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Gut–neuroimmune interactions: the unexpected role of the immune system in brain development

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How does the immune system impact brain development?

The exciting and somewhat unexpected relationship between the immune system and the brain has become one of the most fascinating topics in neuroscience. Even though the immune system was initially implicated in resolving viral and bacterial threats, it is now becoming more evident that it also plays a role in processes in the brain, both under healthy and pathological conditions. This novel role of the immune system in brain health has been implicated in various psychopathologies where neurodevelopment, stress and mood are central. In particular, its role in healthy brain development is becoming more evident, and understanding neuroimmune communication is becoming crucial in treating neurodevelopmental and mood disorders in later life. In the brain, glia function as part of the innate immune system and are programmed to respond to pathogens and physical injury. They also play an important role in neuronal development and pruning. These cells communicate with and respond to chemical signals, such as cytokines and chemokines, which can then initiate or downregulate inflammatory responses. Finally, the trillions of microbes residing in the gut can also stimulate cytokine and chemokine responses in the periphery and play an important role in both immunity and brain development.

Before we can tell you how your immune system impacts your brain, we need a primer on the main cellular and chemical components involved (Figure 1).

Innate immunity – glial cells

Glial cells comprise approximately 50% of the brain. The word 'glia' is derived from the Greek word meaning 'glue', an apt name for these cells that hold the brain together and ensure proper development. The star-shaped cells, called astrocytes, are the most common type of glia in the brain. These cells help to strengthen and modulate connections between synapses, recycle excess neurotransmitters, release their own messengers and participate in the early immune response in the brain. A smaller subset of glia, called microglia, are derived from monocytes in the bloodstream and infiltrate the brain in early life. They are crucial in synapse refinement processes during brain development, as well as contributing to the immune response in the brain. Oligodendrocytes are another type of glial cell that ensheath neuronal axons to increase signal conductance. However, during different disease processes, these cells can initiate inflammation through microglia and disrupt normal neuronal signalling. Finally, mast cells can also prime the microglia in the brain. These immune cells release granules filled with histamine during normal development, which are recognized by the microglia.

Glia, as well as neurons, can recognize specific pathogens through different toll-like receptors, which will initiate an immune response. Microglia have the most diverse expression of these receptors in the brain.

Priming immunity – chemokines and cytokines

Although the glia in the brain may have all the necessary machinery to respond to different challenges, communication within the brain and the rest of the body is necessary for proper development and immunity. Glia themselves and many other cell types release signalling molecules, called chemokines or cytokines, that can direct

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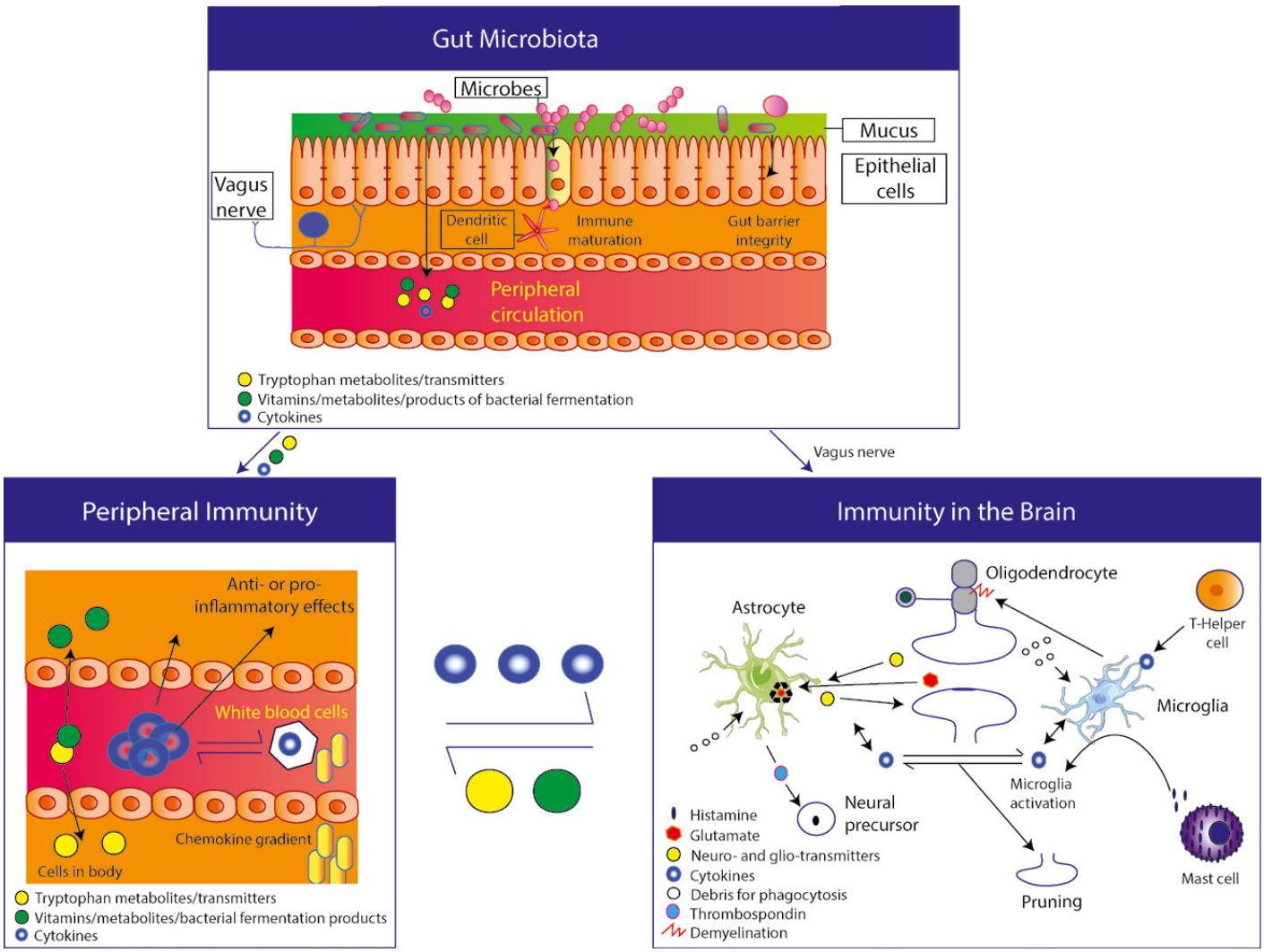

Figure 1. The main components of the immune system in brain development. The gut microbiota is comprised of trillions of bacteria, fungi and viruses on the gut mucosal surface. In early development, they help with the formation of barriers between epithelial gut cells. These barriers are called tight junctions and they prevent bacteria, viruses and endotoxins from leaking into the bloodstream. They also help develop gut immunity. Different components of the microbiota are trafficked by Microfold (M) cells and sampled by dendritic cells. M cells are found in both the gut-associated lymphoid tissue and the mucosa-associated lymphoid tissue, both regions involved in initiating and maintaining gut immunity. Sampling by dendritic cells generates adaptive immunity and a tolerance to the healthy microbes that reside in the gut. These microbes digest and ferment food into different metabolites, produce vitamins and even neurotransmitters. They generate serotonin and tryptophan metabolites which can act on neurons in both the brain and the periphery. These microbial by-products travel through the bloodstream to affect different cell types in the brain. In addition, they can directly signal to the brain through the vagus nerve. In the periphery, these by-products, especially cytokines can interact and even prime immune cells in the blood. They have pro- or anti-inflammatory effects on different cells. Chemokines can also direct immune cells from the periphery into different organs such as the brain through gradients of molecules that either attract or repel these cells. Finally, cells in the brain can be affected by these peripheral metabolites – even those produced in the gut! Astrocytes can release thrombospondins to influence neural precursor cell differentiation and proliferation, recycle a neurotransmitter called glutamine, regulate synapses through pruning, communicate with microglia using cytokines, release and recognize different transmitters, and remove debris in the brain. Microglia can be primed by histamine, which is released by mast cells and this will influence their synaptic pruning in early life. In addition, microglia can communicate with astrocytes using cytokines, remove debris, react with oligodendrocytes to cause inflammation during disease and can participate in synaptic pruning. T-Helper cells produce cytokines that can act on many cells within the brain.

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movement or prime a pro- or anti-inflammatory response in astrocytes and microglia, respectively.

What doesn't kill you makes you stronger – adaptive immunity in the brain

A subset of T-Helper cells migrate towards the brain in early life. They reside in the meninges, a protective membrane for the brain, and learn to recognize and tolerate different components of the brain, such as oligodendrocytes. They have been shown to be involved in demyelinating disease, where they no longer tolerate the oligodendrocyte sheaths and cause inflammation in the brain.

Microbiota

The gut microbiota – the trillions of microorganisms, mainly comprised of bacteria and viruses, residing in the gut is highly implicated in the proper development of immune responses in the body, as well as stimulating the development of a strong gut barrier to prevent bacteria and bacterial by-product translocation into the bloodstream. The mechanisms involved in how the microbiota signals to the brain are slowly being unravelled but it is clear that it incorporates the immune system, the vagus nerve and via metabolites with brain cells, such as glia.

Now that we have a good understanding of the main characters of this story, let's start at the beginning – before birth…

Gestational gesturing: the prenatal impact of the immune system

Genes are not the only things that are passed on from mother to child. Factors such as maternal stress and infection may increase the risk of disorders such as schizophrenia and autism spectrum disorder by affecting brain development. This idea is supported by the animal model of maternal immune activation whereby maternally administered bacterial lipopolysaccharide (LPS) or viral (polyinosinic:polycytidilic acid) mimetic administered to a mother impacts offspring neurodevelopment and behaviour.

Prenatal pathogenicity – when the barriers fail

LPS is a component of bacteria that take the opportunities provided by infection. They may translocate into the blood and attempt to travel directly to the brain. Luckily, the blood–brain barrier begins forming during gestation (Figure 2) to act as a physical barrier for brain entry to many potentially toxic molecules. Once tight junctions are formed between the endothelial cells of the blood–brain barrier, the entry of molecules such as LPS is blocked. However, if the LPS manages to reach the brain, it may first be spotted by astrocytes which are recruited to the blood vessels at this barrier. Astrocytes can then initiate an inflammatory response which can disrupt neurodevelopment and potentially the maturation of the blood–brain barrier.

Immune infiltration initiating inflammation

Once LPS has made its way past the blood–brain barrier and has been recognized by neighbouring astrocytes, they can release different cytokines and chemokines to attract the microglia. Indeed during gestation, microglia infiltrate the brain from the periphery, and can then mature and differentiate. Microglia use chemokine signals, both chemoattractant and chemorepellent gradients in the brain to direct their movement and distribution. However, in the presence of inflammatory cytokines and chemokines from the LPS, this process will be disrupted.

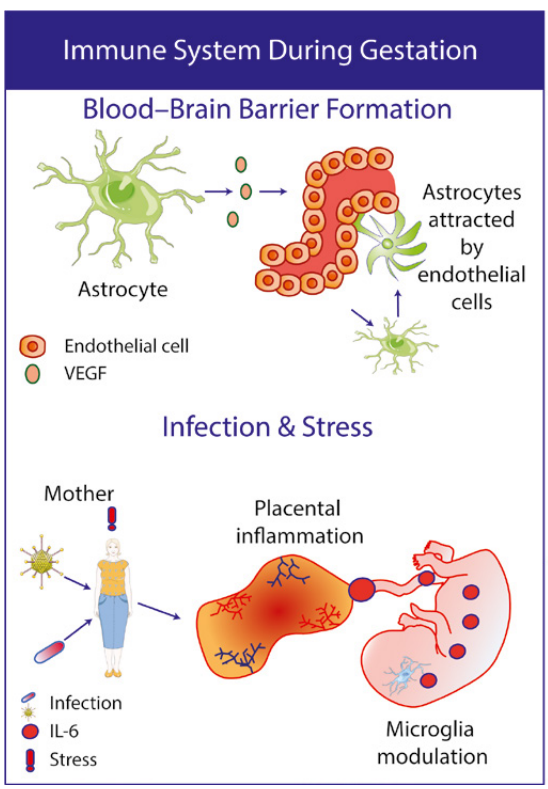

Figure 2. The immune system during gestation. In gestation, the process of forming the blood–brain barrier begins. Astrocytes release vascular endothelial growth factor (VEGF) which stimulates endothelial cells and leads to the production of blood vessels that will later form the protective barrier around the brain. Later in life, the endothelial cells will attract more astrocytes to connect with the blood vessel and help regulate blood–brain barrier function. This will protect the brain from large molecules and endotoxins by preventing their entry into the brain. Maternal stress and bacterial/viral infection can also impact neurodevelopment. It is thought that this may occur through the placenta, which acts as the communication interface between the mother and the fetus. These insults result in the upregulation of a cytokine called interleukin-6 that can then impact microglia development. This leads to negative downstream effects on behaviour and neurodevelopment.

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How does the immune system develop after birth?

Getting down and dirty – establishing the gut microbiota

Early microbial colonization is thought to occur during birth, with the composition of the community being dependent on the method of delivery. The microbiota composition in the gut will fluctuate, and depends on many factors such as diet, genetics and stress. The microbiota will begin to stabilize in parallel with brain development, where connections between neurons become more refined and unnecessary connections are pruned. In early life, they also aid in the development of a mucus layer in the gut and facilitate the development of the adaptive immune system which mounts specific responses to different pathogens. In fact, bacterial endotoxins such as LPS and peptidoglycan are recognized by toll-like receptors and help facilitate tolerance of healthy microbes in the gut. A thick mucus layer prevents bacteria and bacterial by-products from translocating into the bloodstream and causing inflammation, which also prevents exaggerated responses to commensal members of the microbiota. Recently, it has been proposed that short-chain fatty acids, produced by the microbiota in early life may mediate microglia maturation and function in a sex-specific manner throughout life. In fact, the maternal microbiota can affect the microglia in prenatal stages of development!

When intestinal barriers fail

In 2013, researchers at Caltech found that maternal immune activation altered the offspring gut microbiota, resulting in a serum increase of 4-ethylphenylsulfate (4-EPS) and anxiety-like behaviours in rodents. 4-EPS can be produced by microbes and it can then leak through the gut and into the bloodstream. In fact, this metabolite alone could induce anxiety-like behaviours in offspring, illustrating the strong connection between the microbiota and behaviour. Since stress and other factors are known to increase gut permeability, many different metabolites may leak from the gut and could lead to downstream inflammation affecting brain development and behaviour.

Stressing the small stuff – bacterial metabolites

Remarkably, stress in early life has also been linked to changes in the microbiota. These changes may result in the release of metabolites such as 4-EPS early in life, which can mount an immune response in the brain. Many psychiatric disorders, such as schizophrenia and depression have been linked to some degree of inflammation in the brain. Stress itself can impact the response of white blood cells to bacterial endotoxins and metabolites as well.

By disrupting the function of immune cells in the periphery in early life, these metabolites may impart an effect on brain development. CD4+ T cells are involved in innate immunity – specifically recognizing pathogens and attracting other immune molecules. A subset of these CD4+ T cells migrate to and can reside in the meninges, the protective membrane surrounding the brain. They are involved in cognition, inflammation, stress and learning. However, circulating bacterial metabolites or endotoxins may lead to the downstream activation of these cells, disrupting their normal role in development and causing neuroinflammation.

Cellular scissors – microglia and astrocytes in synaptic pruning

Cutting ties – practical pruning

Over the course of brain development, several new neurons are born and many new connections between neurons are made. This is facilitated by the release of signalling molecules from astrocytes. However, too many connections reduce the overall efficiency of the brain and unused connections need to be pruned during development (Figure 3). Although the astrocytes may be responsible for the formation and modulation of these synapses, once they sense that they are unused they can begin the process of pruning.

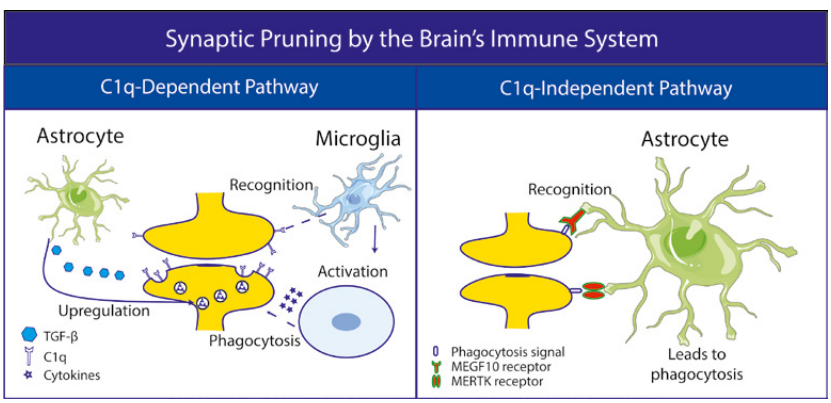

Figure 3. Cellular scissors – synaptic pruning in the brain. During early development, neurons in the brain form many connections. However, some of these connections will be unused and unnecessary and thus they are tagged and removed by the innate immune cells of the brain. In the C1q pathway, astrocytes release tumour growth factor-β (TGF-β) to these connections or synapses. This results in the upregulation of C1q, a tag that calls for cellular destruction. Microglia upon recognition of this tag will retract their many ramifications and become larger and rounder. They will release inflammatory cytokines and will engulf the synapse through the process of phagocytosis. In the C1q independent pathway, astrocytes recognize a different tag through multiple EGF-like-domains 10 (MEGF10) and MER tyrosine kinase (MERTK) receptors, resulting in the destruction of the synapse through astrocytic phagocytosis.

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Astrocytes and microglia communicate with each other through cytokines and through different tags that they leave on these synapses. Astrocytes can regulate the expression of a tag, complement cascade initiating protein (C1q), through the secretion of transforming growth factor-β (TGF-β). Microglia are able to detect this signal and switch into a pro-inflammatory state. When inactivated, microglia are small cells with many thin ramifications but upon activation, they become rounded and enlarged, to facilitate the removal of debris and pathogens. Upon recognizing C1q, microglia release pro-inflammatory cytokines and then begin to engulf the unneeded synapse through the process of phagocytosis. Astrocytes also possess a C1q-independent pathway for pruning, through the recognition of other markers on unneeded connections with their multiple EGF-like-domains 10 (MEGF10) and MER tyrosine kinase (MERTK) receptors.

In addition, both microglia and astrocytes are able to digest dead cells and debris during the course of normal development and in response to pathogens or insults.

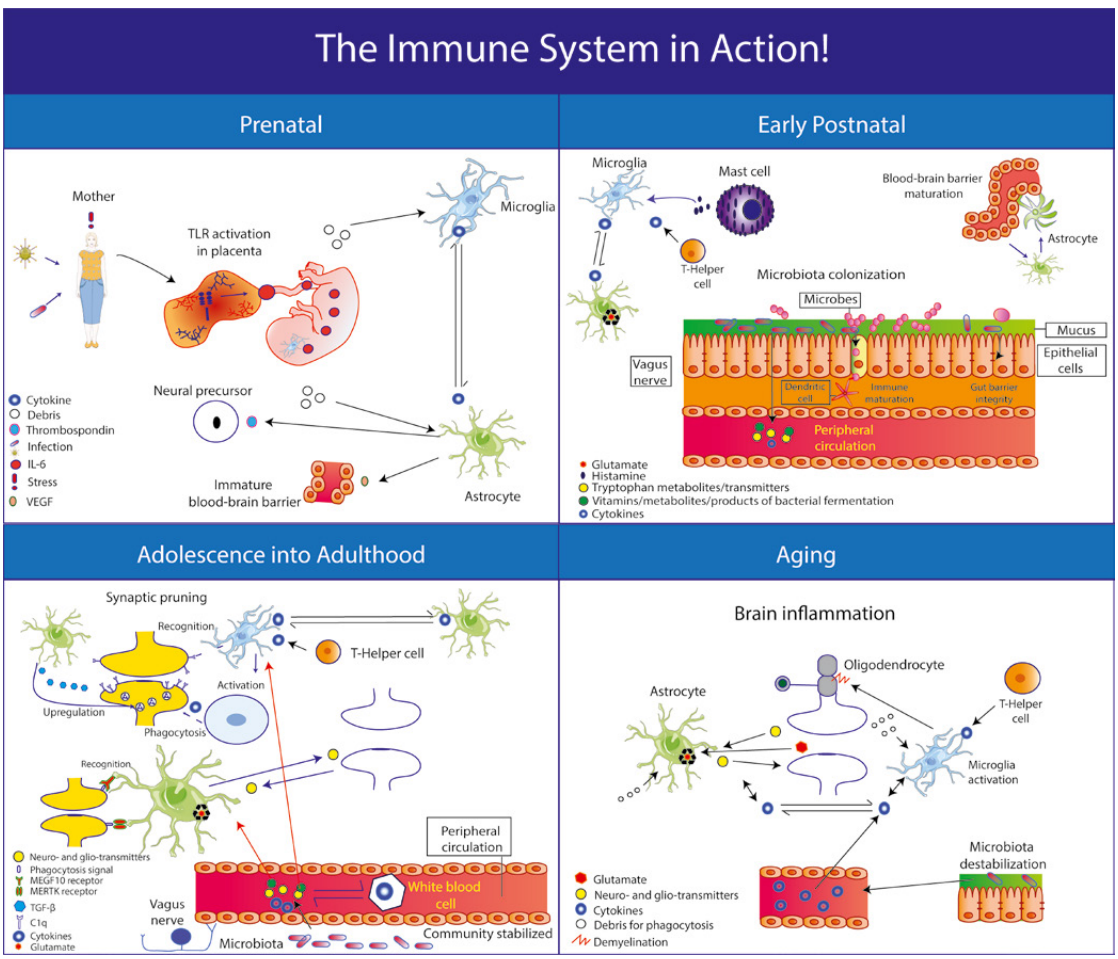

Figure 4. Immune system in action throughout the lifespan. In prenatal life, maternal factors such as stress and infection mediate fetal inflammation through interleukin-6 in the placenta. This signal travels to the brain and affects the microglia. At this point in time, the astrocytes are aiding in the proliferation and differentiation of neuronal cells, as well as beginning the process of blood–brain barrier formation through the VEGF pathway. The microglia survey the early brain environment and sweep up debris and dead cells which may occur through natural brain maturation. In the early postnatal period, the microbiota first colonizes the gut and regulates gut barrier integrity, and gut immune maturation as well as producing metabolites, vitamins and signalling through the vagus nerve. These metabolites have been shown to be important for microglia maturation and function. The microglia receive cytokine signals from T-Helper cells, mast cells and astrocytes to prime them for later development while the astrocytes aid in the maturation of the blood–brain barrier. Astrocytic endfeet will make contact at the blood–brain barrier and help regulate its function. In addition, astrocytes will continue with their regular functions (mediating neurotransmission, glutamate recycling etc.). During adolescence and leading into adulthood, the gut microbiota composition will stabilize and excess synapses will be pruned as described in Figure 3. Pruning is also influenced in a sex-specific manner by mast cells earlier in life. Finally, during aging, the gut microbiota will destabilize and the brain will receive more inflammatory signals from the periphery. The microglia may cause inflammation through the deterioration of oligodendrocytes.

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Neuroimmunity – onto bold new horizons

The immune cells in the brain may play a large role in sexual dimorphism. Specifically, there are many disorders, such as schizophrenia, which have a higher incidence in males, while other disorders, such as anxiety or depression, that have a higher incidence in females. These cells could potentially contribute to some of these differences in incidence and age of onset. Recently, a subset of immune cells called mast cells have been associated with sexual behaviour and dimorphic development of microglia in the preoptic area of the brain. Mast cells release histamine which is able to modulate inflammation in the brain. Researchers found that these cells induced neuronal and microglia masculinization in the area. Microglia recognize histamine and respond by releasing prostaglandins that are able to shape neuronal morphology and downstream sexual behaviour. Other research has found molecular differences in both gene expression and synaptic pruning between male and female microglia, strongly suggesting a role in sex-dependent wiring of brain circuitry. Perhaps a better understanding of sex-specific differences in immunity during early brain development will unlock some of the mechanisms of sexually dimorphic disorders. See Figure 4 for a summary of the unexpected and wonderful ways that the immune system is able to contribute to development! ■

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