*Nature Reviews Genetics* | Published online 3 Jul 2017; doi:10.1038/nrg.2017.55

GENE EXPRESSION

# Microglia — environment defines identity


Microglia are macrophage cells of the central nervous system (CNS) with crucial functions in neurodevelopment, immunity and tissue homeostasis, but this cell population has been notoriously difficult to study. A new study in *Science* describes the transcriptomic and epigenomic profiles of cortical microglia *ex vivo* and *in vitro*, knowledge that will aid in understanding how these cells contribute to the development of human brain disorders.

Gosselin *et al.* isolated microglia from surgically resected human and mouse brain tissue samples to generate a comprehensive atlas of the transcriptional and epigenetic landscapes of these cells using RNA sequencing (RNA-seq), ChIP–seq (chromatin immunoprecipitation followed by sequencing) and ATAC-seq (assay for transposase-accessible chromatin with high-throughput sequencing).

The transcriptional profiles of cortical microglia revealed a high level of correlation between human donors. A core set of 881 transcripts was defined as the unique microglia gene signature by aligning the cortical microglial transcriptome with that of the corresponding intact cortex tissue. When this core set was intersected with 46 publically available microarray or RNA-seq data sets of genes differentially regulated in neurodegenerative and behavioural disorders, 28 of them showed depletion or enrichment of the microglia signature. A high proportion of genes associated with disease risk alleles were preferentially expressed in microglia, in particular in Alzheimer disease and multiple sclerosis, but to a lesser degree in Parkinson disease and schizophrenia, suggesting variable involvement of microglia in different diseases of the CNS.

Comparing human and mouse microglia, genomic regions of open chromatin showed a high level of correlation and the majority of orthologous gene pairs (more than 13,000 of almost 16,000) were expressed with similar patterns. Motif analysis for transcription factors at poised or active chromatin regions (ATAC-seq and H3K4me2 peaks) and super-enhancer identification (H3K27ac peaks) returned overlapping signatures. Nevertheless, despite the overall similarities in the transcriptional and epigenomic profiles of mouse and human microglia, there were a number of remarkable exceptions indicating the presence of species-specific *cis*-regulatory elements.

To better understand the importance of the cortical environment, microglia were cultured for 7 days and compared with freshly isolated microglia. The gene expression signatures between human patients correlated better than those of fresh versus cultured cells taken from the same individual; indeed, culturing resulted in a 33% change in the signature gene set. This strong transcriptional response appeared as early as 6 h after the beginning of *in vitro* culture. During development, primitive macrophages originate in the yolk sac and gain their microglia-specific transcriptomic profile upon migration into the brain. Loss of the microglia gene signature by *in vitro* culture mirrors the acquisition of the microglia gene signature when yolk sac macrophages migrate into the fetal brain. These findings provide an explanation for how microglia establish and maintain their identity based on environmental factors in the brain.

In summary, this work highlights the many similarities and striking differences between human and mouse microglia, as well as between *ex vivo* and *in vitro* microglia. It shows that the microglia gene signature is less dependent on individual factors such as age, sex or disease status and much more dependent on the correct environment with its identity-defining factors. This knowledge has important implications for the design and interpretation of both human and animal studies of CNS disorders.

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**ORIGINAL ARTICLE** Gosselin, D. *et al.* An environment-dependent transcriptional network specifies human microglia identity. *Science* http://dx.doi.org/10.1126/science.aal3222 (2017)