

Astrocyte studies reveal harmful changes in Amyotrophic Lateral Sclerosis

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An MRI with increased signal in the posterior part of the internal capsule which can be tracked to the motor cortex consistent with the diagnosis of ALS. Credit: Frank Gaillard/Wikipedia

Scientists at the Francis Crick Institute have revealed harmful changes in supporting cells, called astrocytes, in Amyotrophic Lateral Sclerosis (ALS) in two publications in *Brain* and *Genome Research*.

ALS, also known as [motor neuron disease](#), is a rapidly progressing degenerative disease of the nervous system, meaning patients suffer loss of strength, speech and eventually the ability to breathe. There are currently no effective treatments and tragically most people die within 3 to 5 years.

When healthy, astrocytes help protect and nurture surrounding motor neurons. However, while recent findings from ALS patients have indicated astrocytes may contribute to the disease, how they go about this remains unclear.

Toxic astrocyte changes in ALS

In the first paper, published in *Genome Research* (in December), the researchers analysed all existing public datasets of astrocytes in ALS, spanning both human and mouse models. Using this meta-analysis approach, they found that in ALS, astrocytes become pro-inflammatory, which is toxic to neighbouring motor neurons.

ALS astrocytes were also found to lose important protective functions, notably the ability to uptake a substance called glutamate. This leads to a build-up of glutamate, which damages motor neurons.

Oliver Ziff, study lead and clinical fellow in the Crick's Human Stem Cells and Neurodegeneration Laboratory, said: "Our work suggests that treatments for ALS will need to reduce or reverse these damaging changes in astrocytes. These cells are not just innocent bystanders but actively contribute to the progression of the disease."

Innate and diverse harmful changes in ALS astrocytes

In the second study, published in *Brain* today (19 January), the researchers found that astrocytes with different ALS-causing genetic mutations also have distinct underlying molecular patterns. This suggests that, during ALS, astrocytes acquire mutation-dependent changes.

As part of their study, the team examined the impact of different mutations known to cause ALS on astrocytes. They observed that in the absence of any neighbouring [immune cells](#), such as microglia, the presence of these mutations alone was sufficient to drive harmful changes in the astrocytes.

The nature of these changes depended on the specific mutations present, suggesting that astrocytes in ALS can appear diverse between different patients. The researchers observed key molecular and functional differences in the cells as a result of the mutation they carried.

However, they also showed that some of these changes converge, which might explain why, in disease, astrocytes have similar characteristics, failing to protect motor neurons from degeneration and increasing inflammation that in turn drives disease.

Doaa Taha, study lead, co-lead author on the first paper and UCL Ph.D. student in the Crick's Human Stem Cells and Neurodegeneration Laboratory, said: "The nature and diversity of astrocyte transformation between ALS mutations was not well known. The insight we've gained

into the different ways this change manifests in early disease could be a helpful starting point in efforts to reverse the cell transformation."

Ben Clarke, co-lead author on both papers and postdoc in the Human Stem Cells and Neurodegeneration Laboratory, said: "We're now working to understand the biology of the distinct molecular patterns we're observing and how they converge. Understanding the early [astrocyte](#) changes in ALS could provide us with new therapeutic targets."

Growing models

While much research into ALS relies on post-mortem samples, where the disease is already well-established, these studies involve growing living cells derived from patients. Master stem cells can be taught to differentiate into any cell from anywhere in the human body, meaning scientists can observe the very earliest cell changes caused by different [genetic mutations](#). The Patani Lab at the Francis Crick Institute are leaders in growing astrocytes and other cells of the nervous system from human induced pluripotent stem cells.

"Our growing understanding of early disease biology is bringing us closer to finding new ways to treat ALS," says Rickie Patani, head of the Crick's Human Stem Cells and Neurodegeneration Laboratory, Consultant Neurologist at the National Hospital for Neurology and Neurosurgery and member of the UCL Queen Square Motor Neuron Disease Centre. "It's at the origin of these 'star' [cells](#) that we might uncover crucial changes that drive the disease."

More information: Astrocytes display cell autonomous and diverse early reactive states in familial amyotrophic lateral sclerosis, *Brain* (2021). [DOI: 10.1093/brain/awab328](https://doi.org/10.1093/brain/awab328)

Oliver J. Ziff et al, Meta-analysis of human and mouse ALS astrocytes

reveals multi-omic signatures of inflammatory reactive states, *Genome Research* (2021). [DOI: 10.1101/gr.275939.121](https://doi.org/10.1101/gr.275939.121)

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