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Suppression of astrocytic immune responses by Nr3c1-mediated epigenetic regulation

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Genetic perturbations often do not cause developmental defects but can be linked to the increased prevalence and severity of mature-onset disease pathogenesis. However, the underlying molecular mechanisms and implications of delayed disease onset are not completely understood. Here, we report a 'shadow phenotype' marked by specific epigenetic alterations in astrocytes at the early postnatal stage, significantly impacting adult immune responses upon autoimmune challenges. Through integrative analyses of the transcriptome, chromatin accessibility, and long-range chromatin contacts during perinatal development with precise temporal resolution, we identify 55 transcription factors involved in mouse astrocyte development. Among these factors, Nr3c1 was notably identified as a key regulator for early postnatal astrocyte development. Yet, mice with astrocyte-specific Nr3c1 deletion did not exhibit any detectable phenotypes. Nevertheless, we found that Nr3c1-deleted astrocytes display epigenetic dysregulation in multiple immune-related genes and mice with astrocyte-specific Nr3c1 deletion are prone to developing exacerbated immune responses upon experimental autoimmune encephalomyelitis (EAE) induction. Furthermore, single-nucleus RNA-sequencing analyses reveal that specific astrocyte subpopulations responded to Nr3c1 depletion, with their gene expression epigenetically primed by the loss of Nr3c1. Together, our study reveals novel epigenetic regulation of astrocytic immune responses through early postnatal Nr3c1 expression, providing insights into how genetic perturbation at the developmental stage can promote delayed mature-onset disease pathogenesis.