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Innate immunity at the crossroads of healthy brain maturation and neurodevelopmental disorders

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Abstract

The immune and nervous systems have unique developmental trajectories that individually build intricate networks of cells with highly specialized functions. These two systems have extensive mechanistic overlap and frequently coordinate to accomplish the proper growth and maturation of an organism. The brain's resident innate immune cells, microglia, have the capacity to sculpt neural circuitry and coordinate copious and diverse neurodevelopmental processes. Moreover, many immune cells and immunity-related signaling molecules are found in the developing nervous system and contribute to healthy neurodevelopment. In particular, many innate immune mediators such as Toll-like receptors, cytokines, inflammasomes, and phagocytic signals are critical contributors to healthy brain development. Further exemplifying the importance of innate immune processes in nervous system formation, dysfunction in innate immune signaling has been functionally linked to many neurodevelopmental disorders including autism and schizophrenia. This review will discuss the essential roles of microglia and innate immune signaling in the assembly and maintenance of a properly functioning nervous system.

Introduction

The classic assertion that the brain is an immune privileged organ has undergone a paradigm shift. In recent years, the interplay between the immune and nervous systems has been well described in a wide array of pathological cases: from autoimmune diseases such as multiple sclerosis to more classical cognitive conditions of dysfunction like Alzheimer's disease. Beyond this, it is now recognized that immune cells also actively contribute to

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homeostatic processes in the nervous system. For instance, neuronal sensing of meningeal γδ T cell-derived IL-17 has been shown to modulate anxiety-like behaviors in mice[1]. The resident macrophages of the central nervous system (CNS), microglia, have also been freshly upgraded from a janitorial role to one of sculpting and maintaining proper circuit function, among other important responsibilities[2,3,4]. More recently, it has been recognized that signaling components commonplace in the immune system are also expressed by nervous system cells and underlie important neurological processes[5,6,7].

The activation of immune signaling pathways is most frequently associated with the detection of danger or other threats to the body. However, recent studies demonstrate that classic immunity-related mechanisms underlie many critical everyday processes in the brain. Signaling pathways that have been characterized in immune cells in response to pathogens are also utilized by neurons and glia to maintain CNS homeostasis and contribute to proper functioning of the brain. The traditional role assigned to microglia — which bear the diminutive name meaning ‘small glue’ — has been one of phagocytosing debris. Mounting evidence now illustrates that microglia contribute to network formation and are key regulators of neuronal communication[8]. Furthermore, there is increasing evidence that perturbations to the immune system during neurodevelopment can have catastrophic repercussions and lead to severe lifelong impacts on CNS function[9,10].

This Review will focus specifically on the role of innate immunity in the developing CNS. It will first give a brief overview of key neurodevelopmental processes. A few of the roles of microglia in contributing to nervous system assembly will then be introduced. The bulk of this Review will cover the functions of innate immune signaling molecules in setting up a properly functioning CNS. This discussion will include Toll-like receptors (TLRs), cytokines, inflammasomes, and phagocytosis-based proteins. Finally, immune activation during gestation and the subsequent innate immune-driven consequences on neurodevelopment will be discussed.

A crash course in neurodevelopment

The human brain contains approximately 86 billion neurons and a comparable number of non-neuronal cells, known as glia[11,12], and these numbers do not even take into account the spinal cord or peripheral nervous system. The cells of the nervous system are exquisitely interconnected and function cooperatively to receive inputs from the body and determine an appropriate output. Precise wiring and exact timing of neuronal activity are critical for proper neurological function. The means through which the nervous system is assembled and maintained throughout the lifetime of the organism is a remarkable feat and the neurobiological underpinnings of this process are beginning to be delineated.

The generation of neurons commences mid-first trimester in humans in ventricular zones whence these cells migrate to their final destinations[13]. Neural progenitor cells divide symmetrically to produce additional progenitors and asymmetrically to generate differentiated neurons[13]. Neurons are produced in these distinct proliferative zones and must migrate to their final destinations where these cells will remain for the lifetime of the organism. A pool of progenitors is retained that will later generate oligodendrocytes

and astrocytes; thus, a balance between the production of neurons and the preservation of progenitors must be maintained to achieve a proper neuron to glia ratio. The final major type of resident CNS cell are the microglia, which derive not from neural progenitors but instead hail from the haematopoietic lineage[14]. Microglia are tissue-resident macrophages that derive from early erythromyeloid precursors in the yolk sac and colonize the CNS parenchyma prior to blood–brain barrier (BBB) closure[15].

One of the common themes of neurodevelopment is overproduction followed by pruning. First, CNS-resident cells are overproduced during development, following which many undergo cell death to achieve the quantity of cells present in the mature CNS[16]. An incorrect number of neurons or synapses in any given region of the CNS can dramatically alter proper circuit function. Indeed, the overproduction of cortical neurons can alter the balance of excitatory to inhibitory neurons, and this is thought to underlie some of the network dysfunction and abnormal behaviours characteristic of neurodevelopmental disorders like autism spectrum disorder (ASD)[17,18]. Most cell death that occurs during healthy neurodevelopment is programmed, and apoptosis is believed to execute most of this neural dieback[16]. Work in recent years has uncovered other novel forms of cell death beyond the well-characterized apoptosis and necrosis. Interestingly, our studies demonstrate that pyroptosis, a gasdermin D-mediated form of cell death, also contributes to proper brain maturation by providing an alternative route of cell death for CNS cells that harbour high levels of DNA damage[19].

A defining feature of the nervous system is the connectivity between cells that underlies circuit function and information-processing capabilities. Neurons must undergo significant elaboration of processes during development to form these connections, and furthermore, the synapses that form must be productive and appropriate. Synaptogenesis involves the formation and strengthening of synaptic connections between neurons and is a process that begins during development but is continued throughout the lifetime of an organism[13]. Like neuronal cells, synapses are also overproduced and must go through a period of refinement. Indeed, the initial number of synapses formed in the developing brain is far greater than the number of synapses present in the mature brain; furthermore, synaptic pruning is crucial for the proper formation and function of many circuits. Less active synapses are actively eliminated whereas more active synapses are spared and become strengthened[20]. Neurodevelopment persists even after birth and into early adulthood, including several key processes such as neuro- and glio-genesis, cell death, synaptic pruning, and myelination.

Microglia in the developing brain

Only recently has a true appreciation been gleaned for immune cell function during homeostasis in the CNS. As the primary resident immune cells of the brain, microglia have been the innate immune cells most extensively characterized in the context of neurodevelopment. Few studies to date have investigated other populations of immune cells in the brain during development. Indeed, a limited amount of immune cells infiltrate into the adult brain parenchyma under non-inflammatory conditions, though many leukocytes and dendritic cells (DCs) can be found at boundary regions[21]. One report found $CD11c^+$ cells (identified as DCs) surrounding ventricles at E16 and P2[22]. Recent studies have

also identified small populations of T and B cells in the developing brain which are thought to support microglia maturation and oligodendrocyte precursor cell (OPC) proliferation, respectively[23,24]. Mast cells are known to reside in the adult and developing brain parenchyma and are implicated in many behaviours[25]. For instance, CNS-targeted modulation of mast cell function specifically in the maturing brain has been reported to influence masculinization and adult sexual behaviour[26]. Beyond this, whether other immune cells are present in the CNS during development and if such cells contribute to neurodevelopment remains to be discovered. In contrast, microglia have begun to be quite extensively studied in the context of nervous system development and it has become increasingly clear that these cells have the capacity to contribute to nearly every aspect of CNS formation. The contributions of microglia to neurodevelopmental processes have been extensively covered in other reviews and is beyond the scope of the current discussion[6,15,27]. This section will thus provide only a topical overview of certain key neurodevelopmental processes that microglia have been demonstrated to modulate.

Identified roles of microglia in neurodevelopment.

The immune functions of microglia are well known but these innate immune cells have essential jobs beyond their stereotypical inflammatory roles. Mounting evidence illustrates that microglia can contribute to CNS development and that disruption of proper microglial function can lead to neurodevelopmental pathology. Microglia begin to colonize the brain at E8.5, proliferate in the parenchyma and then undergo a dieback phase until adult numbers of these brain-resident macrophages are reached[27]. Evidence suggests that microglia in the developing brain are morphologically and functionally distinct from those in the adult brain[15,27]. Immature microglia are more amoeboid (a typical characteristic of activated microglia) and have unique transcriptional profiles, though are not necessarily classically activated as a less ramified morphology might imply[15,27]. Microglia follow a stepwise developmental programme that has been demonstrated to be highly sensitive to environmental perturbations[28,29]. Local or systematic changes in the signaling milieu may contribute to altered microglia development; for example, lipopolysaccharide (LPS) treatment has been shown to accelerate male microglia development[30].

Microglia are not distributed uniformly in the developing brain but associate more densely with zones that, presumably, require microglia support. For instance, microglia are found near blood vessels in the developing brain and evidence suggests that microglia may contribute to angiogenesis during neurodevelopment (Figure 1). Macrophages have the ability to stimulate sprout fusion, and secreted factors released from microglia can stimulate vessel sprouting and branching *in vitro*[31,32]. Additional work probing specifically microglia in the CNS during development will be necessary to bolster support for microglia-stimulated angiogenesis. Furthermore, it remains unknown what factors microglia release that can stimulate angiogenesis and whether additional signaling mechanisms are also at play during neurodevelopment.

It has been posited that microglia are involved in controlling the population size of other resident CNS cell types given findings illustrating that microglia secrete both growth and toxic factors, in addition to reports that microglia can directly phagocytose live neural

progenitors (Figure 1). Microglia have the capacity to directly induce cell death via the secretion of noxious factors, including reactive oxygen species (ROS) and nerve growth factor (NGF)[33-36]. Conversely, evidence suggests that microglia can also actively promote neuron survival via secretion of trophic factors and cytokines[37,38]. Finally, it has been shown *in vitro* that microglia have the ability to support astrocyte and oligodendrocyte differentiation, though *in vivo* evidence of this occurring during neurodevelopment and any functional consequences remain unexplored[39,40].

The title of professional phagocytes is merited for microglia, as these cells engulf a broad array of substances during development including live cells, apoptotic cells, debris, myelin, and synapses[20,41-44]. Microglia can be found nearby dead cells whereby microglia-mediated clearance of apoptotic bodies is likely crucial for modulating the environment[41,42]. Microglia actively phagocytose neural progenitor cells (NPCs) during developmental and adult neurogenesis, in addition to oligodendrocyte progenitor cells (OPCs), which contributes to controlling the size of the progenitor pool (Figure 1)[43,45]. Interestingly, diminishing microglial engulfment of OPCs has been shown to increase adult oligodendrocyte numbers which correlates with higher levels of corpus callosum myelination[45]. Supporting a potential role for microglia in developmental myelination, these professional phagocytes have also been demonstrated to directly engulf myelin sheaths during development, though the functional consequences of this have yet to be explored[44]. Furthermore, microglia can also directly stimulate myelination via secretory factors such as insulin-like growth factor 1(IGF1)[39,46].

The frequent association of microglia with immature axons and spines reflects the putative function of these cells in neurite growth, guidance, and pruning (Figure 1). There is evidence that microglia are involved in modulating axon outgrowth and axon tract fasciculation, suggesting an important role for these cells in neurite development[47,48]. Preliminary evidence suggests that microglia may also directly promote synaptogenesis as well as remodel presynaptic features to alter neuronal synapse function[49-52]. Mounting evidence provides support for the idea that microglia are involved in neuronal circuit formation by contributing to synaptic pruning[53-55]. Multiple studies have begun to characterize various ‘eat me’ signals on dendritic spines and axon terminals that are recognized by microglia and trigger their engulfment of weak or otherwise unnecessary neuronal processes[53,55-59]. A recent report also illustrated a non-phagocytic mechanism by which microglia contribute to the number and structure of synapses during refinement of the visual system[60]. This functional role for microglia in synaptic refinement and plasticity suggests an ability of these cells to sculpt neuronal circuitry and therefore to modulate network function, yet this has not been directly demonstrated[61-63]. Future *in vivo* work using microglia-specific manipulations, conditional knockout/in animals, and critical analysis of circuit function would strengthen support for the concept of microglia-sculpted neuronal circuitry.

The question remains whether microglia are absolutely essential to accomplish these neurodevelopmental processes or if other cell types have similar capacities thereby rendering microglia dispensable. Indeed, ablating microglia by targeted disruption of the key macrophage survival factor, CSF1R, does not overtly affect other CNS cell populations by the parameters investigated in one study[64]. Moreover, these macrophage conditional

knockout mice do not have any impairments in vision or hearing, implying that major neuronal network formation and function is not impacted by the loss of microglia in the brain. This study brings forward the notion that though microglia may be able to accomplish various essential neurodevelopmental processes (i.e. angiogenesis, phagocytosis of cells and debris, synaptic pruning, etc), in the absence of microglia other cell types may be just as competent and effectively accomplish these same functions. Nevertheless, this would not negate any essential roles for microglia during normal neurodevelopment where these cells are typically present and functional. Indeed, one study that transiently depleted yolk-sac-derived macrophages, which include microglia, from E6.5 through the first postnatal weeks found that during this time microglia contribute to proper axon extension and interneuron positioning[47]; arguing for critical roles of microglia in shaping brain development.

These putative roles for microglia are by no means a comprehensive list, moreover, undiscovered functions of microglia in shaping neurodevelopment may yet remain. As previously mentioned, there is conflicting evidence as to whether microglia are necessary to accomplish these neurodevelopmental processes, warranting further work probing all of the posited roles discussed herein. The study of microglia during neurodevelopment has only just begun and the field will benefit from the improvement and expansion of specific tools to probe microglial function. Indeed, due to a paucity of microglia-specific *in vivo* manipulations currently available, many of the reports discussed in this review lack cell-specific targeting. It has historically been quite difficult to distinguish microglia from other myeloid cells, particularly infiltrating peripheral macrophages[65], which altogether limits the ability to conclusively attribute a given process to microglia without eloquent lineage labeling. Moreover, a major limitation faced in many of these studies is the scarcity of tools to effectively study molecular signaling in microglia. Work probing intracellular signaling, receptors, and factor secretion has been more feasible *ex vivo* and *in vitro*. However, transcriptional analyses of microglia removed from the brain microenvironment have demonstrated that isolation procedures and *in vitro* conditions both trigger a loss of homeostatic gene expression and an increase in inflammatory gene expression in microglia[66]. The continued development of tools to probe the function of microglia will shed light on the neurodevelopmental processes that these cells are involved in and furthermore reveal whether microglia are essential or dispensable for such processes.

Microglial dysfunction and neurodevelopmental disorders.

As microglia have the capacity to contribute to such a broad spectrum of neurodevelopmental processes, it follows that abnormalities in microglia programmes may contribute to pathology in neurodevelopmental disorders. Mounting evidence suggests that microglia abnormalities exist in ASD and might act as a driving force or precipitating factor for this neurodevelopmental disorder[67]. A meta-analysis of transcriptomic datasets across psychiatric conditions identified enrichment for microglia and pruning-related modules in patients with ASD[68]. Microglia in the brains of autistic individuals show evidence of residing in a more activated state, characterized by an amoeboid morphology and excessive cytokine production[69-73]. Interestingly, similar microglia dysfunction has also been observed post-mortem in the brains of individuals with schizophrenia[74,75]. Various behavioural

abnormalities, such as autistic-like obsessive-compulsive behaviours and social impairments, have been attributed to neurodevelopmental microglial dysfunction[76-79].

Immune activation during neurodevelopment has been increasingly linked to various cases of neurological dysfunction. For example, maternal immune activation (MIA) has been shown to alter offspring microglial development and contribute to behavioural abnormalities[80,81]. The nervous system is highly vulnerable to environmental perturbations during development and heightened inflammatory conditions may contribute to the pathology of certain neurodevelopmental disorders. Pre- and postnatal environmental stressors can induce altered microglia morphology which is associated with various aberrant behaviours[80-84]. Abnormal immune activity during development has been shown to be a contributing factor for an altered trajectory of microglia development[30], which in turn could conceivably disrupt neurodevelopmental processes that microglia typically orchestrate. This will topic be covered in greater detail later in this review.

It is imaginable that any neurodevelopmental process to which microglia contribute may be impaired in cases of abnormal microglia development. One major contributing factor to the pathology of neurodevelopmental disorders could be impaired synaptic pruning by microglia during development. A transient reduction in microglia during the synaptic pruning phase of postnatal development is associated with impaired neurotransmission, circuit connectivity, and autistic-like behaviours[76]. Furthermore, microglia-like cells derived from individuals with schizophrenia have a higher rate of synaptic phagocytosis, suggesting that abnormal synaptic pruning by microglia might also be involved in schizophrenia pathogenesis[85]. Beyond this, faulty microglia may underlie persistent neuropathology whereby homeostatic processes in the brain controlled by microglia are disturbed as a result of impaired microglia development. Moreover, immune-induced developmental microglia alterations might act as a primer whereby immune challenge later in life acts as a second hit to precipitate adult microglial dysfunction and promote neurological disease. Altogether, these studies provide evidence for a causal link between microglia dysfunction and neurodevelopmental disease but mechanistic work investigating the particular circumstances in which this occurs as well as the specific neurobiological underpinnings will be necessary for a more complete understanding.

Innate immune signaling in the developing CNS

The previous discussion highlighted that immune cells are present in the CNS during early development and are critical regulators of proper nervous system formation and function. Beyond immune cells, molecules used for innate immune signaling are also present in the developing and mature CNS and are expressed by all brain-resident cells. These proteins were first characterized in the immune system but have recently been shown to play integral functional roles during CNS development. Innate immune molecules contribute to diverse neurodevelopmental processes including neurogenesis and gliogenesis, cell migration, regulation of cell proliferation and survival, neurite outgrowth, synaptogenesis, synapse elimination, and more. Many of these molecules are found to be dysregulated in neurodevelopmental disorders, emphasizing the functional importance of innate immune signaling for proper nervous system formation and homeostatic operation.

Toll-like receptors.

Work over the past two decades has revealed unconventional roles for TLRs in the development of the nervous system[86-90]. It is known that TLRs are expressed by microglia and NPCs during neurodevelopment[91], and by microglia, astrocytes, oligodendrocytes, and neurons in the adult CNS[92,93]. TLR1-TLR9 are expressed in the developing brain in temporally and spatially distinct patterns[91]. Microglia express a full repertoire of TLRs and have been shown to utilize such pattern recognition receptor (PRR)-mediated signaling to respond to pathogenic and other damaging insults to the CNS[86,94]. Meanwhile, other CNS cell types only express select TLRs with differing levels throughout development and into adulthood[86]. Multiple TLRs are implicated in the processes of neurogenesis, cell dieback, and in shaping neuronal morphology during development of the nervous system. In many cases, the activating TLR ligands have yet to be identified and the downstream effectors remain under-characterized. It has been posited that the overarching function of TLRs during CNS development is to guide the positioning of neurons in the appropriate microenvironment. For instance, the detection of ligands derived from dead cells might signal through TLR-mediated pathways to promote death or process retraction in that neuron. This could act to ensure that neurons avoid growth near dead cells or noxious stimuli and to regulate the proper distribution of neurons in a given region.

Studies of the adult brain act to demonstrate the functional importance of TLRs in contributing to proper neurodevelopment, as the loss of particular TLRs has been shown to contribute to various behavioural abnormalities. *Tlr2*$^{-/-}$ mice exhibit hyperlocomotion, reduced anxiety, impaired sociability, aggression and cognitive defects[95]. *Tlr2*$^{-/-}$ mice reconstituted with wild type bone marrow are also highly susceptible to high fat diet-induced obesity, suggesting a non-haematopoietic-related involvement of TLR2 in metabolic regulation[96]. Indeed in one study TLR2 was shown to act as a metabolic regulator on hypothalamic neurons to modulate feeding behaviour[96]. *Tlr3*$^{-/-}$ mice have lowered anxiety and enhanced hippocampus-dependent memory[97]. These abnormalities might be driven by an increase in hippocampal neurogenesis in these mice, which correlates with an increase in CA1 and dentate gyrus volumes[97], or as a result of altered neuronal excitability and synaptic transmission, which has been observed following the activation of TLR3 in neurons[98]. Similar memory and anxiety changes are seen in *Tlr4*$^{-/-}$ mice, in addition to disturbances in drug reward behaviour[99,100]. *Tlr7*$^{-/-}$ mice have reduced exploratory behaviours, lowered anxiety, reduced aggression, sharpened olfaction, and impaired contextual fear memory[101,102]. Furthermore, *Tlr9*$^{-/-}$ mice have been reported to have hyper-responsive sensory and motor phenotypes, with no alteration in learning and memory[103]. Finally, the TLR adaptor SARM1 is also critical for proper brain development, as *Sarm1*$^{-/-}$ mice have impairments in associative fear memory, cognitive flexibility, and sociability[104]. While these collective studies point towards roles for TLRs in the regulation of neurodevelopment and behavior, it should be stressed that these studies were largely conducted in full-body knockout mice and the possibility exists that TLR control of peripheral cytokine production and/or microbiota composition could underlie some of these reported phenotypes.

Aberrant TLR activation during development is also a significant risk factor for neurodevelopmental disorders. Neuronal TLR3 activation inhibits dendrite outgrowth, and such activation of TLR3 during postnatal development contributes to altered synaptogenesis[105]. Prenatal activation of TLR7 leads to diverse behavioural deficits alongside altered microglial cell colonization and morphology[106]. Moreover, the most commonly used model of MIA utilizes the TLR3 agonist polyI:C, which recapitulates many of the core phenotypes of ASD in offspring[107,108]. The contribution of gestational inflammation to neurodevelopmental dysfunction will be discussed in greater depth in later sections. Altogether, these behavioural studies point toward important functional consequences of TLR action in the developing brain.

Cytokines.

Multiple CNS cell types are capable of producing cytokines at the steady state and during inflammatory events, with microglia and infiltrating immune cells being the primary sources[92,109-111]. The role of cytokines in CNS infection, neurodegeneration, and injury are beginning to be elucidated, with studies demonstrating that a complicated network is at play[112-115]. Mounting evidence illustrates that cytokines mediate diverse processes such as neurogenesis, controlling the switch to gliogenesis, migration, axon pathfinding, fate specification, differentiation, survival, and likely more[111,116,117]. These processes are important in the CNS during homeostasis and pathogenesis in the developing brain as well as in the adult brain, and as a result, there is a wealth of literature describing various roles for cytokines in the brain. This section will focus on a few fundamental examples of the important roles that cytokines play during CNS development.

The IL-1 family of cytokines includes IL-1α, IL-1β, and IL-33, among others, and these are potent inflammatory mediators that classically act to activate and polarize many cell types of the immune system[118]. IL-1α and IL-1β act on the same receptor, IL-1R1 in conjugation with IL-1R accessory protein (IL-1RAP), to initiate MYD88-dependent downstream signalling that typically activates MAPK and NF-κB pathways[118]. IL-33 signals through the receptor ST2, which recruits the shared receptor subunit IL-1RAP to initiate downstream pathway activation[118]. IL-1α and IL-1β both have known roles influencing neurogenesis[110,111,116]. In some cases, IL-1β and IL-1α can promote neuronal proliferation and differentiation while in other contexts these cytokines are inhibitory to such processes[119-131]. IL-1β and IL-1α have also been shown to influence astrogliogenesis[131,132], and therefore might contribute to fate decisions during nervous system development. IL-1β has also been shown to contribute to various other neurodevelopmental process, including neuronal migration, neurite growth, and axon pathfinding[133-136]. The role of IL-1α and IL-1β during neurodevelopment is complex, and each of these cytokines likely exert effects that depend upon the cell type, microenvironment of the brain region, time point, and converging signaling cascades, among others. IL-1RAP has been shown to act as a trans-synaptic organizer to modulate synapse formation[137-139]. Intriguingly, mutations in IL-1RAP have been linked to various forms of mental retardation[140,141]. Null mutations in *Ilrapl1* in mice are associated with decreased spine density, impaired excitatory synapse formation, and deficits in synaptic plasticity in the hippocampus[139]. The same *Ilrapl1*$^{-/-}$ mice also show impaired excitatory/inhibitory balance in the cerebellum and amygdala

during development[142,143]. These studies point toward an essential role for IL-1RAP in organizing synapses during neurodevelopment.

IL-33 is an alarmin that is released during tissue damage but is also known to play homeostatic roles in tissue development and remodeling both in the periphery and the brain[144-146]. Recently, a role for IL-33 in synaptic pruning by microglia during neurodevelopment has been reported[147]. Astrocytic IL-33 release during the refinement stage of nervous system development can act as a signal to promote microglial engulfment of synapses[147]. This is mediated in part by signaling through the IL-33 receptor, ST2, on microglia (Figure 3)[147]. This process is functionally important for circuit formation in the thalamus and spinal cord, as the loss of IL-33 results in a greater number of synapses which is correlated with altered neuronal firing[147]. *Il33*$^{-/-}$ mice display lower levels of anxiety and impaired social recognition[148], which illustrates the importance for IL-33 generally in the proper function of neuronal circuits.

Many other cytokines have also been described to influence neurodevelopment. The growth factor colony-stimulating factor 1 (CSF1) and its receptor CSF1R are well accepted to be necessary for driving differentiation of tissue-resident macrophages, among other immune cell types[149-151]. It has recently been shown that IL-34, another ligand of CSF1R, produced by neurons is an essential factor for maintaining the microglial cell population in the brain[152,153]. In the immune system, IL-4 is well known to promote T helper 2 (T_H2) cell differentiation and to regulate proliferation and apoptosis of many immune cell types[154]. In the brain, IL-4 acts to promote adult neurogenesis in the dentate gyrus[155-157] and it is produced in part by meningeal $CD4^+$ T cells in response to cognitive activity[158-161]. It remains to be fully elucidated whether IL-4 plays a similar role to promote neurogenesis during development. IL-9 acts to promote T_H9 cell differentiation but is also greatly pleiotropic and exerts diverse effects on different immune cell subsets[162]. IL-9 acts on cortical neurons to reduce the expression of the pro-apoptotic factor BAX and mediate a neuroprotective effect during the cell dieback phase of neurodevelopment[163-165]. TNF, IFNγ and IFNα have also been shown to influence neurogenesis, but the majority of these studies have been done *in vitro* or in the adult brain[111]; thus, it remains unclear whether these cytokines also regulate neurogenesis during brain maturation. In summary, cytokines are a diverse set of signaling molecules that mediate multiple arms of neurodevelopment through complex mechanisms. Just as in the immune system, the cytokine network in the developing brain is intricate and pleiotropic, and significant work to understand the diverse roles of individual cytokines is certainly warranted.

Inflammasomes.

Inflammasomes are multi-protein complexes that assemble following the activation of PRRs and mediate the production of inflammatory cytokines which could also be accompanied by cell death[166] (Box 1). Unsurprisingly, microglia and other CNS-resident myeloid lineage cells express the highest levels of inflammasome components. However, inflammasome activation in neurons and astrocytes has also recently been demonstrated[92,167]. Inflammasome assembly in the CNS was first characterized in the context of microglia and other cell types responding to danger signals associated with

infection, injury, or neurodegeneration[167,168]. For instance, inflammasome activation in the CNS has been shown to contribute to the pathogenesis of neurogenerative diseases such as Alzheimer's disease, in which ASC specks, indicative of inflammasome activation, are released from microglia and can seed amyloid β oligomerization to drive disease progression[168].

The rapidly dividing state of cells during development engenders accumulation of genotoxic stress, which can persist if improperly repaired by DNA damage repair pathways[169,170]. We have recently demonstrated that AIM2 responds to DNA damage to initiate inflammasome activation during development and mediate the removal of genetically compromised cells (Figure 2)[19]. This process is dependent on the presence of gasdermin D, and the loss of AIM2 leads to a greater number of neurons in the adult brain harbouring higher amounts of DNA damage[19]. Altogether, these findings suggest that pyroptotic cell death during neurodevelopment, orchestrated by the AIM2 inflammasome, is necessary for proper brain formation[19]. The AIM2 inflammasome has also been demonstrated to regulate neuronal morphology *in vitro* in response to exogenous dsDNA and *in vivo* during development[171].

It has yet to be fully explored whether other inflammasomes (for example, the NLRP3 inflammasome or the NLRP1 inflammasome) contribute to homeostatic neurodevelopment. Nevertheless, behavioural abnormalities seen in caspase-1- and AIM2- deficient mice are absent in NLRP3-deficient mice, suggesting that perhaps other inflammasomes are less necessary for proper nervous system formation[19]. Inflammasomes present an intriguing platform for sensing of internal cellular stress which can be commonplace during development. Additional work on this front utilizing CNS cell-specific knockouts and other more targeted approaches will contribute to a more precise understanding inflammasome function during the formation and maintenance of a properly functioning nervous system.

Phagocytic signals.

Various "find me", "eat me", and "don't eat me" signals regulate the phagocytosis of dead cells, debris, and other cargoes by professional phagocytes. The resident professional phagocytes of the CNS, microglia, employ these signals to engulf such remains. Interestingly, microglia have also been described to phagocytose synapses during development and many innate immune-based phagocytic signals have recently been implicated in this process. The complement system in particular, along with other phagocytic receptors, have been the first to being to be characterized in synaptic pruning during neurodevelopment.

The complement system, comprised of an intricate web of pathways, has been extensively characterized as a key platform for host defense against invading organisms. The primary roles of complement in host protection are opsonization, recruitment of leukocytes, initiation of inflammation, and direct lysis of foreign microbes; thus, complement acts as a first line of defense as well as a bridge between innate and adaptive immunity[172] (Box 2). Complement proteins can be membrane-bound or circulate throughout the body as inactive zymogens. Binding of inactive complement proteins to surface structural motifs triggers proteolytic cleavage and the activation of downstream signaling events[173]. Complement activation drives diverse immunological processes, including the clearance of immune complexes

and debris, discrimination between healthy and apoptotic or foreign cells, angiogenesis, mobilization of haematopoietic cells, regenerative processes, and more[172,174].

Beyond peripheral inflammation, complement has also been implicated in many different states of brain dysfunction with inflammatory pathology, including but not limited to meningitis, traumatic brain injury, stroke, and neurodegenerative diseases such as Huntington's disease, Alzheimer's disease, and Parkinson's disease[175,176]. The majority of complement proteins are produced by the liver[177]. The brain is protected by the BBB, the arachnoid barrier, and the blood–CSF (cerebrospinal fluid) barrier at the choroid plexus, which together limit immune cell infiltration and plasma protein influx under homeostatic conditions[178]. Inflammatory conditions in the brain are associated with barrier leakage, which might account for the roles of complement in diseases characterized by such immune infiltration; however, two decades ago complement proteins were identified in the brain even under healthy conditions[179,180]. It is now known that CNS-resident cells are capable of synthesizing select complement proteins and receptors with varying levels across developmental ages and often diminishing levels through maturation, and more recent work has shown that complement plays a role in the brain during homeostasis[20]. Complement has been shown to be involved in neurogenesis, neural migration, neuronal survival, and synaptic pruning during neurodevelopment[20,176], but the discussion here will be limited to its putative role in synapse elimination.

Mice deficient in C1q, C3, or C3R fail to undergo proper retinal ganglion cell (RGC) circuit refinement in the lateral geniculate nucleus (LGN) that is necessary for eye-specific segregation[53,56,181]. Interestingly, C1q and C3 localize to RGC synapses *in vivo* during the synaptic refinement period[181], and microglia have been shown to engulf RGC synapses in a manner dependent on CR3 and neuronal activity (Figure 3)[53]. Early *in vitro* work demonstrated that the presence of astrocytes induces the upregulation of C1q in neurons[181]. A follow up report showed that astrocytic release of TGFβ was necessary and sufficient to induce RGC C1q expression *in vitro*. Further, mice lacking the TGFβ receptor in the retina lack C1q-tagged RGC synapses and phenocopy the eye-specific segregation defects seen in C1q, C3, and CR3 deficient mice[56]. Together, this work suggests a mechanism whereby weak synapses are tagged by complement components to be engulfed and eliminated by microglia. However, these studies were all conducted using germline knockout mice, thus, it remains feasible that the loss of complement signaling outside of the CNS may contribute at some level to the observed phenotypes. Future work will be required to elucidate the full extent to which CNS-specific versus peripheral events are involved in developmental synapse elimination.

Astrocytes are also able to directly engulf C1q-tagged synapses via MEGF10, a known C1q receptor, and MERTK, which is known to function in the phagocytic clearance of dead cells via recognition of extracellular phosphatidylserine (Figure 3)[182,183]. The finding that these phagocytic receptors typically utilized for the clearance of dead cells raises the possibility that synapses might use 'eat me' signals similar to that of dead cells in order to recruit and promote glial phagocytosis. It is indeed likely that local apoptotic-like mechanisms regulate the removal of complement-tagged synapses, as C1q-labeled synaptosomes are associated with caspase-3 and annexin V (Figure 3)[184]. Diminished neuronal activity leads to higher

levels of synaptic C1q and elevated caspase-3 cleavage, suggesting that neuronal apoptotic-like signaling aids microglial-mediated process removal of complement-tagged synapses[184]. The caspase-mediated apoptotic cascade results in the transfer of phosphatidylserine from the inner to the outer leaflet of the plasma membrane[185,186]. Intriguingly, newly published work and pre-print articles demonstrates that neuronal synapses to be pruned expose phosphatidylserine, which acts as an ‘eat-me’ signal for microglial phagocytosis (Figure 3)[57-59]. Pushing the system by forcing continuous phosphatidylserine exposure on neurons leads to specific elimination of inhibitory post-synaptic terminals[57]. Phosphatidylserine can be recognized by phagocytes via both the phagocytic receptor triggering receptor expressed on myeloid cells 2 (TREM2) and by an alternatively spliced isoform of the adhesion G-protein coupled receptor GPR56 (Figure 3)[59,187]. Interestingly, the loss of C1q leads to an increase in synaptic phosphatidylserine but a decrease in microglia-mediated synaptic pruning during development[187], suggesting that phosphatidylserine acts as a common signal in microglial phagocytosis of synapses along multiple pathways. An explanation for how the decrease in one ‘eat-me’ signal leads to the elevation of another is lacking, as the precise link between these two pathways has yet to be worked out.

Receptors involved in phagocytosis do not exclusively promote engulfment, indeed, a variety of ‘don’t eat me’ signals and receptors have been characterized in the immune system and may also play a role in limiting phagocytosis during neurodevelopment. In the immune system, the receptor CD47 is expressed by many cells throughout the body and acts to limit inappropriate engulfment of healthy cells by binding its receptor, SIRPα, on professional phagocytes[188]. CD47-SIRPα interaction has been observed in the context of the nervous system whereby CD47 can act as a presynaptic receptor for postsynaptic SIRPα, and activity-dependent shedding of SIRPα can drive synapse maturation in the hippocampus[189]. At an earlier developmental stage in the LGN, CD47 can also be found on synapses while SIRPα is enriched specifically in microglia[190]. Here, CD47 acts as a ‘don’t eat me’ signal recognized by SIRPα and is specifically upregulated on more active synapses during development, thereby preserving the pruning of strong synapses (Figure 1)[190]. The complement pathway can also be directly inhibited to limit synapse elimination during development. Specifically, the sushi domain protein SRPX2 binds C1q and evidence suggests that this interaction can preserve synapses from microglial engulfment in certain developing brain regions (Figure 3)[191]. It should be stressed that the studies discussed here were conducted primarily using global knockout animals or isolated cell cultures; thus, the cell specificity and developmental importance of these processes require further interrogation. Nevertheless, these studies highlight the varied use of innate immune-based receptors during neurodevelopment.

The importance of phagocytic signaling for homeostatic CNS development and function is highlighted by the association between disturbances in complement and neurodevelopmental disorders. A risk for schizophrenia is associated with certain *C4* risk alleles that tend to produce heightened levels of C4[192]. It is intriguing to consider that the deposition of C4 may promote increased synapse elimination by microglia and promote neuropathology of schizophrenia[85,192]. Certain alleles of complement control-related genes have also been identified as risk factors for schizophrenia[193]. Evidence for complement-mediated pathogenesis is also found in ASD. Elevated serum C1q levels have been reported in

children with ASD[194,195], and *C4* risk alleles as well as decreased plasma C4B levels have been associated with ASD[196-198]. These links suggest that complement dysfunction may contribute to neurodevelopmental disorder pathology.

Maternal immune activation

Neurodevelopment is a beautifully coordinated and precise process that requires expert timing and organization for proper execution. Disruption at any stage could potentially have dire consequences from the molecular to the circuit level. Countless epidemiological studies in the past few decades have linked maternal infection during pregnancy with a heightened risk for neurodevelopmental disorders[199-201]. Maternal infection with rubella and influenza viruses, *Toxoplasma gondii* and multiple other diverse types of pathogens have been increasingly correlated with many complex cases of neurological dysfunction[107,202,203]. Maternal risk factors for abnormal immune system activation during pregnancy, such as autoimmune disease, diabetes, and certain genetic risk variants, have also been tied to offspring neurologic dysfunction[204]. Environmental insults capable of causing inflammation, such as maternal stress, maternal obesity, pesticides and pollution, are additional risk factors for future offspring neuropathology[205]. These studies paired with clinical observations have illustrated that maternal immune activation is a significant risk factor for neurodevelopmental disorders including ASD, schizophrenia, cerebral palsy, and epilepsy as well as being a potential precipitating factor for neurodegenerative disease[9].

In reality, many factors likely converge to contribute to disease onset, which might include the level of immune activation and the type of immune response, as well as other factors such as genetic predisposition, maternal diet, prenatal stress, and more. Nevertheless, immune activation certainly accounts for a piece of the puzzle, and the commonalities in signaling pathway between the nervous and immune systems described in this review provide a basis for such interaction. For instance, neurons use many of the same signaling pathways as immune cells, such that immune infiltration and inflammatory signaling could possibly converge to incite dysfunction during development. Immune activation alone could alter the delicate signaling milieu of nervous system tissue enough to cause lifelong alterations. Furthermore, abnormal maternal immune activity might permanently alter the fetal immune system or prime it for dysfunction later in life. This idea is supported by the observation that patients with autism or schizophrenia often show immune dysfunction[69,206,207].

Studies conducted over the past two decades have provided direct links between MIA and offspring brain dysfunction and behavioural abnormalities that are typical of ASD or schizophrenia[9,10,107,202,203,208]. Numerous mouse models of MIA have been used to study this phenomenon, with differences in the type of immunogen, timing and dose used for challenge all contributing to distinct phenotypes[9,10,107,202,209]. Importantly, maternal infection in humans does not always lead to neurodevelopmental disorders in offspring but instead might act as a primer for future ‘hits’, including risk factors such as genetic predisposition, stress or other environmental insults[9,10,205,210-212]. Maternal inflammation likely acts as a primer for synergistic effects precipitating disease symptoms. The MIA mouse model is amenable to incorporating multiple hits, for instance, one version combines

prenatal low-dose polyI:C exposure with postnatal sub-chronic stress[213]. Such work using these heterogeneous models has begun to unravel the biological underpinnings of MIA-driven neurological dysfunction. The phenomenon of MIA-induced neurological dysfunction and current animal models of MIA have been thoroughly reviewed in the past decade[9,10,67,107,202,204,209]; here, we will highlight a few examples and emerging key players. MIA has been linked to a wide array of neurological conditions, but below we will focus here on MIA as a precipitating factor for ASD.

Autism-spectrum disorders are a group of multifactorial disorders in which a convergence of genetic and environmental risk factors is posited to contribute to the onset of neurological dysfunction as a result of developmental abnormalities[214]. The symptoms of ASD, which are diverse in etiology and severity, are characterized by the American Psychiatric Association as deficits in social–emotional interactions and/or communication as well as stereotypical or repetitive behaviours[215]. Maternal inflammation is a risk factor for ASD diagnosis and signs of neuroinflammation have been reported in individuals with ASD[9,69,216,217]. For instance, elevated levels of TNF, IL-1β, IL-6, IL-13, and CCL2 have been measured in the CSF of individuals with ASD[218]. In the most frequently used mouse model of MIA-induced ASD, pregnant mothers are injected with the dsRNA viral mimetic polyI:C at or around E12 (Figure 4)[9,10,107,202]. Offspring from these mice display core symptoms associated with ASD including communication deficits, impaired sociability, and repetitive behaviors (Figure 4)[9,10,107,202]. There has been immense variability in the field both in the types of MIA models employed as well as the resulting phenotypes observed. The baseline immunogenicity of dams, strain microbiota composition, type of immune response induced, and polyI:C treatment regimen all have been shown to contribute to the susceptibility of the pregnancy to induce offspring behavioral phenotypes[219,220]. These factors are notable as it speaks to the variability that is also associated with the human condition; however, it also complicates interpretation of data from these studies.

MIA induces alterations in fetal brain cytokine and cytokine receptor levels that differ in levels across brain regions in an age-dependent manner (Figure 4)[221,222]. The first reports identified placental IL-6 as a key mediator of neuropathology and long-term behavioural deficits in the MIA model of neurodevelopmental disorders[108,223,224]. MIA-induced IL-6 production promotes excess neurogenesis and contributes to an overabundance of cortical neurons, particularly in layers IV and V[225,226]. Interestingly, human maternal IL-6 levels have been shown to predict child working memory performance[227]. The cytokine IL-17a has also been linked to MIA-induced behavioral abnormalities in mouse models[228]. T_H17 cells, a subset of helper T cells that respond to extracellular bacterial and fungal infection, characteristically produce high levels of IL-17A. One study found that maternal RORγt-expressing T_H17 cell-mediated production of IL-17A is necessary and sufficient for the induction of atypical cortical development and ASD behavioural phenotypes in offspring[228]. Importantly, the acute and conditional targeting approaches employed in these studies strongly suggest that the behavioral abnormalities observed in the MIA offspring are due to gestational inflammation-induced changes in neurodevelopment and not due to the ability of IL-17a to affect mucosal barrier function or alterations in microbiota composition in the offspring. Connecting the earlier studies identifying critical roles for IL-6 in the MIA model with these more recent IL-17a findings, it is known that IL-6 is a key cytokine involved in

the differentiation of T_H17 cells. This raises the possibility that IL-6 may be upstream of IL-17a in this model of MIA-induced neurodevelopmental disorders.

The gut not only tunes the immune compartment but also directly influences cognition, acting as a critical nexus of brain–immune interaction. Maternal microflora colonize the fetal gut and commensal bacteria influence immune system development by coordinating the maturation of specific immune cell subsets[229,230]. Dysbiosis and gastrointestinal dysfunction, perhaps primed by maternal microflora, are common in ASD and may modulate immune and neurological dysfunction[231-235]. Interestingly, maternal gut microbiota that calibrate T_H17 cell responses, such as segmented filamentous bacteria (SFB), increase the risk for MIA-induced neurodevelopmental disease pathogenesis in rodent models[220,235]. Moreover, treating MIA offspring orally with *Bacteroides fragilis* is sufficient to correct gut dysfunction and many autistic-like behavioural abnormalities[234]. These studies point toward a critical gut–brain immune connection that is disrupted in ASD and may be influenced by MIA.

One report found that the offspring of mice exposed to MIA harbour atypical cortical patches that localize highly to the dysgranular zone region of the primary somatosensory cortex (S1DZ), and the size of these patches correlates with behavioural abnormalities[236]. These patches contain fewer parvalbumin $(PV)^+$ interneurons, which corresponds to hyperactivation in the region[236]. This work reported that hyperactive S1DZ projections to the striatum and temporal association cortex accounted for abnormal repetitive and social behaviours, respectively, in the MIA offspring[236]. Interestingly, some individuals with ASD experience milder symptoms during the course of fever[237]. One study challenged MIA offspring with LPS to induce systemic inflammation which resulted in a temporary reduction in S1DZ activity and subsequent reversal of behavioural deficits[238]. This effect was driven by a rise in brain levels of IL-17A, and direct IL-17A injection but not artificially induced fever was sufficient to also rescue social behavioural deficits in multiple monogenetic models of ASD, but not controls[238]. This work suggests that MIA might act to prime the immune system during fetal development and provides proof-of-principal evidence that subsequent exposure of neonates to IL-17A-mediated inflammation postnatally can serve beneficial effects. The mechanism(s) underlying the ability of IL-17A to promote improved sociability in mouse models of neurodevelopmental disorders still remains to be further explored. It is possible that some level of tonic IL-17A signaling in the brain is needed to sustain social behavior and that exposure of the developing brain to inflammation causes epigenetic changes to neural cells that render them less responsive to baseline IL-17a later in life. Beyond this, whether IL-17a plays any role in human conditions of neurodevelopmental dysfunction has yet to be investigated.

Conclusion

The long-held belief that the brain is an immune privileged site has undergone a paradigm shift as a large body of work now illustrates that the immune and nervous systems are critically intertwined. Neural cells influence immune function and immune cells impact neurogenic processes from early developmental stages throughout the lifetime of an organism. Immune cells, such as microglia, appear to have the capacity to influence a

number of diverse processes involved in nervous system assembly. Innate immune signaling mechanisms are widespread in controlling neurodevelopmental processes. Indeed, many signaling molecules are conserved among immune cells and CNS-resident cells, while some have unique functions in each system. Although first characterized in the immune system, the importance of these innate signalling molecules for homeostatic processes in the nervous system illustrates that such initial categorical definitions are immaterial. Moreover, immune cells and innate immune signaling molecules have been implicated in a wide array of neurodevelopmental disorders, further exemplifying the functional importance of immune-related pathways in the development and maintenance of the nervous system. Improper activation of the immune system during neurodevelopment can lead to severe and persistent impairments in physiological processes, with effects ranging from aberrations in the gut microbiota composition to altered cognitive function. The future study of innate immunity in neurodevelopment will continue to shed light on homeostatic processes that sculpt the CNS and may also reveal therapeutic strategies to treat various neurodevelopmental disorders.

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Glossary

Axon tract fasciculation
collective axon growth in a bundle that will eventually constitute a nerve tract.

Segmented filamentous bacteria (SFB)
a group of commensal bacteria that attach to the ileal epithelium of mice and promote T helper 17 (T_H17) cell development.

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Box 1:

Inflammasomes.

In the canonical model of inflammasome activation, cytosolic PRR sensors activate in response to intracellular PAMPs or DAMPs, which triggers oligomerization and promotes recruitment of caspase-1. Most inflammasomes use the adaptor protein ASC to bridge the sensor with caspase-1. Assembly of this platform facilitates activation of caspase-1, which then acts to cleave downstream target molecules that promote a pro-inflammatory state. Important effectors of inflammasome assembly include the activation of pro-inflammatory cytokines IL-1β and IL-18, as well as cleavage of gasdermin D which can assemble to form pores in the plasma membrane[166]. Gasdermin D pores facilitate cytokine release from the cell and can also lead to a type of cell death known as pyroptosis, which may be avoided via ESCRT-mediated membrane repair[239].

Box 2:

Complement.

In the periphery, complement can be activated along three arms, the alternative, lectin, and classical pathways, all of which generate a C3 convertase. The alternative pathway is constitutively active at low levels through constant spontaneous hydrolysis of soluble C3. This leads to downstream cleavage events which ultimately produces a membrane-bound C3 convertase made up of C3b and Bb proteins. The lectin pathway is activated by mannose-binding lectin binding to foreign carbohydrate motifs, which stimulates the cleavage of MASP1 and MASP2. The classical pathway requires antibody production and is initiated by antibody-antigen interaction triggering C1q-mediated cleavage of C1r and C1s. The initiation of the lectin and classical pathways triggers the cleavage of C2 and C4 into C2a/C2b and C4a/C4b, respectively, of which C2a and C4b together form another type of a membrane-bound C3 convertase. All of the pathways converge at the formation of a C3 convertase, which cleaves C3 into C3a and C3b, of which C3a acts as an anaphylatoxin to promote inflammation and C3b can act as an opsonin. Binding of C3b to the C3 convertase generates a C5 convertase, which cleaves C5 into the anaphylatoxin C5a and C5b. C5b can initiate the formation of the membrane attack complex, comprised of C6, C7, C8, and C9, which is responsible for direct lysis of the target cell. CNS resident cells express all of the complement components C1-C5 and low levels of components of the membrane attack complex (namely, C6-C9)[172].

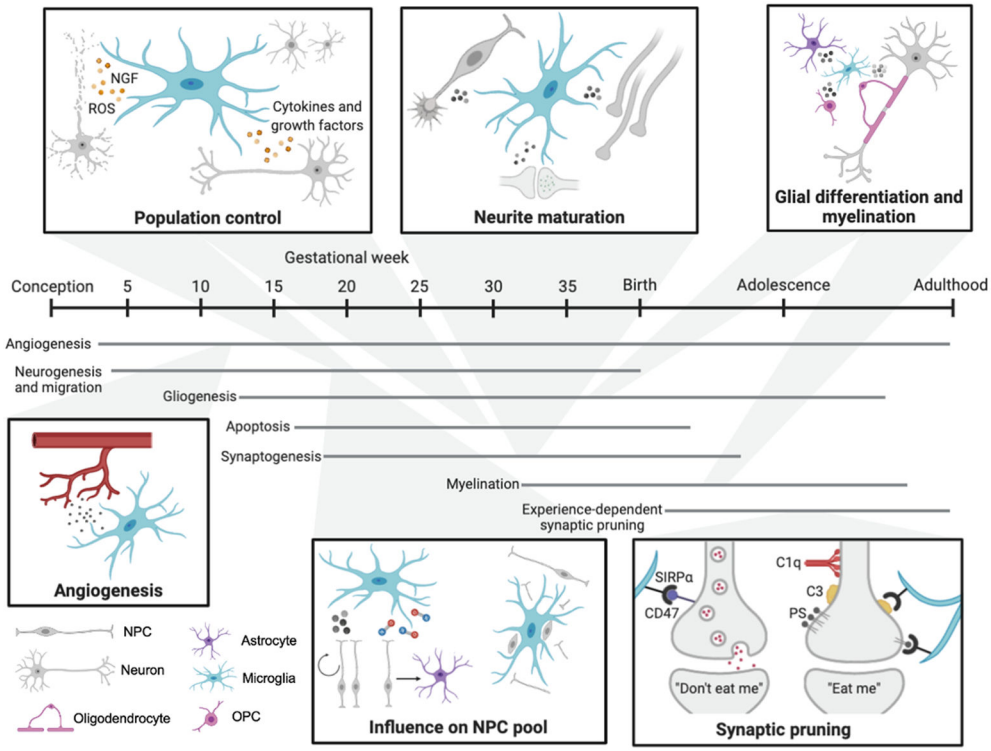

Figure 1. Microglia influence a number of neurodevelopmental processes.

Population control: microglia phagocytose immature neurons in proliferative regions, directly promote cell death (via release of reactive oxygen species (ROS) and NGF), and support cell survival (via secreting pro-survival molecules such as growth factors and cytokines). Neurite maturation: microglia promote synaptogenesis, influence neurite outgrowth, and regulate axon tract fasciculation through released factors. Glial differentiation and myelination: microglial secreted factors support oligodendrocyte and astrocyte differentiation and microglia can influence myelination. Angiogenesis: microglia associate with vasculature and influence angiogenesis via yet to be determined secreted factors. Influence on NPC pool: microglia influence the size of the neural progenitor pool by secreting factors that promote NPC proliferation and by directly phagocytosing live and dead NPCs. Nitric oxide-releasing microglia can promote the switch from neurogenesis to astrogliogenesis, thereby influencing the ratio of neurons to glia. Synaptic pruning: microglia recognize and eliminate inactive synapses. Phosphatidylserine (PS) and complement components tag unnecessary synapses and act as “eat me” signals when recognized by microglia phagocytic receptors. Active synapses are protected by CD47 which, when recognized by SIRPα on microglia, acts as a “don’t eat me” signal.

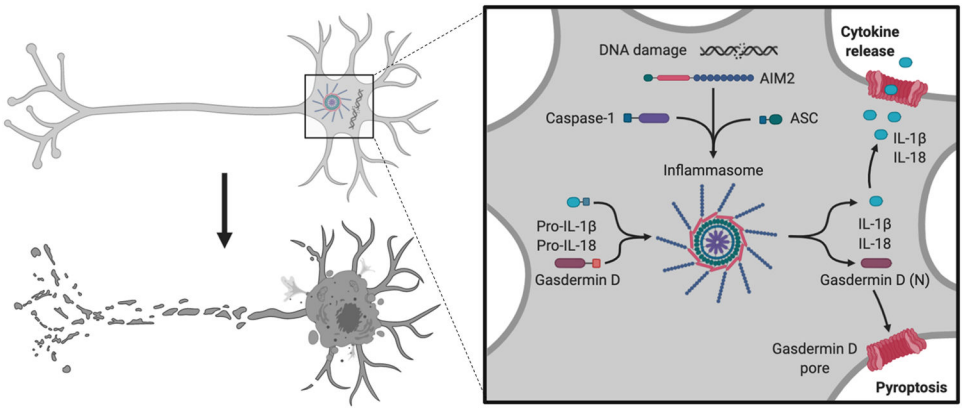

Figure 2: Inflammasome signaling contributes to cell death and neuronal morphology.

Binding of AIM2 to cytosolic DNA initiates assembly of AIM2, caspase-1, and ASC to form the inflammasome multiprotein complex. Inflammasome activation cleaves gasdermin D, of which the N-terminal fragments assemble to generate pores in the membrane to promote cytokine release and pyroptosis. Activation of the inflammasome also cleaves pro-cytokines IL-1β and IL-18 to generate active forms which can be released from the cell; however, cytokine signaling does not appear to be involved in neurodevelopmental removal of genetically compromised cells.

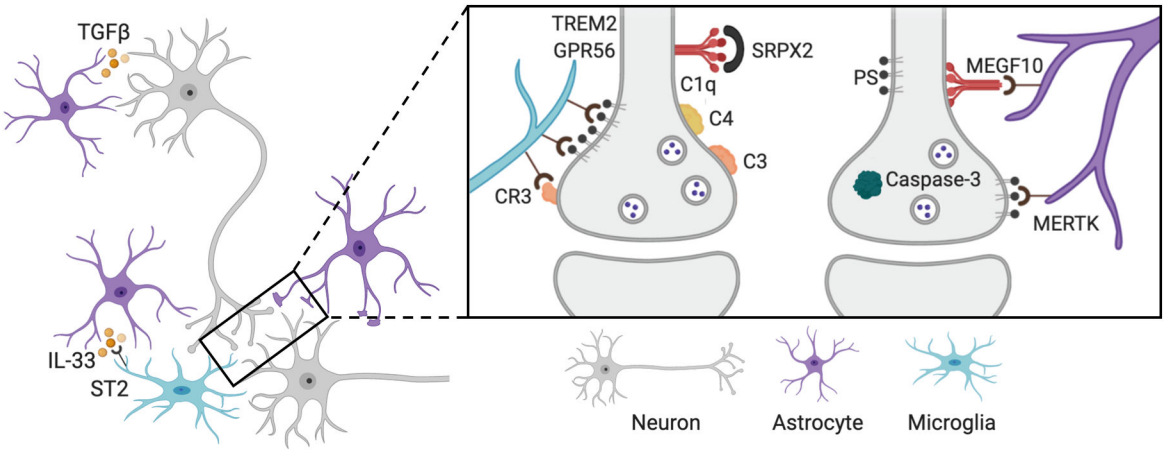

Figure 3: Phagocytic signaling underlies synaptic pruning.

IL-33-ST2 signaling promotes synapse engulfment in the spinal cord and thalamus. Complement proteins (C1q, C4, and C3) are thought to mark synapses for elimination in the LGN. Astrocytes can release TGF-β to upregulate C1q on neurons. Recognition of C1q by MEGF10 is associated with astrocyte synapse elimination while CR3 recognition of C3 is associated with microglia synapse phagocytosis. Complement-mediated synapse elimination can be limited by SRPX2 binding of C1q. C1q-tagged synapses are also associated with caspase-3 and increased extracellular phosphatidylserine (PS). The phagocytic receptors TREM2, GPR56, and MERTK are thought to recognize extracellular PS and promote synapse elimination.

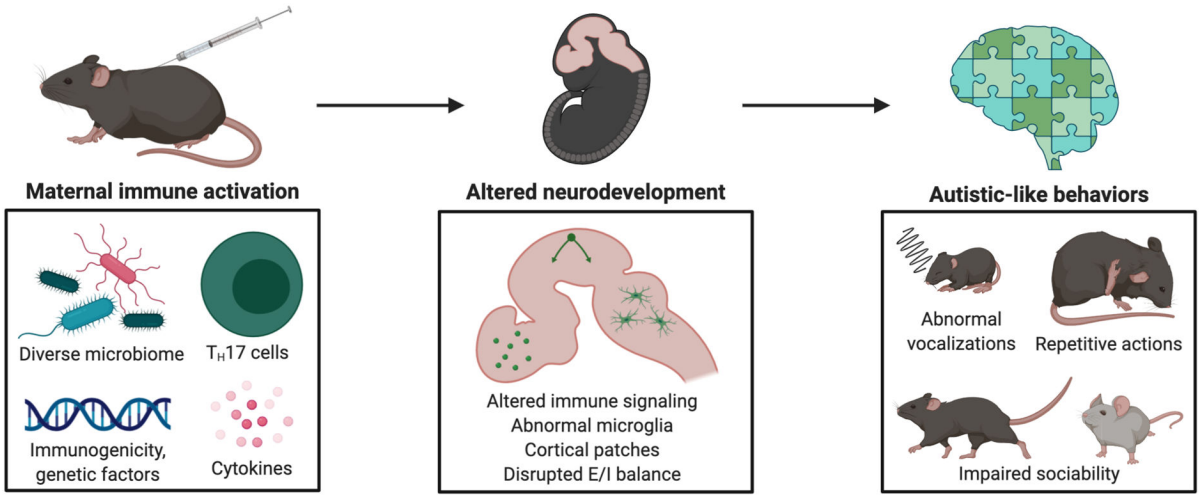

Figure 4: Maternal immune activation promotes abnormal brain development and autistic-like behaviors.

Induced inflammation during pregnancy promotes inflammatory signaling that can influence embryonic development. Many factors including the maternal microbiome, T_H17 subset, baseline immunogenicity, genetic factors, and cytokine response may impact the susceptibility of the pregnancy to downstream offspring neurodevelopmental defects. Inflammatory mediators at the maternal-fetal interface may impact brain maturation through diverse mechanisms; including altered brain immune signaling, abnormalities in microglia, and cortical malformations that contribute to an altered balance of excitatory to inhibitory neurons (E/I). MIA offspring display autistic-like behaviors characterized by abnormal communication, stereotyped/repetitive actions, and impaired sociability.