Temporal lobe epilepsy (TLE), the most common type of focal epilepsy, is frequently associated with hippocampal sclerosis that primarily affects CA1 pyramidal neurons. There is growing evidence that the hippocampal CA1 layer is comprised by diverse cell-types including superficial and deep pyramidal cells, GABAergic interneurons and glial cells. However, the role and contribution of each cell-type within CA1 to hippocampal sclerosis in epilepsy is largely unknown. To address this question, we adopt here an integrative, data-driven approach that leverages in transcriptomics profiling of laser capture microdissected subfields (LCM-RNAseq) and isolated nuclei (snRNAseq) from medial CA1 hippocampi in rodent models of epilepsy. In the current study, we show that delayed neurodegeneration in epilepsy primarily affect a specific pyramidal cell population (evCA1 cells) that is segregated across the deep-superficial axis of the hippocampal CA1 region. Furthermore, we demonstrate a causative role for microglia in evCA1 cell attrition and hippocampal sclerosis. We show that in the epileptic hippocampus, activated microglia populate CA1 subfields and impinge on evCA1 cells activity via a complex signaling network that involves microglial-specific P2ry12 receptors. These novel findings define a role for microglia in delayed neurodegeneration following acute seizures. Our results critically extend previous mechanistic evidence on epilepsy-associated neurodegeneration and lead us to propose a network of interacting cell-types that is responsible for hippocampal sclerosis in TLE.