Maternal immune activation and abnormal brain development across CNS disorders

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Abstract | Epidemiological studies have shown a clear association between maternal infection and schizophrenia or autism in the progeny. Animal models have revealed maternal immune activation (mIA) to be a profound risk factor for neurochemical and behavioural abnormalities in the offspring. Microglial priming has been proposed as a major consequence of mIA, and represents a critical link in a causal chain that leads to the wide spectrum of neuronal dysfunctions and behavioural phenotypes observed in the juvenile, adult or aged offspring. Such diversity of phenotypic outcomes in the mIA model are mirrored by recent clinical evidence suggesting that infectious exposure during pregnancy is also associated with epilepsy and, to a lesser extent, cerebral palsy in children. Preclinical research also suggests that mIA might precipitate the development of Alzheimer and Parkinson diseases. Here, we summarize and critically review the emerging evidence that mIA is a shared environmental risk factor across CNS disorders that varies as a function of interactions between genetic and additional environmental factors. We also review ongoing clinical trials targeting immune pathways affected by mIA that may play a part in disease manifestation. In addition, future directions and outstanding questions are discussed, including potential symptomatic, disease-modifying and preventive treatment strategies.

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Introduction

The link between disturbances of early CNS development and neuropsychiatric and neurological disorders later in life[1] has been increasingly recognized in the past 20 years.[2,3] Dynamic and interactive models of neural development highlight the crucial interplay of genetic, epigenetic and environmental factors in guiding, shaping and supporting the increasingly complex and elaborate architecture of the growing brain.[4] Considering the highly orchestrated processes of neural development—starting with proliferation of glia and neurons and their migration, followed by programmed cell death, formation of synapses, myelination, and establishment of neuronal circuits (Figure 1)—inflammation in the mother during pregnancy can affect several vulnerable aspects of fetal brain development. This disturbance may contribute to causal chains of events, leading to a wide spectrum of neuronal dysfunctions and behavioural phenotypes observed in the juvenile, adult or aged progeny (Figure 2).

Two canonical neurodevelopmental disorders recognized as particularly sensitive to early insults to the CNS are schizophrenia and autism. In both disorders, epidemiological studies have shown an association between maternal infection and the child's subsequent risk of the condition.[5,6] Parallel studies in rodents that employed prenatal infections with human influenza virus revealed potent detraction from the fundamental processes of neurodevelopment, which were sufficient to induce long-term structural and functional changes in the offspring's brain.[7–11] Further investigations in animal models revealed that the behavioural changes were attributable to the maternal immune response to the pathogen and not caused by the virus itself.[12–14]

More-recent evidence from experimental models and clinical observations suggests an interaction between the timing, intensity and possibly the nature of the immune exposure, together with additional environmental factors and genetic predisposition, thereby defining symptom clusters[15] and, ultimately, the phenotype of the resulting neurological disease. As will be discussed here, critical mediators of these effects are the microglia, which direct and maintain neuronal differentiation and maturation while playing a pivotal part in synaptic pruning, neural circuit formation and homeostasis.

In this Review, we present the epidemiological, preclinical and clinical evidence bridging maternal immune activation (mIA) models to various CNS disorders in humans, starting with the strongest epidemiological links: schizophrenia, autism spectrum disorder (ASD) and epilepsy. We further evaluate the emerging evidence for a putative link between mIA and cerebral palsy, Alzheimer

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Key points

- The developing brain is particularly sensitive to environmental signals that influence genetically determined developmental processes
- Infection-induced maternal immune activation (mIA) during pregnancy can have a profound impact on developing neural circuits
- Strong epidemiological associations exist between exposure to various infections during pregnancy and greater risk of schizophrenia, autism or epilepsy in the progeny
- Emerging evidence suggests similar links for disorders like cerebral palsy and ageing-associated neurodegenerative diseases, positioning mIA as a factor in the brain's responsiveness to cumulative lifetime exposure to environmental insults
- Microglia constitute the primary immune mediators of neural functions, and their mIA-induced priming is thought to underlie some of the persistent immunological and/or neurological changes associated with mIA
- Targeting of immune-related pathways might represent a promising therapeutic strategy for neurodevelopmental, psychiatric and neurological disorders

disease (AD) and Parkinson disease (PD); discuss convergent and divergent pathogenetic mechanisms, including the pivotal event of microglial priming that might underlie mIA; and assess the validity of preclinical mIA models for studying these neurological disorders. We conclude with a comprehensive overview of disease prevention, diagnosis and treatment strategies that focus on symptomatic aspects of diverse CNS disorders, as well as emphasizing the potential implementation of therapies that target immune pathways, guided by genes and biomarkers that indicate immune dysregulation, and that are timed to different disease stages.

Clinical evidence for a role for mIA

Schizophrenia

For schizophrenia (Box 1), strong epidemiological associations have been found with various maternal infectious exposures[6,16] including influenza,[17–20] *Toxoplasma gondii*,[21,22] herpes simplex virus type 2,[23–26] as well as urinary tract and other types of infections.[27–29] Increased expression of cytokines—including IL-6, tumour necrosis factor (TNF) and CXCL8 (previously known as IL-8)[30,31] and, as discovered recently, C-reactive protein levels[32]—during pregnancy is significantly associated with an increased risk of schizophrenia in the offspring. The highest odds ratios for infectious exposures and subsequent risk of schizophrenia were found in children of parents with schizophrenia,[27] pointing to an interaction of immune activation with genetic components.

Structurally, prenatal exposure to infection might contribute to morphological abnormalities of the CNS, including cavum septum pellucidum elongation in patients with schizophrenia,[33] and intracranial sonographic ventricular abnormalities associated with prenatal cytomegalovirus exposure.[34] T1-weighted MRI has also revealed volumetric decreases in entorhinal and cingulate cortices in adults with schizophrenia, associated with fetal exposure to maternal elevations of CXCL8.[35] At the cellular and molecular level, glial activation has also been demonstrated. In patients with schizophrenia, glial activation has been observed *in vivo* in PET studies (discussed further below), and in several postmortem studies. The latter studies consistently revealed neuropathological changes in microglial morphology and protein levels, including increased expression of the microglial markers CD68 and HLA-DR in patients with schizophrenia compared with healthy controls.[36,37] A meta-analysis has revealed that medication-naive patients with schizophrenia also demonstrate elevated blood levels of IL-1β, soluble IL-2 receptor, IL-6 and TNF.[38]

ASD

Epidemiological studies support an association between ASD (Box 2) and prenatal infection with herpes simplex virus type 2, rubella, *T. gondii* or cytomegalovirus, as well as bacterial infections.[5,39] Birth cohort data have associated ASD with specific immune-related—particularly so-called inflammatory—markers *in utero*[40,41] and/or maternal admission to hospital for infection,[5] as well as with the presence of maternal antibodies against fetal brain antigens.[42–44] As in schizophrenia, elevated levels of

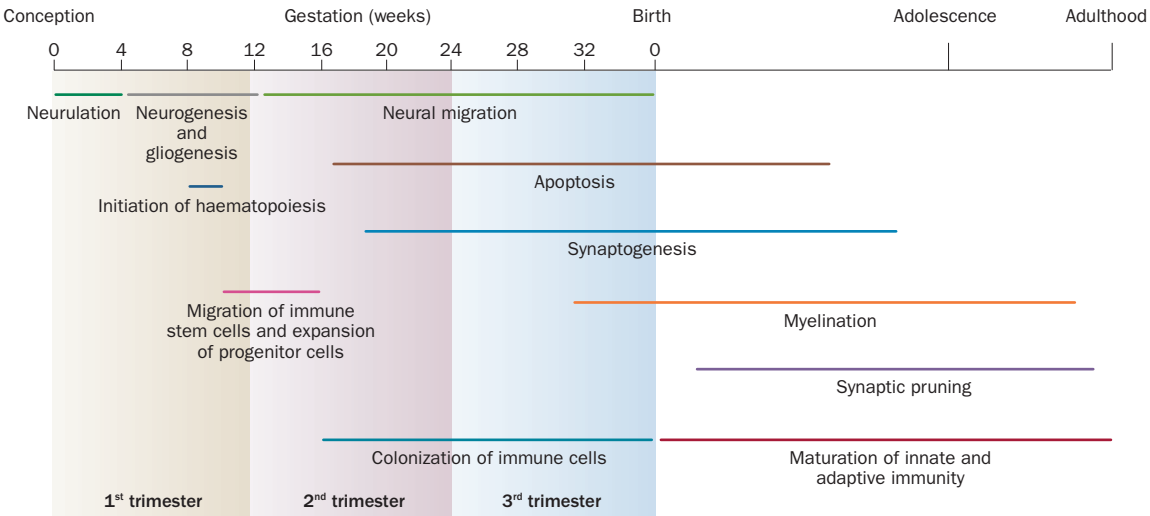

Figure 1 | The timeline of development. The steps of human brain and immune system development from gestation to early postnatal life are highly orchestrated.[243] Short-term and long-term effects of maternal immune activation depend on genetic predisposition, time window of fetal or postnatal brain development, and strength of insult.

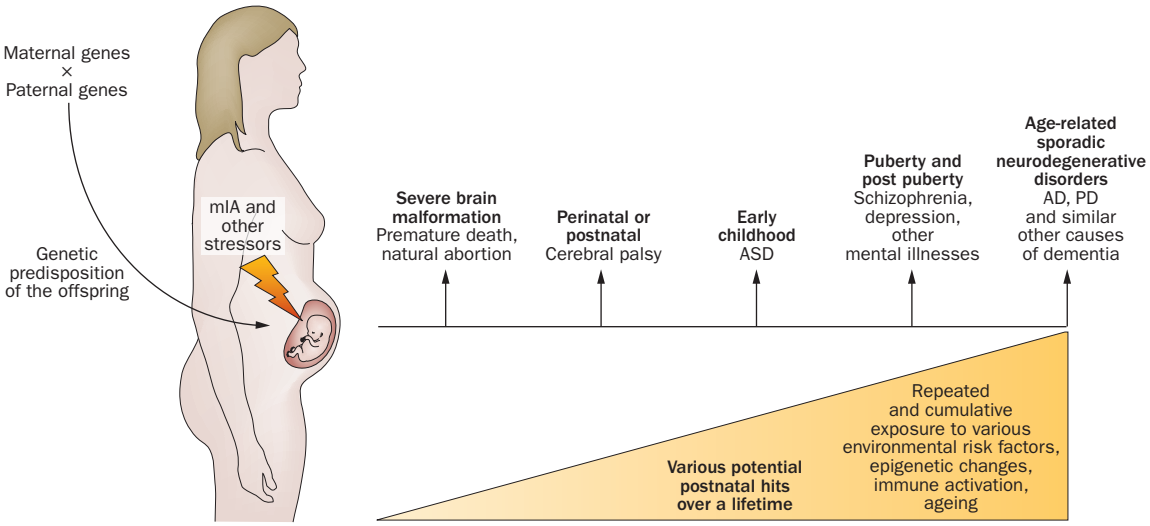

Figure 2 | Proposed causal chain of events. In humans, mIA can lead to the wide spectrum of neuronal dysfunctions and behavioural phenotypes observable in the juvenile, adult or aged progeny. Abbreviations: AD, Alzheimer disease; ASD, autism spectrum disorder; mIA, maternal immune activation; PD, Parkinson disease.

C-reactive protein during pregnancy were significantly associated with increased risk of ASD in the offspring.[30] A large case–control study (the CHARGE trial) found that women who contracted fevers due to influenza during pregnancy were more likely to have children with ASD.[45] In addition, the California Department of Developmental Service has reported a 'winter baby' phenomenon, wherein higher risks of ASD were observed in babies conceived during winter months,[46] possibly owing to higher infection rates.

Similar to patients with schizophrenia, cortical samples from young adults with ASD revealed increased microglial activity in comparison with healthy individuals.[47–49] These changes were paralleled by elevated levels of TNF, IL-1β, IL-6, IL-13, and C-C motif chemokine 2 (formerly known as MCP-1) in the cerebrospinal fluid (CSF) of patients with ASD.[49–52]

Genetic risk factors in schizophrenia and ASD

Although the molecular basis of the elevated glial activation in patients with schizophrenia and ASD remains to be elucidated, mounting evidence indicates that the disorders share genetic risk factors related to immune function. For instance, genome-wide association studies (GWAS) have revealed that novel genetic risk factors for schizophrenia relate to alterations in specific glial cell type functions.[53,54] In addition, the largest GWAS conducted to date in patients with schizophrenia showed that the most affected region was within the MHC locus.[55] A substantial proportion of the genetic modules identified in these studies are enriched in immune genes and glial markers, and linked to astrocyte-mediated modulation of synaptic signalling.

In line with shared dysregulated immune pathways in patients with these disorders, a postmortem transcriptome analysis of brains from patients who had ASD also revealed alterations in expression of genes governing glial cell functions.[56] Other investigations have also reported transcriptional profile abnormalities in circulating monocytes of patients with schizophrenia[57] and in people with ASD.[58] These studies suggested aberrant expression of a particular cluster of innate immune gene networks, which was particularly evident in patients with active psychosis[57] and in a subset of children with ASD and persistent gastrointestinal symptoms.[58]

Besides confirming the strong genetic underpinning,[59] complementing neuronal risk alleles[60–62] and *de novo* mutations,[63,64] these genomic findings provide support for dysfunctional innate immunity and glia-associated neuromodulation as additional susceptibility factors in both schizophrenia and ASD. The findings also suggest that mIA might potentiate the effects of risk genes—an idea that is supported by preclinical studies that have begun to demonstrate marked interactions between mIA and risk genes.

Epilepsy

As for schizophrenia and ASD, the prevalence of epilepsy (Box 3) is significantly increased in so-called winter

Box 1 | Schizophrenia

Schizophrenia is a severe, persistent brain disorder with a worldwide lifetime prevalence of 4 per 1,000 people.[244] The disease onset is typically in late adolescence or early adulthood, and includes positive, negative and cognitive symptoms.[245] Positive symptoms include visual and/or auditory hallucinations, delusions, disorganized speech, and grossly disorganized or catatonic behaviour, whereas negative symptoms refer to social withdrawal, apathy, anhedonia and alogia. Cognitive symptoms in patients with schizophrenia involve disturbances in executive functions, impairment of working memory, and inability to sustain attention.[245] Besides strong genetic risk factors with heritability estimates of ~80%,[59] adverse environmental factors during development and peripubertal stages have fundamental roles in the disease aetiology.[213]

Box 2 | Autism spectrum disorder

Autism and autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders that manifest in the first 36 months of life, with expression of symptoms ranging from mild to severe.[246] Symptoms include impairments in reciprocal social communication and interactions, and restricted or repetitive behaviours, interests or activities.[246] As in schizophrenia, the strong genetic basis of ASD is supported by the concordance rate of 60–91% between monozygotic twins.[247] The majority of disease risk genes are related to brain circuit formation, synaptic and neuronal plasticity, and glial functions.[60,62] Convergence of genetic and environmental factors has been suggested to contribute to the molecular and functional abnormalities that characterize ASD.[56,80]

Box 3 | Epilepsy

Epilepsy is typified by recurrent seizures characterized by abnormal, concurrent and excessive firing of multiple cortical neurons.[248] Fever is the most common cause of isolated seizures during early development and they are more common in children with developmental disabilities.[249,250] Maternal infections during pregnancy have been suggested to play a crucial part in the aetiology of epilepsy[66,67,251] In line with these observations, seizures develop in 22–30% of children with ASD, in the absence of identifiable underlying pathology.[252] Such rates are up to 10 times higher than those reported in the general population.[68]

babies.[65] Indeed, in several large population-based cohort studies (with samples of 86,000–124,000 children), maternal infections during pregnancy were found to be significantly associated with the subsequent occurrence of childhood epilepsy.[66–68] These studies revealed that the highest risks of epilepsy were associated with maternal cystitis, pyelonephritis, diarrhoea, coughs, vaginal yeast infection, and urinary infections, all of which were accompanied by maternal fever, during early to mid gestation. Potentially supporting a long-term dysregulated inflammatory state associated with mIA, PET imaging findings in adults with temporal lobe epilepsy have revealed elevated glial activity in the hippocampus.[69] This finding is similar to above-mentioned profiles of patients with schizophrenia, and it is of note that patients with temporal lobe epilepsy—in whom psychotic symptoms are frequently observed clinically—and patients with untreated schizophrenia both show increases in hippocampal glutamate levels during acute phases of illness.[70,71] These results provide a putative link between immune mechanisms and neurochemical dysregulation observed across the disorders.[72]

Preclinical evidence of a role for mIA

Pioneering investigations have provided direct experimental evidence in mice for a causal link between *in utero* infections with the influenza virus and structural, functional and behavioural abnormalities in offspring, thus representing a back translation of the reported association between prenatal influenza infection and schizophrenia. These abnormalities included decreases in neocortical and hippocampal thickness and forebrain expression of reelin, increased immunoreactivity for glial fibrillary acidic protein (GFAP),[7–9,73] and abnormalities in open-field behaviour, prepulse inhibition, object recognition and social behaviour compared with typically developing mice.[13]

Use of the viral mimic poly I:C (polyriboinosinic–polyribocytidylic acid) made it possible to demonstrate that the maternal immune reaction—driven by the pleiotropic factor IL-6, and not the virus itself—was responsible for the observed changes in the offspring.[13,74] Subsequent investigations demonstrated that mid and late gestational periods (with gestation lasting, on average, 20 and 22 days in mice and rats, respectively) correspond to two windows with differing vulnerability to acute fetal cytokine responses, as well as differing behavioural dysfunction later in life. Some abnormalities, such as prepulse and latent inhibition, preferentially manifested following mid-gestational poly I:C exposure (gestational day 9), and impairments in cognitive flexibility were more pronounced following poly I:C exposure at late gestation (day 17).[75] Many studies using poly I:C or the bacterial mimic lipopolysaccharide (LPS) to trigger mIA have confirmed the early viral studies, showing adult behavioural abnormalities in selective attention, social behaviour, exploratory behaviour and working memory, as well as increased sensitivity to psychotomimetic drugs, that were independent of the precise timing of mIA.[76–80]

The impairments in emotional processing, social and communicative behaviours in rodent models of mIA may be relevant not only to the negative symptoms of schizophrenia but also to ASD.[81] A prenatal poly I:C model in rhesus monkeys shows increased repetitive behaviours, abnormal communication and impaired social interactions, which start at weaning and increase in intensity during maturation.[82] More specific to ASD, the offspring of rhesus monkeys exposed to human IgG antibodies isolated from mothers of children with ASD showed hyperactivity and whole-body stereotypies,[83] as well as deviations from species-typical social behaviours such as preferentially approaching familiar peers over unfamiliar peers.[84] These behavioural effects were accompanied by abnormal white matter growth in the frontal lobes compared with those monkeys exposed to antibodies from mothers with typically developing children.

Given the large overlap between schizophrenia, ASD and epilepsy from epidemiological, clinical and preclinical perspectives, it is not surprising that mIA also has a profound impact on neuronal excitability and the evoked seizure threshold. In mice, maternal restraint stress combined with LPS injection on gestational day 14 exaggerated seizure responses, perhaps causally related to increased plasma IL-1β levels, in the offspring.[85] Similar findings have been reported in mice exposed to poly I:C between gestational days 12–16, which show a significantly reduced membrane threshold for seizure induction in adulthood.[86] Together, these results suggest that mIA can indeed facilitate or 'prime' the development of epilepsy.

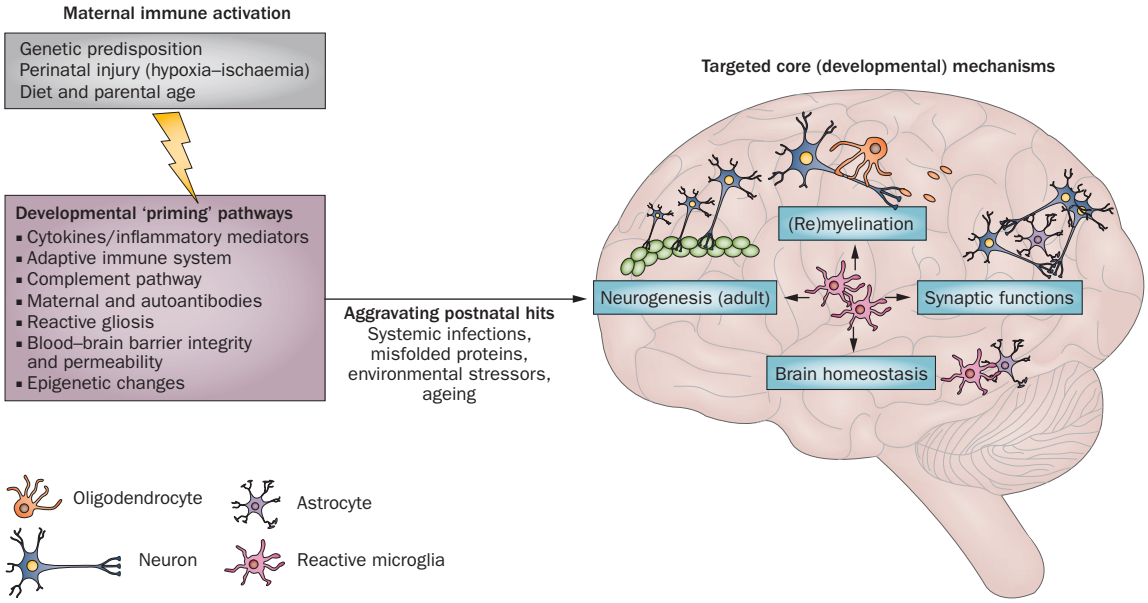

Figure 3 | Developmental priming pathways. Signalling pathways implicated in neuroimmune crosstalk act in concert with genetic and environmental factors to target core neuronal functions in the developing, adult or ageing offspring.

A role for mIA in other CNS disorders

Though the clinical evidence for an association between maternal infection and neurodevelopmental disorders is strong, epidemiological support for such a link in other neurological diseases is either sparse or completely missing. The concept that even neurodegenerative diseases might have a neurodevelopmental origin could seem rather unexpected, despite the appreciation that disease initiation occurs decades before manifestation of clinical symptoms.[87,88] However, as discussed below, recent clinical and preclinical findings indicate that both genetic and mIA-induced dysregulation of fundamental neurodevelopmental programmes affect juvenile and adult brain functions alike, and may also be deterministic in the brain's responsiveness to cumulative exposures to detrimental environmental insults during adulthood and ageing (Figures 2 and 3).

Cerebral palsy

Clinical evidence

Neurodevelopmental disturbances or injuries to the immature brain are linked to cerebral palsy (Box 4). Several studies reported significant associations between intrauterine bacterial infection with a maternal response (consisting of chorioamnionitis) and cerebral palsy in the progeny.[89,90] Also, maternal infection accompanied by blood coagulation has been linked to stroke-like events in the fetal brain.[91–93] A study of CSF from newborn infants with perinatal hypoxic–ischaemic brain injury reported significantly elevated levels of inflammatory mediators derived from microglia or macrophages, with apparent neurotoxic effects.[94] Together with the increased risk of preterm delivery and intraventricular haemorrhages, inflammation associated with hypoxia–ischaemia has been proposed to be causally involved in the neonatal white matter damage that is particularly evident in the most severe cases of spastic cerebral palsy.[95–100]

Viral infections during pregnancy have been estimated to account for 5% or fewer cases of cerebral palsy.[89] This finding seems to be consistent with a birth cohort study in 261 early preterm infants that revealed no apparent association between *in utero* infection and neurodevelopmental disability after approximately 6 years' follow-up, even though indirect mechanisms such as brain immaturity and neonatal complications associated with early preterm birth may have confounded potential associations.[101]

The existing data suggest that abnormal activation of fetal microglia, release of neurotoxic immune-mediators, and inheritance of cerebral palsy risk alleles that affect innate immune functions[102] all contribute to brain injury and persistent inflammatory effects in children with this disorder.[98] Of note, the development of human *in vivo* fetal quantitative MRI[103–105] might help relate maternal risk factors to the differing patterns of fetal brain malformation, and should provide more insight into the contribution of maternal infection to the development of cerebral palsy.

Box 4 | Cerebral palsy

Cerebral palsy is the most common cause of motor disability in children, and is often accompanied by varying degrees of impairment in movement, coordination, balance and posture, including spastic and nonspastic forms. This neurodevelopmental disorder also presents with substantial impairments in behaviour and cognition. Early brain injury constitutes a major aetiological factor.[253,254] Reported precipitating insults include placental abnormalities, intrauterine growth restriction, pre-eclampsia, circulation disorders, perinatal asphyxia, and maternal infections[95,96,255–257] Clinical diffusion tensor imaging studies have shown that the majority of children with spastic cerebral palsy present with white matter injuries, and the extent of the myelin loss correlates with the severity of motor impairments.[258]

Box 5 | Alzheimer disease

Alzheimer disease (AD) is the most common type of dementia, affecting approximately 24 million people worldwide, and the number of patients is continuing to increase as a consequence of the ageing population.[259] The disease is characterized by progressive neurodegeneration and loss of cognitive abilities, and has a complex aetiology involving both genetic (dominant mutations in a small fraction of patients; minor risk genes in the majority of patients) and environmental factors.[260] Neuropathological hallmarks include neuronal and synaptic loss, and proteinaceous aggregates in the form of senile plaques, which are enriched in cleaved products of amyloid precursor protein—including amyloid-β peptides—as well as intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau.[261] The neuropathology is accompanied by neuroinflammation, indicated by astrogliosis and microgliosis.[127]

Preclinical models

Many studies have focused on animal models of perinatal hypoxic–ischaemic brain injury, which is accompanied by complex spatiotemporal inflammatory processes.[106] More-recent investigations have also targeted molecular mechanisms underlying maternal infection to study the aetiology of cerebral palsy. The models are generated by exposing pregnant rats to either LPS or poly I:C fairly late in the gestational period (days 17–20),[107–111] or by direct intrauterine administration of LPS to induce preterm birth.[112]

After prenatal exposure to LPS, elevated expression of IL-1β was observed in newborn rats, associated with postnatal cell death, astrogliosis and hypomyelination.[110] The same group also reported that rat neonates exposed to LPS *in utero* displayed exacerbated responses to intracerebroventricular injections of ibotenate (also used to model cerebral palsy), including upregulation of microglial markers, astrogliosis, and reduced white matter myelination.[111] The latter effect is consistent with previous findings in a rabbit model of cerebral palsy, which demonstrated pronounced white matter injury and motor deficits following intrauterine endotoxin administration.[113]

The data also point to a putative priming effect of prenatal infection, as animal models of neonatal hypoxic injury show potentiated encephalopathy following chronic late-gestational low-dose LPS exposure.[108] Likewise, neonatal administration of poly I:C has been shown to aggravate cerebral hypoxia–ischaemia,[114] including increases in inflammatory response, white matter damage, oligodendrocyte precursor cell degeneration and apoptosis, and decreases in the regenerative capacity of microglia. Overall, the current preclinical literature supports a profound effect of late-gestational systemic or intrauterine infections on the developing brain.

AD

Clinical evidence

Sporadic AD is a progressive neurodegenerative disorder associated with advanced age (Box 5), and the apolipoprotein E ε4 (*APOE*ε4*) allele constitutes the main genetic risk factor. Interestingly, two recent paediatric MRI studies revealed that compared with noncarriers, infants expressing the *APOE*ε4* allele had significant white matter changes and reduced grey matter volume in areas preferentially affected by AD.[115,116] This result indicates that at least part of the risk conferred by the *APOE*ε4* allele is associated with abnormal brain development. Similarly, analysis of a large collection of postmortem human brain tissue revealed that precursors of neurofibrillary tangles can develop during childhood.[117]

The biological significance of this phenomenon, and particularly the mechanisms involved in the ageing-related conversion of soluble to stable fibrillary inclusions, remains to be elucidated, but it is conceivable that alterations in microglia-mediated immune functions are involved in this pathophysiological process. In support of this hypothesis, GWAS, functional genomics[118–121] and proteomic analysis of blood and CSF[122–124] have confirmed dysfunctional immune pathways as prominent susceptibility factors in sporadic AD. The relevance of these findings is illustrated by the fact that several of the risk genes involved in these pathways encode proteins that are required for appropriate microglial responses toward cell damage in the brain, which allow efficient phagocytosis of debris and protein aggregates, and promote neural repair and remyelination.[125,126]

Preclinical models

Experimental research has investigated the putative link between immune system abnormalities and alterations in microglial function as a driving force for ageing-associated neurodegenerative diseases. Besides studying the direct effects of factors and mediators of immune activation, including reactive oxygen species, nitric oxide, TNF and IL-1β, on neuronal function and cell death in AD (reviewed extensively elsewhere[127]), some have focused on the complement system, a powerful effector of immune responses.

We have recently demonstrated that mIA results in long-term functional alterations of microglia in mice exposed to poly I:C during late gestation, as suggested by morphological changes indicative of a hyperactive state and differential expression of several cytokines and chemokines in aged offspring.[128] These changes were accompanied by strong reactive gliosis, as well as severe spatial learning and memory deficits.[128] Similar findings were reported in rats that were prenatally exposed to LPS[129] or postnatally infected with *Escherichia coli*.[130] Besides increased immunoreactivity for GFAP and a significant decline in spatial learning and memory performance with advancing age, which were evident in both studies, these rats also demonstrated an ageing-associated increase in levels of microglial markers (CD11b and MHC class II), as well as selective changes in *N*-methyl-D-aspartate receptor subunit expression in the hippocampus. Prenatal LPS exposure also seemed to promote synaptic loss, as shown by decreased expression of synaptophysin—a crucial regulator of synaptic vesicle function and neurotransmitter release—as well as by neuronal loss during ageing.[129]

In agreement with the existing literature, which has consistently reported long-term effects of prenatal and

perinatal infections on synaptic function and cognitive abilities,[15,128–133] we also detected structural synaptic and neuritic abnormalities in the hippocampus in aged offspring of poly I:C-exposed mice.[134] In comparison with age-matched controls, 3D electron microscopic analyses revealed that the mIA offspring showed a significantly higher density of neuritic varicosities containing mitochondria, vacuoles and cellular debris—confirming their intracellular origin and degenerative state—in the layer II projection zone of the entorhinal cortex.[134] Importantly, these neuropathological changes were not unique to the mIA offspring, but they manifested significantly earlier and more aggressively than in aged control mice,[132,134] indicating that mIA can be a potent accelerator of brain ageing in the offspring.

In support of this observation, a significant age-associated increase in levels of amyloid precursor protein and its proteolytic fragments, as well as mislocalization of tau and hyperphosphorylation of this protein in somatodendritic compartments, were found in prenatally immune-challenged mice compared with controls.[128] These findings are strikingly similar to neuropathological alterations observed in the brains of aged humans patients with early-stage AD. The acceleration of this distinct ageing-related neuropathology following a prenatal infection was substantially worsened by a subsequent viral-like infection.[128] Taken together, the data collected in this mIA model of accelerated brain ageing (and possibly a model of AD) support the hypothesis that microglial dysfunction and cellular stress provoked by chronic inflammation are sufficient to initiate a vicious circle of neuropathological changes that culminates in the formation of amyloid plaques in the projection zones of neurons bearing tau pathology.[135]

PD

Clinical evidence

As in the case of AD, a clear epidemiological association between mIA and PD (Box 6) remains elusive. A putative link to maternal influenza was discussed in the 1980s;[136] however, statistical evaluations failed to support such a relationship.[137] In adults, influenza infection, and in particular the number of episodes and severity of infections, has been associated with PD-like motor deficits, but not with an increased risk of developing PD.[138] Nevertheless, the possibility that mIA might have an impact on microglial properties in patients with PD remains intriguing, as many genetic risk factors for the disease, including *LRRK2*, *NR4A2*, *PARK7* and *CD74*,[139] have known immune functions. An early hit like mIA could prime microglia (see section 'mIA models: mechanistic considerations') to become drivers of the inflammatory processes and the progression of α-synucleinopathy associated with PD, owing to disturbed responses to protein aggregation and neuronal death (as reviewed elsewhere[127,140]).

Preclinical models

Exposure to LPS during early gestation (day 10) in rats impaired striatal dopaminergic innervation[141] and resulted in increased TNF levels, accompanied by progressive loss of dopaminergic neurons that persisted over the offspring's lifespan.[142] In addition, following poly I:C challenge at gestational day 17 in mice, development of midbrain dopaminergic neurons was disturbed—an effect that was further aggravated by deficiency of *NR4A2*, which encodes the nuclear orphan receptor NURR1.[143] As well as being a key regulator for the development of dopaminergic neurons,[144] this protein promotes neuroprotective functions in glia toward dopaminergic neurons that are under inflammatory stress.[145]

Although not specific to PD, in response to mIA the murine fetal brain upregulates many neuroprotective genes including crystallins.[146] Interestingly, α-crystallin B chain is a potent regulator of microglia,[147] and accumulations of this protein have been found in multiple brain regions in patients with PD.[148] Support for a possible role for secondary insults in PD across the lifespan was provided by experiments with the neurotropic influenza virus (H5N1). The virus alone was able to initiate microglial activation, as well as phosphorylation and aggregation of α-synuclein, in wild-type mice infected at 6–8 weeks.[149] Analogous to AD,[128] mIA followed by postnatal hits, such as infections during the lifetime, might contribute to the development of PD-related neuropathology in humans (Figure 2).

Box 6 | Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disorder after Alzheimer disease (AD). Clinically, patients with PD experience motor deficits (bradykinesia, resting tremor, rigidity and postural instability) and a variety of nonmotor deficits (hyposmia, constipation, sleep disturbances, impairments in autonomic and cognitive functions, and dementia).[262] Neuropathologically, dopaminergic neurons of the substantia nigra pars compacta degenerate, leading to decreased dopaminergic innervation of the striatum.[263] In addition, the protein α-synuclein misfolds and accumulates in various regions of the brain in intraneuronal aggregates,[264] and similar pathological features can also be found in the PNS many years before onset of motor symptoms.[87] As in AD, prominent cellular alterations in the brain include astrogliosis and microgliosis.[127,140]

mIA models: mechanistic considerations

The clinical and preclinical evidence discussed above strengthens the hypothesis that mIA underlies some of the persistent immunological and neurological changes in the offspring, and that microglia have a major role. Among the neuroglia, microglia are distinguished by specific innate immune properties. In rodents,[150,151] microglia derive from myeloid progenitors that migrate from the periphery to populate the brain parenchyma during early gestation, and a similar process presumably occurs in humans.[152] Microglia are regulated by various soluble and membrane-associated factors, including cytokines, chemokines, (neuro)trophic factors, complement factors and neurotransmitters.[127,153,154] Through crosstalk with neurons, astrocytes, oligodendrocytes and

circulating immune cells, microglia function as primary CNS guardians and contribute to the maintenance of tissue homeostasis.[155] In concert with astrocytes, they also regulate neuronal differentiation and maturation, and have a pivotal role in synaptic pruning and neural circuit formation.[127,156–160]

In the sections that follow, we discuss how the data generated from experimental mIA models indicate that the fundamental roles and functions of microglia could be affected by mIA.

Role of cytokines

As mentioned above, several cytokines have been implicated in mIA models for schizophrenia, ASD and epilepsy. Levels of one of the key factors, IL-6, were enhanced in the maternal serum, as well as in the amniotic fluid, placenta and fetal brain, in mIA models.[74] Interestingly, mIA could also be induced directly by a single injection of IL-6, yielding offspring with the same behavioural abnormalities seen in viral infection, poly I:C or LPS models.[74] Complementing such findings, co-administration of an anti-IL-6 antibody in pregnant dams exposed to poly I:C prevented behavioural deficits and normalized the variation in brain gene expression normally observed in the brains of the offspring that experienced mIA, and mIA in IL-6 knockout animals did not lead to the behavioural changes typically seen in mIA offspring.[74]

Although IL-6 seems to have a crucial role in mIA, other inflammatory mediators have been identified, including CXCL8,[35] TNF[107,161] and IL-1β.[107,110] Of note, constitutive overexpression of IL-10 in macrophages[162] prevented the emergence of behavioural defects in adult mIA-exposed offspring. In the absence of a prenatal inflammatory stimulus, however, overexpression of IL-10 in macrophages was sufficient to precipitate deficiencies in spatial exploration and associative learning.[162] These data illustrate that in addition to the disruptive effects of excess of the pleiotropic factors IL-6, IL-1β, CXCL8 and TNF (often called 'proinflammatory' cytokines), enhanced IL-10 (often considered 'anti-inflammatory') signalling in prenatal life can similarly affect cognitive and behavioural development. Hence, a shift in the balance between specific immune signalling pathways constitutes a critical determinant of the impact of maternal infection on neurodevelopmental processes in the fetus.

Adaptive immune responses

Preclinical data have also revealed persistent immune alterations—including hyperresponsive $CD4^+$ T cells, decreased levels of regulatory T cells,[163] and increased cell-mediated immunity[164]—in adult offspring following gestational exposure to mIA. Bone marrow transplantation experiments have sought to test whether haematopoietic cells derived from mIA offspring can confer immunological deficits. These studies showed that immune abnormalities were not transferred when bone marrow from mIA mice was transplanted into irradiated host mice. However, bone marrow taken from control mice could correct some of the abnormalities seen in mIA mice, such as increased repetitive and anxiety-like behaviours.[164] These results suggest that although immune system abnormalities contribute to abnormal behaviours, aspects of the host environment beyond bone marrow are necessary for preserving the mIA phenotype.

Another key factor might be the presence of specific maternal antibodies. In line with the effects of maternal inflammation on fetal immune responses, developmental abnormalities are observed in rhesus monkeys exposed prenatally to human IgGs isolated from mothers of children with ASD.[84] This result supports the pathogenic potential of specific maternal antibodies in some forms of ASD.

Blood–brain barrier and white matter

Although a complete discussion is beyond the scope of this Review, we believe it is important to mention injuries to the blood–brain barrier and white matter as potential contributory factors to the deficits associated with mIA. Inflammation during development can cause damage to the blood–brain barrier and, depending on the time and duration of the insult, this damage could result in loss of highly vulnerable neurons (including dopaminergic cells), production of neuroinflammatory sites, and focal white matter injury.[165,166]

Hypomyelination, associated with degeneration of oligodendrocyte progenitor cells, has been described in various models of mIA.[109–111,167] At least one study reported that decreases in myelin basic protein levels observed in mice treated with poly I:C at gestational day 9.5 could be a transient phenomenon, indicative of retarded rather than defective myelination.[167] However, preliminary diffusion tensor imaging data have shown that early prenatal challenge (gestational day 9) has a greater impact on white matter tract integrity in the adult offspring than does late challenge (day 17).[168] This result suggests that early inflammatory insults are more likely to lead to widespread connectivity anomalies in the brain. These findings support the idea of impaired integrity in the blood–brain barrier and white matter after mIA; however, additional experimental data are required to substantiate the precise pathophysiological role.

Synaptic development and neurotransmission

Efforts to discover molecular mechanisms of synapse and circuit formation have indicated a crucial role for several immune molecules, including complement protein C1q and MHC class I.[158,159,169–171] C1q can localize to synapses, where it is involved in pruning and refinement of the developing nervous system.[159] Whether mIA influences C1q-based synaptic pruning during early development remains to be explored. Interestingly, C1q protein levels in mouse and human brains were recently shown to be dramatically increased during normal ageing, particularly in the hippocampus, substantia nigra and piriform cortex.[172] These findings support an emerging—but yet to be demonstrated—concept that misregulated complement protein activity contributes to synaptic dysfunction and cognitive impairments during brain ageing.[173]

A possible role for C1q in the accelerated brain ageing associated with mIA also awaits investigation.[128]

In addition to the complement proteins, MHC class I also regulate the density and function of cortical synapses during their initial establishment.[170,174] Experimental loss of function and molecular rescue of crucial components of MHC class I indicated that this complex is involved in the postsynaptic insertion of Ca^{2+}-permeable AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors. These receptors are required for the induction of long-term depression and are crucial for synapse elimination.[174] In line with these findings, neurons from rats exposed to mIA have increased levels of MHC class I, accompanied by lower synapse density and impairments in neural connectivity.[175]

The latter study also recorded reductions in glutamate receptor levels, and mIA has been associated with disturbances in other neurotransmitter systems, including a hyperdopaminergic state following repetitive gestational immune activation induced by poly I:C in mice (between gestational days 12 and 17) or LPS in rats (from days 1–21).[176,177] Similarly, single poly I:C or LPS exposures were associated with changes in serotonergic[178,179] and γ-aminobutyric acid-mediated (GABAergic) neurotransmission[15,133,180,181] in exposed offspring. A significant increase in AMPA receptor-mediated neurotransmission was recently recapitulated in hippocampal slices obtained from transgenic mice harbouring a loss-of-function mutation in *TYROBP*, a crucial microglial network regulator gene.[182] These findings indicate that overactivation of microglia during brain development is sufficient to induce persistent changes in glutamatergic neurotransmission. Furthermore, these results suggest that mIA-evoked alterations in expression levels of MHC class I molecules could trigger changes in activity-dependent plasticity and synaptic pruning during critical periods of brain development, which might foster long-lasting alterations in circuits and behaviour.

Neuronal migration

Another potential target of mIA is neuronal migration during brain development.[183] Offspring born from rodent dams infected with influenza virus or treated with poly I:C or LPS exhibit reduced expression of reelin, a major regulator of radial migration of cortical principal neurons.[9,132,184] In line with this finding, alterations in the levels of reelin expression were accompanied by decreases in neocortical and hippocampal thickness,[9] as well as alterations in the expression of several gene products required for the tangential migration of GABAergic neurons into the cerebral cortex, including members of the DLX family of homeobox proteins, and glutamate decarboxylases 1 and 2.[133,185]

In support of these preclinical findings, reduced density of reelin-expressing interneurons has been found postmortem in brain tissue from patients with schizophrenia,[186,187] and low expression of reelin has been found in blood samples from individuals with ASD.[188] Loss of reelin expression has also been associated with hippocampal granule-cell dispersion in temporal lobe epilepsy,[189] as well as with pronounced reduction in the number of reelin-expressing cells in the entorhinal cortex during the earliest stages of AD.[190] Such impairments in neuronal migration might considerably affect early neuronal trajectories and neurotransmitter homeostasis, thereby contributing to the long-term consequences of mIA.

Transcriptional and epigenetic effects

The first gene expression study of prenatal influenza virus infection in mice revealed significant transcriptional alterations in the neonatal brain, primarily affecting basic cellular functions, including the cytosolic chaperone system, as well as the glycine receptor, the noradrenaline transporter and myelin basic protein.[191] Several follow-up studies in mice that investigated mIA-induced transcriptional changes in the juvenile or adult offspring of poly I:C-treated dams reported similar alterations in a small but consistent group of genes.[74,133,192,193] A direct comparison of the transcriptional changes associated with mIA induced by administration of the influenza virus, poly I:C or IL-6 reported overlapping gene expression changes in the three mIA groups that were distinct from the expression profiles in control mice.[146] Most notably, acute upregulation of the crystallin gene family was observed in the embryonic brain. Although the exact function of these cytosolic chaperone system proteins remains to be elucidated, these findings position them as potential converging molecular mediators of mIA. Intriguingly, abnormal brain crystallin levels have been observed postmortem in brains of patients with ASD or schizophrenia, as well as in patients with AD or PD.[148,194–196]

An emerging question in preclinical research is whether some of the persistent transcriptional changes seen in mIA models (such as in the GABAergic neurotransmitter system in the prefrontal cortex[133]) could be linked to epigenetic changes, which, in turn, might contribute to the delayed behavioural abnormalities seen after mIA. The first reports of promoter-specific histone modifications (for example, trimethylation or hyperacetylation) are emerging; however, only subtle changes between treatment groups have been found, many of which are evident in juvenile but not adult offspring.[192,193] Clearly, the association of mIA with robust alterations in epigenetic regulation of gene expression in the offspring remains to be confirmed.

Microglial priming

Microglial priming refers to a heightened response to an inflammatory stimulus that is much stronger than that observed in stimulus-naive microglia.[197] This state has been associated with apparent changes in morphology, upregulation of cell surface antigens, and elevated levels of cytokines and other inflammatory mediators, as well as an increase in the number of microglia.[197] As discussed above, systemic injections of compounds like poly I:C and LPS induce distinct immune responses in the nervous system, as demonstrated by the significant but transient increase in numbers of morphologically

and functionally activated microglia after a single intraperitoneal injection.[107,198] In contrast to the temporally restricted microglial activation in adult mice, several studies have shown that LPS or poly I:C exposures across gestational windows induce persistent changes in the microglia of the offspring. For example, elevation of several inflammatory modulators, and morphological changes indicative of an activated state of microglia, have been observed both in adult[199,200] and aged offspring[128] of poly I:C-exposed dams.

The first studies investigating the synergistic pathological effects between prenatal, perinatal and postnatal insults on microglial activity are emerging.[114,128,199] As predicted, following prenatal[128,199] or neonatal[114] exposure to poly I:C, a second hit—irrespective of the type of insult, including hypoxic–ischaemic damage, peripubertal social stress, or postnatal poly I:C challenge—resulted in a significantly heightened inflammatory response, including expression of several cytokines and chemokines, increased numbers of morphologically hyperreactive $CD68^+$ microglia,[128,199] and decreased numbers of reparative (so-called M2-like) $CD11b^+$ microglia.[114] These data indicate that mIA represents a potent microglial primer, independent of the timing (gestational day 9 or day 17) and strength (1, 5 or 10 mg/kg body weight) of the primary immune challenge. The combination of these microglial priming events with different secondary insults culminates in entirely different phenotypes, ranging from schizophrenia-like behavioural abnormalities,[199] through promotion of protein aggregation and cognitive deficits,[128] to severe cerebral infarcts.[114]

Together, the preclinical data support the concept that mIA, together with postnatal disease-modifying factors, has a strong effect on microglial development, and interferes with the neuromodulatory and immune functions of these cells. This disturbance of fetal brain maturation in turn disrupts core mechanisms required for proper fetal and adult neurogenesis, neuronal migration and myelination, as well as the formation of neural circuits and refinement of synaptic functions (Figure 3). These myriad effects can culminate in long-term impairments in brain function and behaviour (Figure 2).

Preclinical mIA: a modular toolbox

The development of the poly I:C and IL-6 models from the earlier viral translational model was pivotal to the establishment of mIA models. Further support for mIA models came from the observation that prenatal influenza or exposure to poly I:C or IL-6 resulted in overlapping gene expression in the embryonic murine brain, suggesting that shared molecular pathways were disturbed by each treatment.[146] Another level of validity was provided by the finding that prenatal poly I:C exposure in rhesus monkeys induced abnormal behaviours in the offspring that overlapped with observations from rodent models.[82]

The ongoing refinement of the mIA model in rodents includes modulation of the intensity and timing of the insult, as well as the type of immune stimulus. Despite the notable similarities, potential differences between the cytokine-associated inflammatory responses triggered by poly I:C and LPS have been presented.[78] Direct comparisons between poly I:C and LPS studies have been difficult to make owing to overt differences in experimental designs. Nevertheless, the differences in timing and intensity seem to be much stronger drivers of the phenotypic differences than is the type of stimulus.

The importance of timing is probably best exemplified by the mIA models of schizophrenia, ASD and cerebral palsy. The original poly I:C model was designed to mimic the window of gestational exposure to maternal infection described in people with schizophrenia or ASD (predominately the first and second trimester). Accordingly, rodent mIA models of schizophrenia or ASD have largely used mid or late gestational windows (gestational days 9 or 17), when the exposure should be roughly equivalent across species in terms of its impact on the developing CNS.[184]

The poly I:C model has been adjusted to address the epidemiological relationship between perinatal infections and cerebral palsy. In this case, direct intrauterine or repetitive gestational immune challenges at the time of myelination (mostly applied between gestational day 18 and postnatal day 7) have been applied. However, the precise administration parameters that are required to induce long-lasting effects on myelination and localized white matter injuries need to be explored further.

The model has also been adjusted to precipitate AD-like neuropathological changes by combining poly I:C exposure during a time window that is critical for immune development (gestational day 17) with a second immune challenge during ageing (Figure 1).[128] A mIA model for PD has not yet been established, although administration of LPS on gestational day 10 or poly I:C on gestational day 17 produces long-term effects on dopaminergic neurotransmission in mice.[141–143] However, the overlap between the gestational day 10 LPS phenotype and the hyperdopaminergic phenotype described for the schizophrenia mIA model[176,177] might challenge the validity of this particular study for PD, although loss of dopaminergic neurons during ageing was observed after the former protocol.

Another refinement approach is to combine the mIA model with genetic (immune) risk factors. For instance, *Disc1*,[201,202] *Nr4a2*,[143] and *Tsc2*[203] showed synergistic effects with mIA on behavioural parameters in mice, such as social behaviour (*Disc1*, *Tsc2*), and locomotor hyperactivity, sensorimotor gating deficits and impaired attentional shifting (*Nr4a2*), as well as on a variety of neurochemical and anatomical parameters. Further refinement is introduced by adding environmental factors or 'postnatal hits' (Figures 2 and 3), such as cannabinoid exposure during adolescence,[178] peripubertal stress,[199,204,205] or immune challenges during ageing,[128] which are reported to have synergistic effects with the priming event of mIA.

The preclinical mIA paradigm, alone and in multiple combinations with other genetic or postnatal environmental hits, offers a versatile toolbox for

research that generated novel animal models with aetiological construct validity and improved translatability for schizophrenia, ASD, epilepsy and cerebral palsy. However, epidemiological data that have identified prenatal infections as putative risk factors for AD and PD have not been confirmed, and more clinical data are required to validate the mIA models of these neurodegenerative disorders.

Implications

Disease prevention

The increasing awareness of mIA and its mechanisms may offer guidance for improvement of public health interventions such as vaccinations, antibiotic and/or antiviral therapy, immune modulators, and dietary adjustments. These interventions might help to minimize the incidence of mIA-associated diseases beyond what has been achieved by public health recommendations for maternal–fetal health that are already firmly in place. Interventions specifically targeted at mIA-associated diseases must, however, be carefully evaluated in controlled studies before they can be recommended. Indirect evidence in the form of epidemiological associations and case reports serve as a guide for further testing of this approach. For example, the decline in schizophrenia incidence in some developed countries might be associated with the widespread use of anti-infective agents[206] and the consequent reductions in maternal infections, including genital and reproductive infections. By contrast, decreases in inflammatory conditions owing to disruption to gut microbiota (secondary to increased hygiene and antibiotic use in developed countries) might increase the likelihood of autoantibody production during pregnancy, thereby increasing the risk of disorders such as ASD.[207]

Vaccination against influenza is already recommended in women planning to become pregnant in the near future, or who are already pregnant,[208] owing to the risks associated with infection during pregnancy, and favourable safety and efficacy data.[209–211] The existing safety data regarding maternal vaccination during pregnancy mainly focuses on maternal outcomes, and on early fetal and infant development; long-term follow-up data on the incidence of neurodevelopmental disorders in the offspring of mothers vaccinated during pregnancy is scant. At issue here is whether the mother's immune response to vaccination might cause an mIA response of its own accord through generation of antibodies against influenza-related epitopes.[212] Against this background, treatment or prophylaxis targeting bacterial and viral infections in pregnant women may offer considerable potential for reducing the incidence of a wide range of CNS disorders.[213,214] Several antibiotics are considered safe for mother and fetus, and are, therefore, in common use in pregnancy.[215]

In influenza, clinical investigations confirmed both efficacy and safety of neuraminidase inhibitor antiviral therapy during pregnancy, and antiviral therapy has now been established in the management of influenza in pregnancy.[216–219] Preclinical support for a role for antivirals in mIA prevention came from a study in which oseltamivir treatment, combined with H1N1 influenza infection on gestational day 16, prevented most of the virus-induced gene expression changes in the hippocampus in newborn mice.[77]

The use of immune modulators in the presence of maternal infection will require close monitoring and, probably, judicious titration of therapy to overall clinical response. This type of intervention seems to have been successful on a limited scale in nonpregnant women given anti-IL-6 therapy for severe influenza H7N9 infection (S. Toovey, unpublished data). A preclinical study has shown that flavonoids acting on the JAK2/STAT3 signalling pathway can attenuate the effects of *in utero* IL-6 administration, suggesting that dietary flavonoid supplements might help to minimize the incidence of mIA-associated diseases.[220] Options for neonatal treatments, particularly relevant for cerebral palsy, have been reviewed extensively elsewhere.[98] These options include hypothermia, recovery of oligodendroglia precursor cells and reduction of long-lasting inflammation, and stem cell therapies for immunomodulation.[221]

Diagnosis

Given the link between gestational vulnerability and adult symptom clusters, several mIA-induced proteins and candidate neuropathological factors can potentially be used as diagnostic and predictive biomarkers. Potential markers, including elevated levels of TNF, lymphotoxin-α, IL-4 and IL-10 in the amniotic fluid,[41] and quinolinate and galectin-3 in CSF,[94] have been investigated in the context of ASD. In medication-naive patients with schizophrenia, levels of several immune-related markers, such as IL-1β, soluble IL-2 receptor, IL-6, and TNF, were found to be increased in blood[38] in association with the severity of psychotic symptoms.[222] In addition, a genome-wide methylation analysis revealed distinct blood biomarker signatures that could be linked to environmental insults, including hypoxia and infection, in patients with schizophrenia as compared with controls.[223] These novel data indicate that pathogenic events may be preserved in the epigenome, and that the methylation status could serve as a novel biomarker to distinguish aetiologically distinct disease subtypes and improve disease management.[223]

Several studies in patients with AD point to dysfunctional systemic immune pathways, as indicated by the abnormal expression pattern of cytokines, chemokines and other secreted cellular communication factors in the plasma and/or CSF.[122–124] This signature seems to be predictive, with high accuracy for the conversion from a prodromal state to mild cognitive impairment and clinical diagnosis of AD.[122–124] However, this predictive power appears to be highly dependent on the specific detection platform, as a study using a different platform could not accurately predict disease progression.[224] Still, it remains possible that immune-related factors in plasma—perhaps in combination with a person's genetic profile[225]—could become helpful for identifying patients at risk of progression to AD, and that immune-function-related therapy could be beneficial in the prevention of AD.

Analysis of systemic molecular biomarkers could potentially be combined with imaging techniques, such as novel PET tracers that are specific to microglial activation states. In three small cohort studies involving patients with schizophrenia, binding of translocator protein (TSPO, a mitochondrial marker that shows increased expression in activated microglia and astrocytes) was associated with increased activation of glia in (paranoid) patients compared with healthy volunteers.[226–228] Preliminary evidence has also been collected showing glial activation in a group of predominantly drug-free patients with schizophrenia.[229] Another study found no such increase; however, a positive correlation between glial activation and the severity of psychotic symptoms was observed.[230]

Although these data are encouraging for the hypothesized central role of activated microglia in schizophrenia, further research is required to understand which brain areas are differentially targeted; establish how inflammatory processes correlate with—or predict—neurochemical, brain functional or behavioural and cognitive impairments; and, finally, characterize subgroups of patients in whom inflammatory processes might be readily identified, thereby allowing immune-targeted therapies to be applied.

Treatment

The key implication of the evidence reviewed here is that in disorders where mIA has a continuous role in the causal pathway of disease manifestation, immune-related mechanisms might represent a promising therapeutic target. Immune modulation would probably work best when added to more-conventional therapies that target neurochemical or other molecular dysfunction found across diverse CNS disorders, such as amyloid-β plaques or tauopathies in AD, or monoaminergic or glutamatergic dysfunction in schizophrenia. Such adjunctive immune-targeted therapies could be selected on the basis of the particular molecular pathway implicated in a disorder, as guided by biomarkers in the brain or periphery. As symptomatic neurochemical treatments are available for most neuropsychiatric disorders, combination approaches promise to bring mechanistically meaningful improvements to patient outcomes.

To date, few clinical trials have prospectively targeted immune-system-related mechanisms in CNS disorders. Nonetheless, within schizophrenia, add-on treatment with NSAIDs in combination with antipsychotic treatment was shown to be effective.[231] Interestingly, a study in rats prenatally exposed to poly I:C showed that treatment with the COX-2 inhibitor celecoxib during puberty (postnatal days 35–46) protected the adult rats from hyperlocomotion induced by MK-801 challenge,[232] suggesting that NSAIDs could be explored as prodromal treatments. Promising results were obtained with the nonspecific microglia modulator minocycline in adult rats exposed to poly I:C *in utero*,[233] but these results have not been clearly confirmed in patients with first-episode schizophrenia.[231]

With the emerging role of inflammation in the development and perpetuation of seizures, there is increasing interest in novel immune-modulatory therapies for epilepsy. Besides anti-inflammatory therapies involving corticosteroids (such as adrenocorticotropic hormone, prednisolone and prednisone), intravenous immunoglobulin and plasmapheresis are currently used in patients with epilepsy to target disease-related autoantibodies that are associated with several forms of limbic encephalitis.[234] However, a need exists for rigorous assessments of these and novel immune-modulating therapies, specifically for use in patients with pharmacoresistant focal epilepsies.

With respect to AD and PD, epidemiological data support a benefit of long-term NSAID treatment: people receiving chronic treatment for an underlying inflammatory disease have a lower risk of developing these neurodegenerative disorders.[235–237] However, large clinical trials of NSAIDs in patients with AD did not find a protective effect.[238] A possible explanation is the existence of particular disease-stage windows during which an anti-inflammatory strategy is most effective for preventing or ameliorating the symptoms of AD or PD. This possibility needs to be further explored in prospective clinical trials or retrospective meta-analyses. One novel approach currently under clinical investigation is to directly target glia-mediated inflammatory aspects of age-related neurodegeneration by reducing the release of reactive oxygen species in the brain with a monoamine oxidase B inhibitor.[239]

The development of approved biological therapies for autoimmune diseases also provides new opportunities to target cytokine signalling directly as a treatment strategy for mIA-related disorders. For example, systemic elevation of IL-6 levels in patients with schizophrenia[38] creates a rationale to target peripheral IL-6 signalling pathways in this disease, for example, via IL-6-receptor-inhibiting recombinant monoclonal antibodies. However, whether targeting of the peripheral IL-6 signalling pathway is sufficient to produce therapeutic effects remains to be determined empirically. Nonspecific immune modulation may have harmful effects by disturbing the delicate balance between disruptive and homeostatic effects of immune factors, including risk of inappropriate immunosuppression.

We believe that the most promising advance is the description of the unique molecular and functional signature of microglia. This signature will probably advance the identification of novel therapeutic pathways,[240] including those that potentially bypass the peripheral immune system. A new generation of compounds, capable of selectively and specifically modulating innate immune functions mediated by microglia, could be on the horizon.[241,242] Such targeted immunomodulatory drugs might be effective across a range of disorders if administered in a prodromal phase. Apart from immunomodulatory treatments, other disease-modifying treatments, such as those targeting myelination or neuronal plasticity (Figure 3), could be personalized to the current state of the patient's immune system, the presence of other known risk factors, and CNS or peripheral biomarkers.

Conclusions

The developing brain is particularly sensitive to environmental signals that influence genetically determined developmental processes. Clinical and preclinical evidence highlights infection-induced mIA as a source of potentially profound effects on developing neural circuits, and as a priming factor for microglia in the offspring. Though sufficient in the rodent mIA model, the initial prenatal insult alone—depending on the timing and strength (Figure 1)—may not be enough for clinical manifestation in humans. A specific genetic background in the offspring, as well as additional immune challenges and adverse events involving immune responses, might be required to trigger the symptoms later in life (Figure 2 and 3).

The hypothetical link with mIA is particularly strong for schizophrenia, autism and epilepsy, but the links between mIA and other neurological diseases, including cerebral palsy and the ageing-related neurodegeneration that leads to AD and PD, are just beginning to emerge. Further preclinical and clinical insights are clearly needed to establish the exact relationships between the complex and interwoven signalling pathway disturbances that take place after mIA, and the long-lasting effects of these disturbances in affected offspring. Nonetheless, convergent empirical evidence is beginning to link dysregulated immune mechanisms with their molecular consequences across CNS disorders. These emerging themes provide a unique opportunity to reconceptualize causal pathways underlying CNS disorders on the basis of shared underlying mechanisms, which might help us to identify novel biomarkers and develop more-effective therapies for disorders on the basis of this enhanced understanding.

Review criteria

PubMed was searched for articles published in any language before May 2014 using the following search criteria in various combinations: "prenatal", "maternal", "*in utero*", "infection", "immune", "inflammation", "microglia", "epidemiology", "schizophrenia", "autism", "cerebral palsy", "epilepsy", "Parkinson", "Alzheimer", "neurodegenerative disorders", "aging", "neurodevelopmental disorders", "microglia priming", "epigenetic", "synapse formation", "myelination", "blood–brain-barrier", "cytokine", "chemokine", "MHC", and "complement". Articles were then screened for relevance, and some reviews were cited rather than the original articles. Additional articles published during the revision of the manuscript were also considered for inclusion. References relating to biomarkers and therapies were collected from the authors' own literature database.

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Mark R. Baker
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