Stem cells may help identify new schizophrenia drugs

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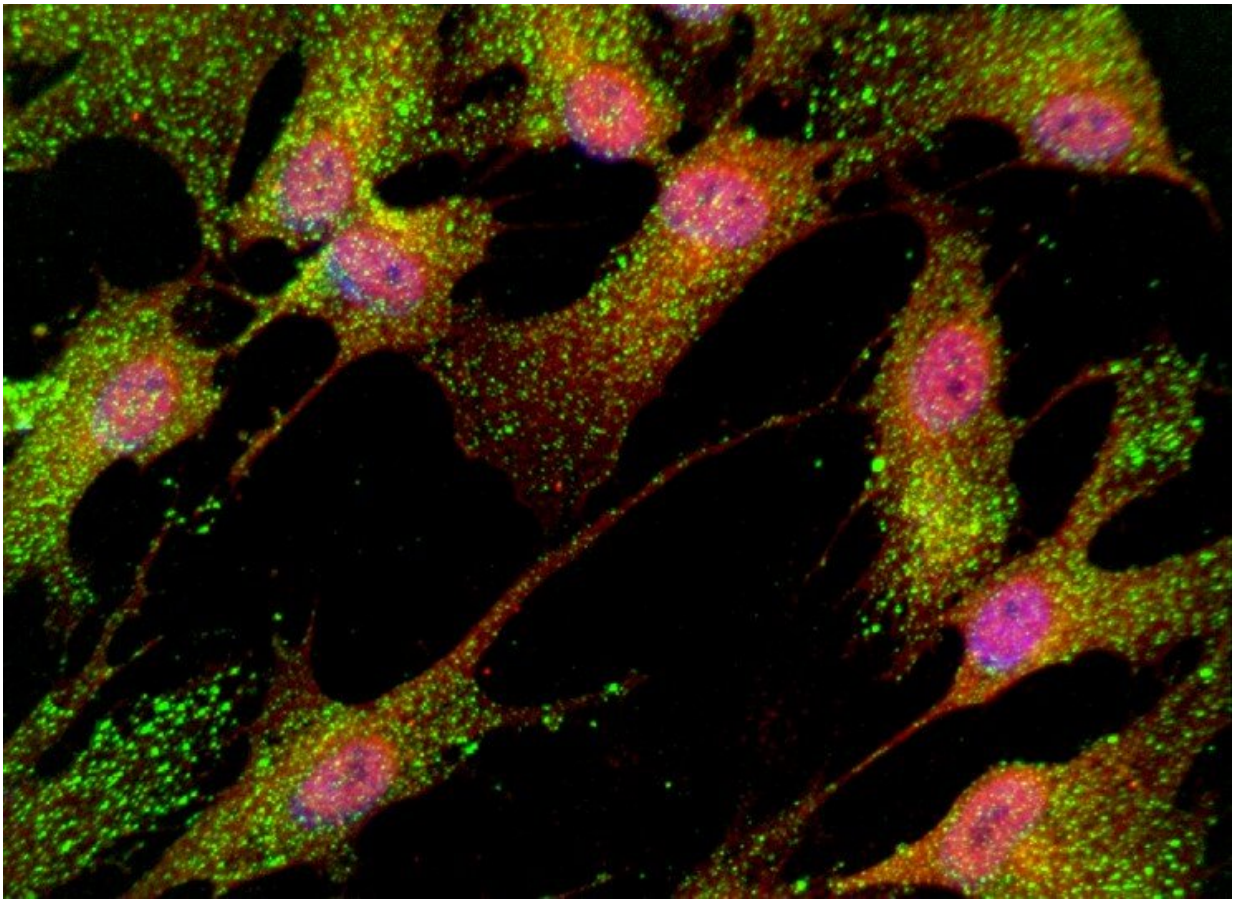

Human astrocytes were produced from iPSCs using 3D methods described in the paper. The astrocytes were then stained with antibodies against C4 (green; the target of the work), ALDH1L1 (red; a marker for astrocytes) and DAPI (blue – which looks purple in the image -- a nuclear marker). Credit: Francesca Rapino, Harvard University, USA

Inflammation and overactivation of the immune system in the brain can cause loss of synapses and the death of neurons, leading to neurodegenerative and psychiatric diseases.

In schizophrenia, increased levels of the immune protein C4 have been measured in patients' brains, and increasing C4 levels due to variations in copy number are associated with an increased risk for developing schizophrenia. Therapies lowering C4 levels in the brain and reducing inflammation may benefit schizophrenia patients but are currently not available.

Brain cells called astrocytes regulate the immune response and inflammatory environment in the brain by secreting immune proteins such as C4. Consequently, astrocytes are a primary target for C4-lowering therapies.

To identify effective drugs, Francesca Rapino, Lee Rubin, and colleagues from Harvard University, U.S., have developed an efficient method to make large numbers of C4-secreting human astrocytes from stem cells.

In a paper recently published in *Stem Cell Reports*, the researchers followed-up with a screen of 464 drugs and identified a small group of about 20 that reduced C4 secretion from astrocytes. These drugs were effective both in healthy astrocytes and in astrocytes made from schizophrenia patients' stem cells.

This research opens up new avenues for studying inflammatory responses and their regulation in human astrocytes and serves as a platform to identify therapeutic drugs in large-scale screening approaches.

More information: Lee L. Rubin, Small molecule screen reveals

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pathways that regulate C4 secretion in stem-cell derived astrocytes, *Stem Cell Reports* (2022). DOI: 10.1016/j.stemcr.2022.11.018. www.cell.com/stem-cell-reports … 2213-6711(22)00551-3

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