed neurons had far fewer changes in chromatin-accessible regions, and barely any disease-induced peaks, despite also having evidence of RNA-seq or IFN- γ signaling. Why the epigenetic changes are only seen in the hippocampal neurons is unclear. The authors speculate that intrinsic differences in neuronal adaptability in hippocampal vs. brain stem neurons may contribute, given their differential roles in the brain and organismal physiology. These findings suggest that regulatory mechanisms may operate in specific CNS regions to limit maladaptive inflammatory memory in certain cells. In line with this, it was recently described that the glucocorticoid receptor NR3C1 operates in astrocytes to prevent the acquisition of long-lived epigenetic inflammatory memory early during development,⁶ suppressing the development of exacerbated CNS inflammation upon stimulation later in life. In addition, it is possible that neuronal synaptic activity, the degree to which they experience excitotoxicity during viral infection, their relative connectivity to other neurons or proximity to various glial cells, or their functional heterogeneity (e.g., excitatory vs. inhibitory) may affect their ability to acquire inflammatory epigenetic memory or the specific transcriptional modules that govern it. Continuing to address these questions may yield further insights into how epigenetic inflammatory

memory is differentially coordinated between cell types and cell states, leading to a more refined understanding of this process and how it can ultimately be modulated therapeutically.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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