Widespread loss of the silencing epigenetic mark H3K9me3 in astrocytes and neurons along with hippocampal-dependent cognitive impairment in C9orf72 BAC transgenic mice

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Background: Hexanucleotide repeat expansions of the G4C2 motif in a non-coding region of the C9ORF72 gene are the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Tissues from C9ALS/FTD patients and from mouse models of ALS show RNA foci, dipeptide-repeat proteins, and notably, widespread alterations in the transcriptome. Epigenetic processes regulate gene expression without changing DNA sequences and therefore could account for the altered transcriptome profiles in C9ALS/FTD; here, we explore whether the critical repressive marks H3K9me2 and H3K9me3 are altered in a recently developed C9ALS/FTD BAC mouse model (C9BAC). Results: Chromocenters that constitute pericentric constitutive

heterochromatin were visualized as DAPI- or Nucblue-dense foci in nuclei. Cultured C9BAC astrocytes exhibited a reduced staining signal for H3K9me3 (but not for H3K9me2) at chromocenters that was accompanied by a marked decline in the global nuclear level of this mark. Similar depletion of H3K9me3 at chromocenters was detected in astrocytes and neurons of the spinal cord, motor cortex, and hippocampus of C9BAC mice. The alterations of H3K9me3 in the hippocampus of C9BAC mice led us to identify previously undetected neuronal loss in CA1, CA3, and dentate gyrus, as well as hippocampal-dependent cognitive deficits. Conclusions: Our data indicate that a loss of the repressive mark H3K9me3 in astrocytes and neurons in the central nervous system of C9BAC mice represents a signature during neurodegeneration and memory deficit of C9ALS/FTD.

ALS

Astrocyte

Brain

FTD

H3K9me3

Memory

Neuron

animal cell

animal experiment

animal model

Article

astrocyte

C9ORF72 gene

cognitive defect

dentate gyrus

epigenetics

gene

gene silencing

hippocampal CA1 region

hippocampal CA3 region

histone methylation

motor cortex

mouse

nonhuman

priority journal

spinal cord