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NEUROIMMUNOLOGY

Social support from the immune system

> a role for IFNγ in regulating social behaviour

An intriguing new study suggests that a key immune signalling pathway may regulate behavioural responses. Jonathan Kipnis and colleagues show that interferon-γ (IFNγ) acts on inhibitory neurons in the brain to regulate neuronal connectivity and social behaviour in mice.

Mice can be tested for social behavioural disorders on the basis of their preference for a novel mouse over a novel object. Wild-type mice show a social preference for the mouse over the object, but the authors found that SCID mice (which lack lymphocytes) did not show this social preference. Strikingly, repopulation of SCID mice with lymphocytes restored their social preference for the mouse in these assays. Brain imaging studies have shown that patients with autism spectrum disorder display hyper-connectivity among frontal cortical nodes; the authors found that SCID mice also show hyper-connectivity of fronto-cortical brain regions, but this was reversed if they were repopulated with lymphocytes.

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The authors had previously reported that meningeal T cells influence learning behaviours, and they found that a partial loss of meningeal T cells resulted in a loss of social preference. As meningeal T cells do not enter the brain parenchyma, the authors used gene set enrichment analysis to identify T cell-derived mediators that may regulate social behaviour. Notably, transcriptomes from the cortices of mice that had been exposed to social aggregation were enriched for IFNγ-regulated genes, suggesting a role for IFNγ in regulating social behaviour. In agreement with this, mice deficient in IFNγ or lacking the IFNγ receptor showed social deficits and hyper-connectivity between frontal and insular brain regions. Furthermore, repopulating SCID mice with IFNγ-deficient T cells did not restore social preference. By contrast, injection of IFNγ into the cerebrospinal fluid (CSF) of IFNγ-deficient mice restored social preference.

Both microglia and neurons in the brain express the IFNγ receptor, but mice with a macrophage-specific deletion of STAT1 (which mediates signalling downstream of the IFNγ receptor) showed normal social preference behaviour. By contrast, loss of IFNγ receptor expression in prefrontal cortex neurons abolished social preference in mice. Injection of IFNγ into the CSF activated layer I neocortical neurons (which are predominantly inhibitory) and deletion of STAT1 from GABAergic inhibitory neurons also induced social deficits, suggesting that IFNγ predominantly signals through inhibitory neurons. In further support of this, mice that had received CSF injections of IFNγ were partially protected from chemically induced seizures. Moreover, treatment of mice with diazepam (which augments GABAergic transmission) restored social preference behaviour in IFNγ-deficient mice.

As social behaviour increases the likelihood of spreading infections, the authors wondered whether there was co-evolutionary pressure to increase anti-pathogen responses during increased social aggregation and whether the IFNγ signalling pathway may have contributed to this. To this end, they analysed publically available transcriptomes from multiple organisms. They found that brain transcripts from social rodents (acutely group-housed) were enriched for an IFNγ responsive gene signature, whereas transcripts from socially isolated rodents showed a loss of this gene signature. Furthermore, transcriptomes from low-aggressive flies (which are socially experienced) were enriched for STAT1-responsive immune genes. As flies lack IFNγ and T cells — but still show an association between social behaviour and upregulation of STAT1-responsive genes — the authors propose that IFNγ may have evolved in higher species to more efficiently regulate immunity to pathogens during increased social aggregation. They also suggest that subtle changes in meningeal immune responses may affect neuronal circuits that determine behaviours and personalities in humans.

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ORIGINAL ARTICLE Filiano, A. J. *et al.* Unexpected role of interferon in regulating neuronal connectivity and social behaviour. *Nature* http://dx.doi.org/10.1038/nature18626 (2016)
FURTHER READING Miller, A. H. & Raison, C. L. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* **16**, 22–34 (2016)