Ally and enemy? Scientists explore immune cell suspect in Alzheimer's disease

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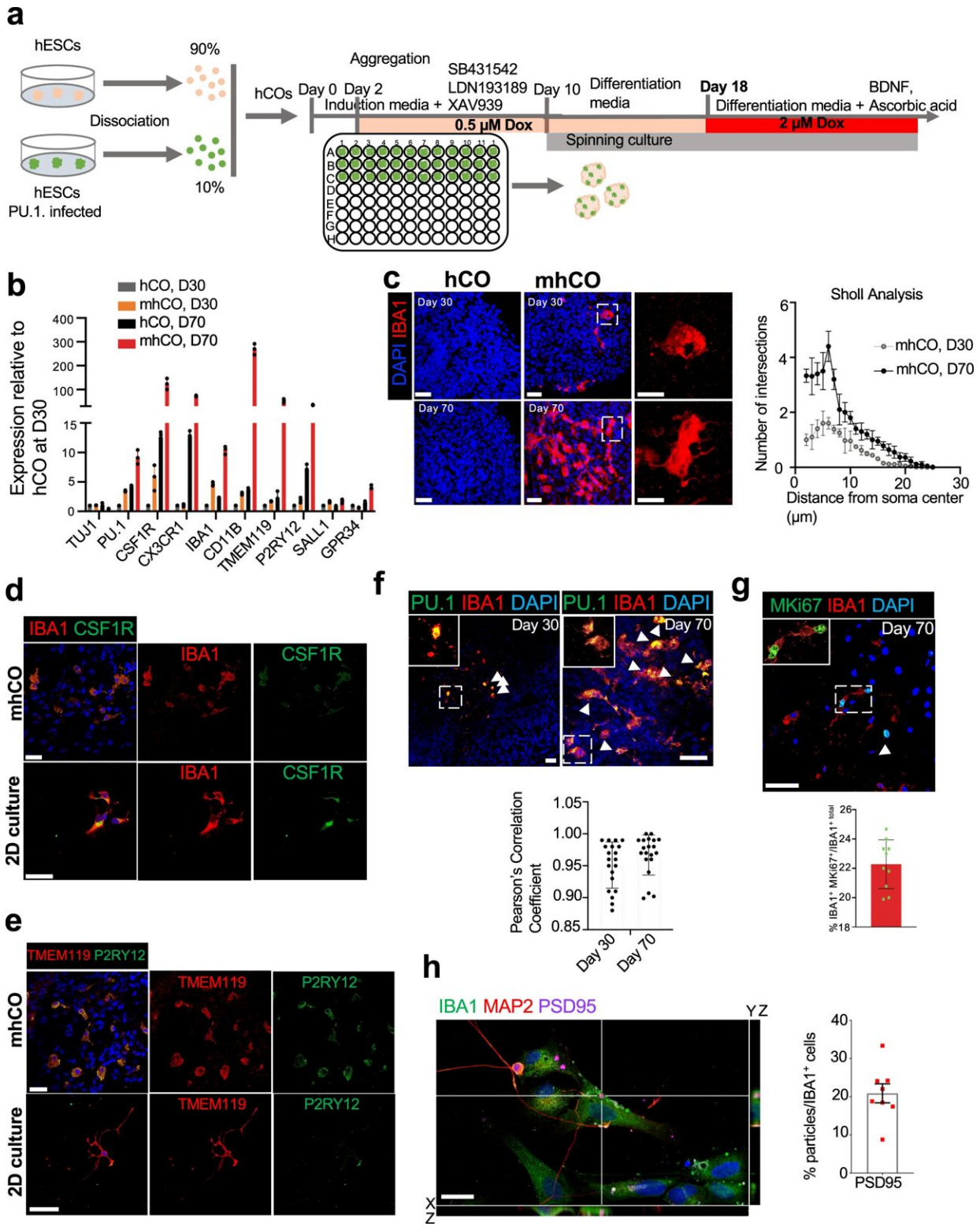

Fig. 1: Characterization of microglia-like cells in mhCOs. a Schematic for generating mhCOs. 10% of PU.1-infected hESCs were mixed with 90% parental

HES3 hESCs, and PU.1 priming and full induction were performed on day 2 and 18, respectively. b Expression of microglia-related genes from control hCOs and mhCOs (30-day and 70-day old). Gene expression was measured relative to control organoids on day 30 and normalized to β-Actin. Data represent the mean ± SEM (n = 5, three independent batches). c Left, immunostaining for IBA1 reveals the production of microglia-like cells in sectioned-mhCOs at days 30 and 70. IBA1+ cells were not found in control hCOs. Right, Sholl analysis of IBA1 + microglia-like cells from mhCOs at different time points. Data represent the mean ± SEM (n = 5 organoids from three independent differentiation replicates of two hESCs lines). d and e Immunostaining of mhCOs at day 70 and isolated microglia co-cultured with neurons (2D) for IBA1 and CSF1R (d) TMEM119 and P2RY12 (e). Representative images were shown (n = 5, from two independent batches). f Top, co-expression of PU.1 and IBA1 in hCOs and mhCOs at day 30 and 70. Bottom, quantification of Pu.1-derived IBA1 microglia-like cells. Data represent the mean ± SEM (n = 5 organoids from three independent differentiation replicates of two hESCs lines). Bottom, Pearson's correlation coefficient of IBA1 with PU.1 in mhCOs at days 30 and 70. g Top, co-immunostaining for Ki67 and IBA1 in mhCOs at day 70. Bottom, quantification of proliferating IBA1 microglia-like cells. Data represent the mean ± SEM (n = 5 organoids from three independent differentiation replicates of two hESC lines). h Left, high-resolution imaging showed microglia isolated from mhCOs at day 90 and co-cultured D90 cortical neurons for 3 days contained inclusions of PSD95. Right, quantification of PSD95 particles in IBA1+ microglia-like cells. Data represent the mean ± SEM (n = 8, from three independent differentiation replicates of hESCs lines). The scale bar represents 50 μm in c–g and 20 μm in h. Credit: DOI: 10.1038/s41467-022-28043-y

As scientists search for the roots of Alzheimer's disease, they have had a hard time determining whether microglia, an immune system cell crucial to brain development and maintenance of the adult brain, is a friend or foe.

Evidence shows that a lack of microglia contributes to accumulation of

amyloid plaques, a hallmark of Alzheimer's. Alternately, an excess of microglia has been implicated in the destruction of neurons and brain synapses which also characterizes neurodegeneration in the disease.

Now, Yale researchers have developed a way to tease out factors that may determine which of those roles microglia might play, they report in the journal *Nature Communications*.

"All microglia we possess as adults are created before we are born," said In-Hyun Park, associate professor of genetics at the Yale Stem Cell Center. "Microglia are crucial in neurogenesis because they do the synaptic pruning that allows neurons to communicate properly."

In adult brains, they act as a kind of cellular trash collector, identifying and disposing of debris from dead neurons.

But microglia have been a challenge to study because they form soon after conception and migrate quickly to the developing nervous system. Once they find a home in the developing brain, microglia are cut off from most interaction with other parts of the body by the blood-brain barrier, which protects the brain from pathogens. Dysfunction of microglia has been associated with neurodevelopmental and neurodegenerative diseases, but studying the link has been difficult due to the limited models of the human brain.

For the new study, Bilal Cakir and Yoshiaki Tanaka from Park's lab developed a method to generate functional microglia in human cortical organoids, which are small, three-dimensional replicas of the developing brain formed from early-stage stem cells. In laboratory tests, they identified an active gene created very early in development that is crucial to the birth of microglia. They were then able to activate the gene to coax the creation of microglia in the brain organoid.

In preliminary experiments, they found organoids lacking microglia were susceptible to accumulation amyloid, a protein that forms plaques linked with Alzheimer's disease. But organoids with functioning microglia were not. The findings suggest that in this case microglia play a protective role.

The organoids can be used to study effects of other genes linked to the development of Alzheimer's, the researchers said.

More information: Bilal Cakir et al, Expression of the transcription factor PU.1 induces the generation of microglia-like cells in human cortical organoids, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28043-y

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