

# News & views

## Neurodegeneration

# Alzheimer's risk gene works the gut–brain axis

Alfonso Martín-Peña & Malú Gámez Tansey

Signals from gut microorganisms to the brain might be involved in neurodegeneration. It emerges that the gene *APOE* – variants of which each confer a different risk of Alzheimer's disease – has a role in modulating this gut–brain communication.

The best biological marker of neurodegeneration is the accumulation of misfolded and aggregated proteins in the brain. These aggregates are often surrounded by brain-resident immune cells called astrocytes and microglia, tasked with removing debris and keeping neurons healthy<sup>1</sup>. Writing in *Science*, Seo *et al.*<sup>2</sup> identify a gene that determines how gut microorganisms affect such immune responses and protein aggregation in the brain. This gene, *APOE*, exists in three common forms (*APOE2*, *APOE3* and *APOE4*), of which *APOE4* confers the highest risk factor for late-onset Alzheimer's disease<sup>3</sup>. Seo and colleagues' work sheds light on how interactions between genes and the environment feed into neuro-immune crosstalk during neurodegeneration.

It is not uncommon for people who have neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease or amyotrophic lateral sclerosis to exhibit alterations to their immune systems and changes in the make-up of the bacterial communities that inhabit their guts<sup>4,5</sup>. In turn, this gut microbiota can regulate gene expression in microglia in a sex-specific manner<sup>6</sup>, and a person's *APOE* status (that is, which of the *APOE* variants they carry) influences this process<sup>7,8</sup>. However, it is not clear whether disruption of the gut microbiota is a cause or a result of neurodegeneration. It is also not known whether timely correction of this gut dysbiosis could slow neurodegeneration.

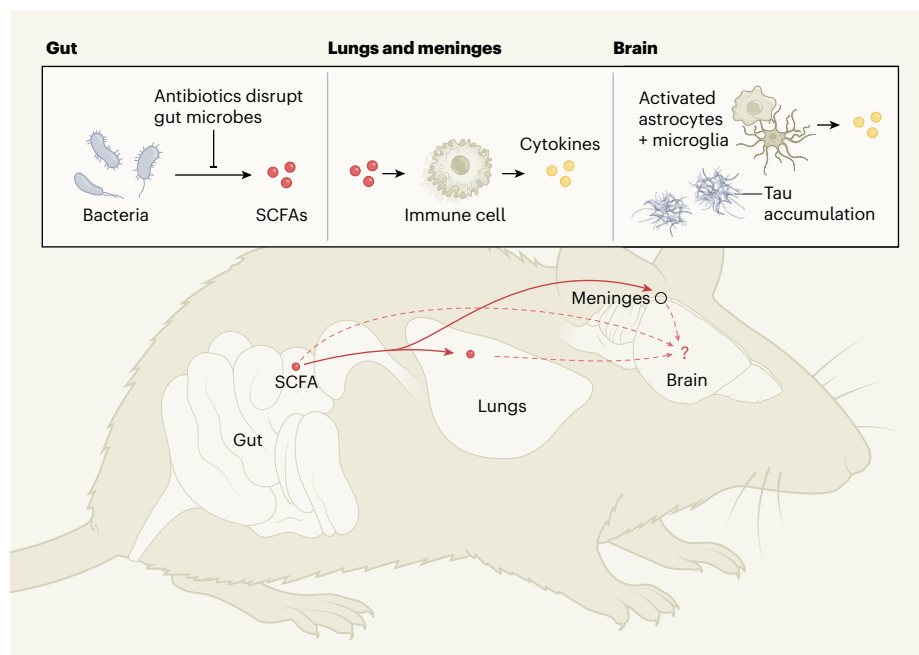
Seo *et al.* set out to examine a strain of mice engineered such that a human form of tau, a protein associated with cognitive decline, accumulated in the animals' brains. The group genetically engineered these mice to express different forms of human *APOE*, and raised the animals in either a conventional environment

or a germ-free environment (meaning that they lacked gut microbes). The authors found that the signs of neurodegeneration and neuroinflammation typically observed in conventionally reared animals carrying the high-risk variant *APOE4* were drastically reduced in animals raised under germ-free

conditions (and so lacking a gut microbiota).

Similarly, Seo and colleagues found that diminishing the gut microbiota of the *APOE*-carrying animals using antibiotics mitigated neurodegeneration. Interestingly, the protective effect of both antibiotic treatment and germ-free rearing was more pronounced in male mice harbouring *APOE3* (a variant that does not confer as much risk as *APOE4*)<sup>3</sup> than in males carrying *APOE4* or in females.

Some evidence<sup>9,10</sup> suggests that short-chain fatty acids (SCFAs) produced by the gut microbiota could be involved in modulating astrocyte and microglia functions (such as the production of signalling molecules called cytokines). It is not known whether SCFAs act directly on brain cells, but Seo *et al.* demonstrated that, as well as reducing SCFA levels, the antibiotic treatment reduced the numbers of various types of immune cell in the meninges (tissues that border the brain) in *APOE3*-carrying mice; it also altered gene expression in lung immune cells called alveolar macrophages (Fig. 1). These cell types also release cytokines that might signal to the



**Figure 1 | Messages from the gut influence neurodegeneration.** The gene *APOE* exists in four variants, of which *APOE3* and *APOE4* confer a higher-than-average risk of a person developing late-onset Alzheimer's disease (*APOE* variants not shown). Seo *et al.*<sup>2</sup> showed that, in mice carrying *APOE3* or *APOE4*, bacteria in the gut release short-chain fatty acids (SCFAs), which can signal to immune cells in the lungs and in tissues called the meninges that border the brain. These cells release cytokines that might signal to the brain (broken arrows), where immune cells called astrocytes and microglia become activated and release more cytokines, and tau protein accumulates (a key hallmark of Alzheimer's disease). It is possible that SCFAs also signal directly to the brain, although this was not tested. The authors show that treating mice with antibiotics to disrupt the gut microbes blocks this pathway and reduces neurodegeneration; this treatment is most effective in mice carrying *APOE3*.

brain, and might present antigen molecules to circulating immune cells called T cells that, in turn, could move to the brain to trigger neuroinflammation. This finding is interesting because the role of crosstalk between immune cells in the body and brain is not yet fully understood in the context of neurodegenerative disease<sup>11</sup>.

Finally, the researchers added SCFAs to the drinking water of germ-free mice carrying *APOE4*. This SCFA administration altered gene expression in alveolar macrophages, increased the proliferation of astrocytes and microglia (a process known as gliosis) and exacerbated neurodegeneration. The results raise the possibility that SCFAs might be key mediators of the microbiota's effect on tau-mediated neurodegeneration. The clear next steps are to delineate the direct mechanisms by which these fatty acids act, the cell type that they target, and how *APOE* status matters in terms of orchestrating this process.

It is not entirely surprising that raising mice germ-free or treating them with antibiotics can reduce tau aggregation, because another research group has shown that gut microbes are required for another type of aggregate, mutant  $\alpha$ -synuclein, to have harmful effects<sup>12</sup>. But the finding that these effects involve *APOE*-dependent changes in the peripheral immune system is remarkable. *APOE* status

is typically thought of as affecting mainly the brain, but Seo and colleagues' evidence for a mechanistic link between this genetic risk factor and the gut microbiota suggests that the gene might be a target of environmental triggers that promote neurodegeneration<sup>11</sup>. However, in what tissue and cell type *APOE* might be affected by these triggers remains to be seen.

It will be interesting to further investigate the sex differences that the authors observed in their experiments involving antibiotics. In a human study, higher SCFA levels in the stools of men who had Parkinson's disease correlated with later onset of motor symptoms<sup>13</sup>, the implication being that SCFAs might be protective (although clinical trials would be needed to establish this link). Researchers should also aim to better understand the effect of the gut microbiota on brain-border immune cells, especially in light of work demonstrating that gut immune cells called B cells make immunoglobulin proteins that affect brain physiology<sup>14</sup>.

Turning to humans, is it possible that antibiotic treatments to combat chronic infections might influence the course of neurodegenerative diseases? If so, would this be the case only in men, or for everyone? The answers to these questions will require clinical studies. Clinical trials could also begin

to address whether manipulating the gut microenvironment – using pre- or probiotics, SCFA supplementation or faecal microbiota transplants – has the potential to protect some subsets of people from neurodegeneration.

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The authors declare no competing interests.