Maternal immune activation can affect the development of embryos, but the underlying mechanisms have been unclear. In a new study, Bridget Ostrem and colleagues show that embryonic microglia detect maternal inflammation, resulting in transcriptional changes in neighbouring brain-cell types. To find out more about the behind the paper story, we caught up with the first authors, Bridget Ostrem and Nuria Domínguez-Iturza, and corresponding author Paola Arlotta, Chair of the Department of Stem Cell and Regenerative Biology at Harvard University, USA.

Paola, can you give us your scientific biography and the questions your lab is trying to answer?

PA: Our laboratory is interested in decoding the mechanistic principles by which the vast diversity of cortical cell types is established, integrated and subsequently maintained for the lifespan of the organism. This is important because the molecular logic that generates, maintains and is wired into circuits of a multitude of cell types found in the mammalian brain is poorly understood, yet these processes are crucial for complex brain function, and their disruption leads to neurodevelopmental disease. We pioneered the development of stem cell-derived brain organoids that model the human cortex to study previously inaccessible mechanisms of human neurodevelopment and disease. These organoids can achieve advanced neuronal maturation and the generation of spontaneously active neuronal networks that are sensitive to sensory stimuli. Recently, we have shown that we can generate chimeric organoids (chimeroids) incorporating cells of many individual donors, and we applied this human brain chimeroid model to uncover inter-individual variation in response to disease triggers. In the future, we are excited to bring these discoveries to bear for unearthing poorly understood mechanisms of human brain development and disease.

Bridget and Nuria, how did you come to work in the lab and what drives your research today?

BELO: I am a developmental neuroscientist and a neurologist with a particular clinical interest in maternal-fetal neurology. This burgeoning field encompasses diseases of the nervous system in pregnant individuals and fetuses, and neurological implications of maternal-fetal interactions. I was drawn to the lab because of Dr Arlotta’s expertise in defining cell types, cell-cell interactions and intercellular communication, to study how neurons and glia interact to form complex cortical circuits during normal development and in neurodevelopmental disorders.

ND-I: During my PhD, I became fascinated with the processes that regulate brain development and how they go awry in neurodevelopmental disorders. I was excited to join Dr Arlotta’s lab for my postdoctoral work where I could integrate my background with the lab’s expertise in cortical development, cell identity acquisition and intercellular communication, to study how neurons and glia interact to form complex cortical circuits during normal development and in neurodevelopmental disorders.
Tell us about the background of the field that inspired your work
PA: Previous epidemiological studies in humans have demonstrated that maternal infections result in long-term neuropsychiatric consequences in affected offspring. These effects persist even in the absence of direct fetal brain infection; fetal exposure to maternal infection is sufficient to disrupt normal fetal brain development. There has been increased interest in understanding the cellular and molecular basis for this effect in recent years, particularly given the high rate of COVID-19 infections during pregnancy. We sought to identify the cellular basis for the fetal brain response to maternal inflammation, and the corresponding transcriptional changes at a single-cell level in the developing brain. Microglia, the resident immune cells of the central nervous system, have been implicated in the fetal brain response to specific pathogens. We hypothesized that microglia are essential for the fetal brain response to maternal inflammation.

Can you give us the key results of the paper in a paragraph?
PA, BELO & ND-I: In this study, we built a comprehensive transcriptional atlas of microglia during cortical development, emphasizing their remarkable diversity and highlighting their expression of receptors relevant to maternal infection. We found that maternal inflammation in rodents leads to gene expression changes within microglia that persist until juvenile age. Importantly, we showed that maternal inflammation triggers extensive transcriptional changes in various neuronal and glial cortical cell types, and identified microglia as a key mediator of that response; in the absence of microglia, this response is abolished. Collectively, our data emphasizes the crucial and durable role of microglia in regulating the brain’s response to maternal inflammation, thus highlighting microglia as a potential therapeutic target for neuropsychiatric conditions originating from maternal infection.

We were amazed that the widespread transcriptional changes induced by maternal immune activation in multiple cell types were nearly eliminated in the absence of microglia. These data convinced us that microglia play a crucial role in the fetal brain response to inflammation in utero.

And what about the flipside: any moments of frustration or despair?
BELO: We spent a lot of time using different bioinformatic tools to analyse lineage relationships between embryonic microglial substates. We hoped that a clear, linear trajectory would emerge between substates that would help illuminate the process of microglial substate diversification during late embryonic development. However, as our FLOW-MAP analysis depicts, microglial lineage relationships appear to be complex, dynamic and likely not unidirectional. Although the process was frustrating, we had to accept what the data were showing us. Clearly, we still have a lot to learn about these fascinating cells!

Why did you choose to submit this paper to Development?
PA, BELO & ND-I: Development is a not-for-profit, scientist-led journal that publishes compelling and inspiring work in developmental biology. We believe that the findings of our study will be interesting for the field and, altogether, we felt Development was a great fit for our work!

What is next for you after this paper?
ND-I: I am intrigued by how a broader set of glia cells interact with neurons. In particular, I am very interested in expanding my work to study the biology of oligodendroglia as it relates to the remarkable diversity of myelin patterns present in the mammalian cerebral cortex. My current work focuses on investigating how neurons and oligodendrocytes communicate during developmental myelination in the cerebral cortex.

And Paola, where will this story take your lab next?
PA: I am excited to extend this work to more cell types. The question of how neuronal diversity impacts the development of glia is very interesting, and one that must be asked in the context of multiple cell types and states. Our next steps will certainly incorporate oligodendrocytes (during developmental myelination) and astrocytes (during circuit refinement) in the picture.

Finally, let’s move outside the lab – what do you like to do in your spare time?
BELO: On weekends, you can often find me enjoying San Francisco’s Ocean Beach with my partner and two children.

ND-I: I enjoy reading, swimming, hiking and traveling to visit different countries and cultures. I also love cooking and, more recently, watercolour painting!

PA: I love the outdoors and art. You will find me hiking mountains in the snow, skiing and climbing, or at the wheel making pottery.

Reference

Fluorescence image of microglia (red) and Hes1 RNA (white) in the mouse juvenile cerebral cortex