Disease-associated astrocyte epigenetic memory promotes CNS pathology

Hong-Gyun Lee[1], Joseph M. Rone[1], Zhaorong Li[1,2], Camilo Faust Akl[1], Seung Won Shin[3], Joon-Hyuk Lee[1], Lucas E. Flausino[1], Florian Pernin[4], Chun-Cheih Chao[1], Kilian L. Kleemann[5], Lena Srun[1], Tomer Illouz[1], Federico Giovannoni[1], Marc Charabati[1], Liliana M. Sanmarco[1], Jessica E. Kenison[1], Gavin Piester[1,6], Stephanie E. J. Zandee[7], Jack Antel[4], Veit Rothhammer[1,8], Michael A. Wheeler[1,2], Alexandre Prat[7], Iain C. Clark[3] and Francisco J. Quintana[1,2†]

[1]Ann Romney Center for Neurologic Diseases, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA.
[2]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA.
[3]Department of Bioengineering, College of Engineering, California Institute for Quantitative Biosciences, QB3, University of California Berkeley, Berkeley, CA 94720, USA.
[4]Neuroimmunology Unit, Montreal Neurological Institute, Department of Neurology and Neurosurgery, McGill University, Montreal, QC H3A 2B4, Canada.
[5]School of Computing, University of Portsmouth, Portsmouth, UK.
[6]Department of Pathology and Laboratory Medicine, University of Rochester Medical Center, Rochester, NY, USA.
[7]Neuroimmunology Research Lab, Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montreal, QC H2X 0A9, Canada.
[8]Department of Neurology, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuernberg, Erlangen, DE.

[†]Corresponding author:
Ann Romney Center for Neurologic Diseases. 60 Fenwood Road, Boston, MA 02115, USA.
Tel.: +1 617 525 5317; Fax: +1 617 525 5305. Email: fquintana@rics.bwh.harvard.edu

Summary

Astrocytes play important roles in the central nervous system (CNS) physiology and pathology. Indeed, astrocyte subsets defined by specific transcriptional activation states contribute to the pathology of neurologic diseases, including multiple sclerosis (MS) and its pre-clinical model experimental autoimmune encephalomyelitis (EAE)[1-8]. However, little is known about the stability of these disease-associated astrocyte subsets, their regulation, and whether they integrate past stimulation events to respond to subsequent challenges. Here, we describe the identification of an epigenetically controlled memory astrocyte subset which exhibits exacerbated pro-inflammatory responses upon re-challenge. Specifically, using a combination of single-cell RNA sequencing (scRNA-seq), assay for transposase-accessible chromatin with sequencing (ATAC–seq), chromatin immunoprecipitation with sequencing (ChIP–seq), focused interrogation of cells by nucleic acid detection and sequencing (FIND-seq), and cell-specific *in vivo* CRISPR/Cas9-based genetic perturbation studies we established that astrocyte memory is controlled by the metabolic enzyme ATP citrate lyase (ACLY), which produces acetyl coenzyme A (acetyl-CoA) used by the histone acetyltransferase p300 to control chromatin accessibility. $ACLY^{+}p300^{+}$ memory astrocytes are increased in acute and chronic EAE models; the genetic targeting of $ACLY^{+}$ $p300^{+}$ astrocytes using CRISPR/Cas9 ameliorated EAE. We also detected responses consistent with a pro-inflammatory memory phenotype in human astrocytes *in vitro*; scRNA-seq and immunohistochemistry studies detected increased $ACLY^{+}$ $p300^{+}$ astrocytes in chronic MS lesions. In summary, these studies define an epigenetically controlled memory astrocyte subset that promotes CNS pathology in EAE and, potentially, MS. These findings may guide novel therapeutic approaches for MS and other neurologic diseases.