combined to enable the formation of hybrid RNA–DNA molecules. Notably, under certain reaction conditions, U and C can survive only in the presence of the thioanhydropurine compounds that act as direct precursors of dA and dI.

Many organic molecules can be produced as left- and right-handed versions, known as enantiomers, which are mirror images of each other. However, modern nucleotides and their building blocks all take the same enantiomeric form. One of the main difficulties in origins-of-life research is to explain how single enantiomers could have been generated from simple precursor molecules that have no handedness and which could have formed on prebiotic Earth. Xu and colleagues' purine synthesis is attractive in this respect, because it is highly selective for the enantiomers and other isomers of nucleosides observed in modern biology.

Alternative routes have been reported for the combined prebiotic synthesis of pyrimidine and purine nucleosides and nucleotides[6,7]. These routes require chemically and enantiomerically pure sugars to be used as starting materials, which poses the problem that other, often unknown, prebiotic processes would have been necessary to provide those starting materials[8]. By contrast, the enantioselectivity reported by Xu *et al.* derives from RAO, which can crystallize as a single enantiomer from reactions in which the starting materials are nearly racemic[9] (that is, the starting materials consist of an almost equal mixture of enantiomers).

Nucleoside synthesis can also lead to products in which the nucleoside's base is attached to the sugar in the wrong orientation. In Xu and co-workers' synthetic pathway, a UV-induced chemical reduction occurs that leads to the strikingly selective destruction of these unwanted by-products, ultimately producing only the biologically relevant isomers of the purines. Given that early Earth was highly irradiated by UV, the remarkable selectivity of this reaction suggests a possible mechanism by which the total pool of potential nucleic-acid isomers was reduced to the subset of isomers observed today in nature.

Xu and colleagues' work supports a vision of early molecular evolution somewhat removed from the conventional 'pure' RNA-world hypothesis, and perhaps offers a more plausible route to the origin of life from mixed and complex chemical environments. Given the lack of 'chemical fossils', and the uncertainty over the exact conditions and chemistry that occurred on early Earth, it is impossible to say which chemical pathways actually took place. Instead, we must ensure that proposed systems conform as closely as possible to our understanding of what could realistically have happened on prebiotic Earth — not just the chemistry, but also the overall complexity of the reaction networks and their compatibility with other processes.

In the current work, the authors show that the four nucleosides can indeed be produced through processes that could reasonably be expected to have occurred on early Earth (such as hydrolysis, drying and UV irradiation), and provide plausible synthetic pathways that could supply the reactions with their required starting materials. However, as for all prebiotic syntheses, it remains hard to envisage the actual microenvironment that could have supported the many specific chemical transformations required to produce the building blocks of life in quantity.

Nevertheless, Xu and colleagues' work impressively demonstrates how a complete genetic alphabet might have arisen. Regardless of whether we think that life developed from RNA alone, or from more-complex mixtures of nucleic acids, systems-level thinking to find mutually compatible prebiotic chemical pathways will be crucial for developing truly plausible models of the first stages of life's emergence.

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Neurodegeneration

Gut microbes tune inflammation and lifespan

Ping Fang & Elaine Y. Hsiao

There is growing evidence that gut microbes can influence disease. Analysis of a mouse model of the neurodegenerative condition amyotrophic lateral sclerosis offers insight into how gut bacteria might contribute to this illness. **See p.89**

Animals have co-evolved with diverse communities of microorganisms that are integral to the development and activity of their immune and nervous systems[1]. Alterations in the composition and function of the community of gut microorganisms (termed the microbiota) are increasingly being implicated in neurological disorders that involve neuroinflammation, including multiple sclerosis[2], autism spectrum disorder[3] and Parkinson's disease[4]. Studies are also emerging that link the gut microbiota to amyotrophic lateral sclerosis (ALS), a neurodegenerative disorder characterized by the progressive loss of motor neurons crucial for movement, speech and cognition. This devastating disease is usually fatal within a few years of diagnosis. On page 89, Burberry *et al.*[5] fill some gaps in our knowledge of how gut microbes might contribute to ALS, from studies of the condition in a mouse model. Their findings might help to shed light on how a gene linked to ALS called *C9orf72* affects this disease.

Initial studies[6,7] have shown that the gut microbiota of people who have ALS differ from those of unaffected individuals. A study of a mouse model of the disease, based on an ALS-associated mutation in the *Sod1* gene[6], has provided strong evidence that alterations in the microbiota can exacerbate neurodegeneration and drive early mortality. That study also identified microbes and microbial molecules that promote improved motor function and longer lifespan in the mice. It showed that the particular positive or negative effects observed might depend on differences in the microbes encountered in the animals' housing facility (termed a vivarium). Mouse models of inflammatory diseases have also revealed that the animals' environment has such an effect[8].

Burberry *et al.* used a mouse model of ALS (Fig. 1) in which the animals have a mutant version of the gene *C9orf72*, resulting in a deficiency in the encoded C9orf72 protein (these mice also model a neurodegenerative condition called frontotemporal dementia). The authors observed that if the animals were reared in the Harvard University animal facility, they had a shorter lifespan,

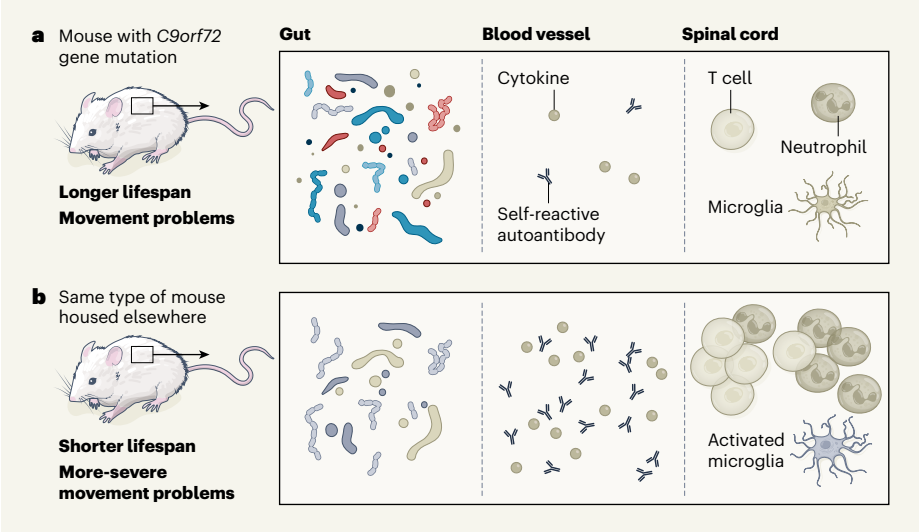

Figure 1 | Gut microbes modulate inflammation and lifespan in a mouse model of neurodegeneration. **a**, **b**, Burberry *et al.*[5] report that mice with a mutation in a gene called *C9orf72*, which is often mutated in the disease amyotrophic lateral sclerosis, had a longer lifespan and less-severe movement problems if they were housed in facilities at the Broad Institute (**a**) than if housed at Harvard University (**b**). The animals housed at the Broad had more-diverse species of gut microbes (different colours indicate different species) than did those kept at Harvard. The mice at the Broad also showed fewer signs of inflammation in their bloodstream (fewer immune signalling molecules called cytokines or self-reactive antibodies associated with autoimmunity) and in their spinal cord (fewer immune cells such as T cells and neutrophils, with immune cells called microglia not in an activated state). Gut microbes contributed to these differences between the animals, and antibiotic treatment (not shown) reduced the inflammation and lessened the movement problems of the animals kept at Harvard.

exacerbated movement problems and an elevated immune response (as indicated by the presence in their blood of pro-inflammatory molecules called cytokines and autoimmune antibodies), compared with mice reared at the Broad Institute of Harvard and MIT. After excluding diet, light cycles and other environmental factors as being responsible for this difference, the authors compared the microbial profiles for the animals in the two facilities, and found that a virus called murine norovirus and the bacteria *Helicobacter, Pasteurella pneumotropica* and *Tritrichomonas muris* were more common at the Harvard facility than at the Broad facility.

The authors investigated the diversity of the gut microbial species further by analysing faecal samples and sequencing a bacterial gene needed for synthesis of the ribosome, the cell's protein-production machinery. This revealed that the ALS mice housed at Harvard or Johns Hopkins University (where mice had a short lifespan) had less microbiota diversity than did mice housed at the Broad or at the Jackson Laboratory research institute (where mice had a longer lifespan). Microbiota profiling of bacterial species revealed alterations in the relative abundances of 62 of 301 bacterial taxa assessed when the ALS mice reared at Harvard and Johns Hopkins were compared with the mice reared at the Jackson Labs and the Broad.

The authors next investigated whether the gut microbiota contributed to the vivarium-dependent differences in the severity of symptoms observed for these animals. They tested the effects of antibiotic treatment and of transplants of faecal microbiota on the inflammation and autoimmune responses of the mice reared at Harvard. Antibiotic treatment of young mice as they aged prevented the induction of pro-inflammatory cytokines and reduced other hallmarks of inflammation – such as a rise in the number of immune cells called neutrophils, the presence of autoimmune antibodies and enlargement of the spleen. Antibiotic treatment of aged mice had a similar effect. Inflammation in the Harvard mice was also reduced if they received transplants of faecal microbiota from animals housed at the Broad.

> **"The effects observed might depend on differences in the microbes encountered in the animals' housing facility."**

To explore whether the microbiota contributed to neuroinflammation in the spinal cord in these mice, animals reared at Harvard were continuously treated with antibiotics. The authors assessed whether inflammation had developed by checking for infiltration of immune cells into the spinal cord and whether the spinal cord contained immune cells called microglia in an activated state. They found that infiltration by neutrophils and by subsets of immune cells called $CD3e^+$ T cells was reduced, as was microglial activation, compared with the situation in untreated animals. These findings are consistent with the results of studies of other disease models, indicating a role for the gut microbiota in modulating inflammation in the central nervous system and the development and function of microglia[9,10].

Burberry and colleagues have shown that alterations in the gut microbiota variously modulate how ALS-related symptoms manifest in mice deficient in C9orf72. Their results suggest that microbial modulation of inflammation outside the brain might be responsible.

More research will be needed to find the particular microbes and microbial functions involved in regulating the different effects on inflammation outside the central nervous system, and to assess whether this peripheral inflammation influences the degeneration of motor neurons in the central nervous system and the associated movement impairments that such neuronal losses cause. It will also be interesting to determine whether particular immune pathways in the central nervous system and/or outside it are responsible for the lifespan changes that occur through C9orf72 deficiency. Unravelling the molecular and cellular mechanisms involved in the neuroinflammation and neurodegeneration observed would advance our understanding of the interactions between environmental factors and genetic risk factors in ALS, and might lead to new targets for clinical intervention.

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