Review

Profound Associations between Maternal Infectious Disease and Fetal Neurodevelopmental Delays

Theodor-Nicolae Carp[1], Michael Metoudi[2,*]

[1].BSc Hons Biomedical Science Alumnus, University of Essex, Colchester Campus; MSc Biomedical Science Student, University of Westminster, Cavendish Campus
[2].Research Scientist, King's College London MSc Molecular Medicine, Trinity College Dublin; MSc Clinical Nutrition, University College Dublin
* Correspondence: mickmetoudi@gmail.com

Abstract: Maternal infectious disease may pose considerable challenges to the fetal health due to the distribution of important elements of the sanguine and lymphatic system from the mother via the umbilical cord. The mother and the fetus have a degree of interdependence that is similar to the one between the eukaryotic cell and the mitochondrion, particularly during the first half term of the pregnancy, which explains the increased appetite of the expecting mother during the first stages of the fetal development. There is a solid bridge between the adaptive immune system and the encephalon that was only discovered a few decades ago. As a result, scientists may still be in the introductory stages of research, and there might be a significant and profound degree of association between the immune system and a healthy neurological development. There is a significant link between the onset of significant maternal infectious disease and the onset of neurodevelopmental disease in the fetus, and virtually all immune cells play major roles in the promotion and inhibition of neurogenesis alike. Likewise, there is a probability that maternal infectious diseases during pregnancy represent a risk factor of fetal neurodevelopmental disease, as a pressurised development of the adaptive immune memory could result in a pressurised or inhibited neurological development, which both can result in a delayed development of certain sub-regions of the brain. For example, the fetus may display poorer social abilities and sharp analytical skills later in life, which is an important sign of neurodevelopmental disease. A pressurised development of the adaptive immune memory could not require the development of a significant form of disease, but rather just a sharp rate of immune preparation against several important pathogenic agents during the introductory stages of life, when the encephalon experiences the sharpest increase rate in development. The problem per se is not the process of immunisation, but a much sharper process of immunisation over the first stages of life in case of an exposure to one dangerous pathogen or more numerous kinds of pathogens and antigens that normally cause moderate disease morbidity. The more dangerous the microbe is, the sharper the development of the adaptive immune memory will be, and the same happens in the case of an increased number of infectious microbes and antigens that infected the cells of the mothers and the fetuses in cause, and this may, in the majority of the situations, still be the case even if the pathogens are already significantly weakened or lifeless, given that the gain of adaptive immune memory alone constitutes an important factor of neurogenesis and an increased rate of neurological development, and that the infant will become almost or fully protected against the pathogens in cause, despite not having had experienced the disease beforehand. In this case, neurodevelopmental delays are possibly not caused by an impaired neurogenesis, but by an excessive one, whilst maternal infection-associated neurodevelopmental delays may be caused by an impaired neurogenesis. Nevertheless, the aetiology of immunity-related neurodevelopmental delays may be more complex in nature and implicate a chronological and spatial sequence of induced excedentary and deficitary rates of neurogenesis, hence reflecting the incredibly complex nature and various forms of neurodevelopmental disease. It is important to mention that a single dose of infant immunisation brings significantly lower risks of adverse neurological events than the onset of a significant maternal infectious disease during pregnancy. The objective of paediatric neuro-immunological studies may be to improve the understanding of the association between a healthy immune developmental rate and a balanced ratio of the developmental rates of important brain regions and sub-regions.

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Keywords: maternal infection; fetal neurodevelopmental delays; neuroimmunology; innate immunity; adaptive immunity; interferon; natural lymphocyte; adaptive lymphocyte; neuroprotection; neurogenesis

Introduction

Maternal infectious disease has represented one of the principal factors for the onset of neurodevelopmental disease in offspring, and the cause of this occurrence is the existence of a fine bridge between immunological and neurological development. The exact resolution of this association is, however, still poorly understood due to the high complexity of the relationship between the immune system and the central nervous system, and the cascade of development stimulation from the activation first-line immune defences and the specialisation of innate and adaptive lymphocytes, to the development of various neurological networks in the encephalon, require extensive further analysis for both immunological and neurological research purposes in prophylaxis and therapy. Given that immune activation and adaptive immune memory gain are ultimately stimulatory of neurogenesis, then it is most likely that immune-related neurodevelopmental delays are caused by prior exaggerated rates of neurogenesis and likewise, the factors of such exaggerations require further analysis. It is probable that part of the research has been limited via efforts to debunk misconceptions and misinformation that have been countering at least vast areas of vaccinology. It is important to hold a multi-dimensional mindset in scientific research in order to remain fully open to receiving knowledge that is outside of our dimension of thinking, as the truth is elongated in such a manner that it includes an infinite number of dimensions. If maternal infectious diseases ultimately bring a deep impact upon the neuro-immunological developmental rates, then it ultimately brings an impact upon the vaccinology-related efforts to utilise up to a couple of dozen of diverse doses to stimulate the development of immunological memory against many pathogens of concern in babies, given that their neurological developmental rates are generally the highest between the sixth month of pregnancy and year 2 after birth. The following question then arrives; will the scientific community be required to innovate additional methods of immunisation that will save lives from pathogens of concern whilst not posing considerable risks for the onset of diverse forms of neurodevelopmental delays?

Louis Pasteur discovered the existence of germs, wrote the germ theory and invented the discipline of vaccinology, thereby discovering the need of immunising the human body against pathogenic agents at the earliest opportunity by means of preventing the onset of severe disease, especially among people with clinical vulnerabilities. As a result, the terrain theory became dismissed among the majority of the scientific communities around the world. Shortly after, a new theory would be discovered in a discipline that seems completely parallel to biology; Albert Einstein discovered the existence of relativity in the Universe and, after an intense period of scientific research, the physicist came with the well-known "E = m x c^2" formula. However, given that physical matter is completely subject to relativity, so are the chemical and biological layers of matter. As a result, there can be the following deduction; any element that is not part of a germ is automatically part of the terrain. Likewise, human and animal immunity belongs to the latter and, as a result, it is both the anti-microbial traits of the terrain and the effects of germ that should matter for modern-day scientific research. Moreover, it is also the germ that is part of the environment and that displays the fundamental molecular signs of life, thereby evidentiating the existence of a degree of dependence to the natural environment, which includes the non-microbial terrain. Likewise, although a solid emphasis upon training human and animal immunity against microbes is necessary for ensuring a continuous natural selection of human and animal species, it is also the regular focus on cleansing the environment

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and empowering human and animal immune systems from their greatest depths that matter enormously in the long-term preservation of the living species. For example, it is necessary to review the evolutionary relationship between human first-line immunity and the ability of new viruses to hijack and inhibit the first-line immune mechanisms in order to limit the ability of such microbes to cause disease and death, particularly at a time when humanity experienced a pandemic with serious negative effects worldwide. Overall, a review of the exact relationship between the germ and the terrain may visibly increase the accuracy of vaccinology and anti-microbial therapeutics, which in turn may support with a higher accuracy the strive to save lives among young children, the elderly and the clinically vulnerable people, as well as to attenuate or even prevent next epidemics and pandemics.

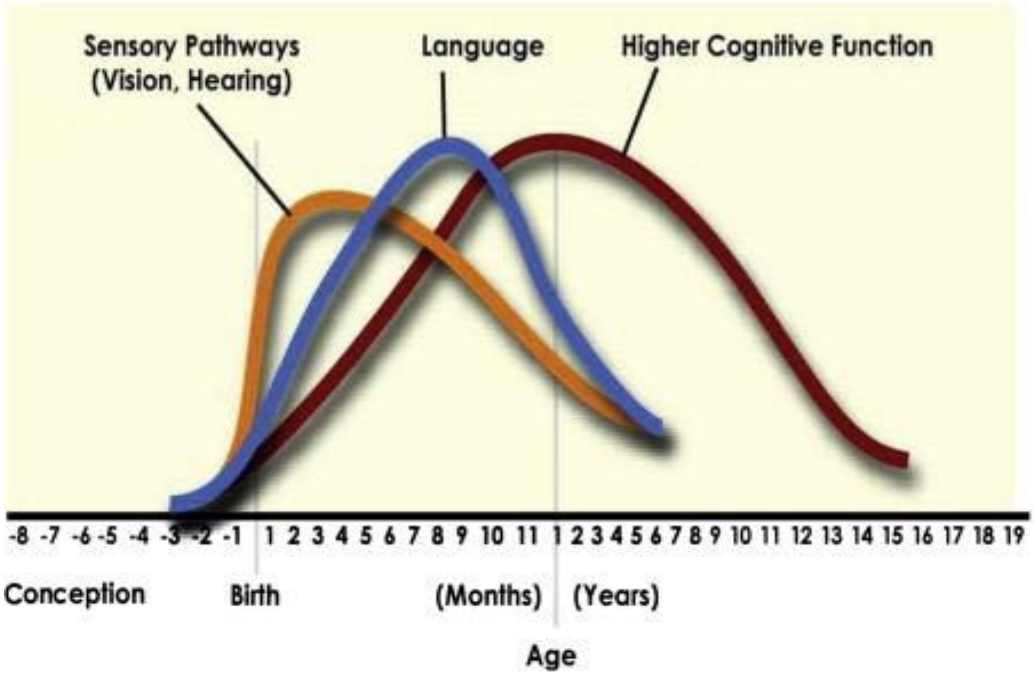

Figure 1: The developmental rate of three important sub-sections of the brain during the first stages of postnatal life (Lutein, Brain and Neurological Functions, 2015).

Evidence collected from numerous studies performed worldwide shows that the administration of low-dose Interferon I and III-based nasal sprays has had prophylactic and early therapeutic effectiveness against one of the most important infectious diseases in the past century. Moreover, a large amount of conclusive evidence has shown that morbid infectious disease is broadly caused by a form of pathogenic suppression of first-line immune responses, and this suppression allows pathogens to suppress and overwhelm the host immune system, particularly in individuals with other co-morbidities. Likewise, there is actually a significant possibility that such prophylactic and early therapeutic interventions will prevent many cases of maternal infectious disease, which in turn will pronouncedly decrease the number of babies that will be born with a form of neurodevelopmental disease. Furthermore, due to the connection of the sanguine and lymphatic system of the mother with the ones of the foetus via the umbilical cord, foetuses could also benefit from a solid degree of immunisation against numerous infectious pathogens. Likewise, there will most likely be no need for intrauterine interventions to help babies develop healthy immune responses against maternal infections and have the risks of the onset of neurodevelopmental delays attenuated or prevented altogether. Overall, the goal should be to help fetuses develop immunity against dangerous microbes without experiencing disease and without developing risks of some forms of collateral damage to other tissues and organs due to the high complexity of the links between certain organ systems.

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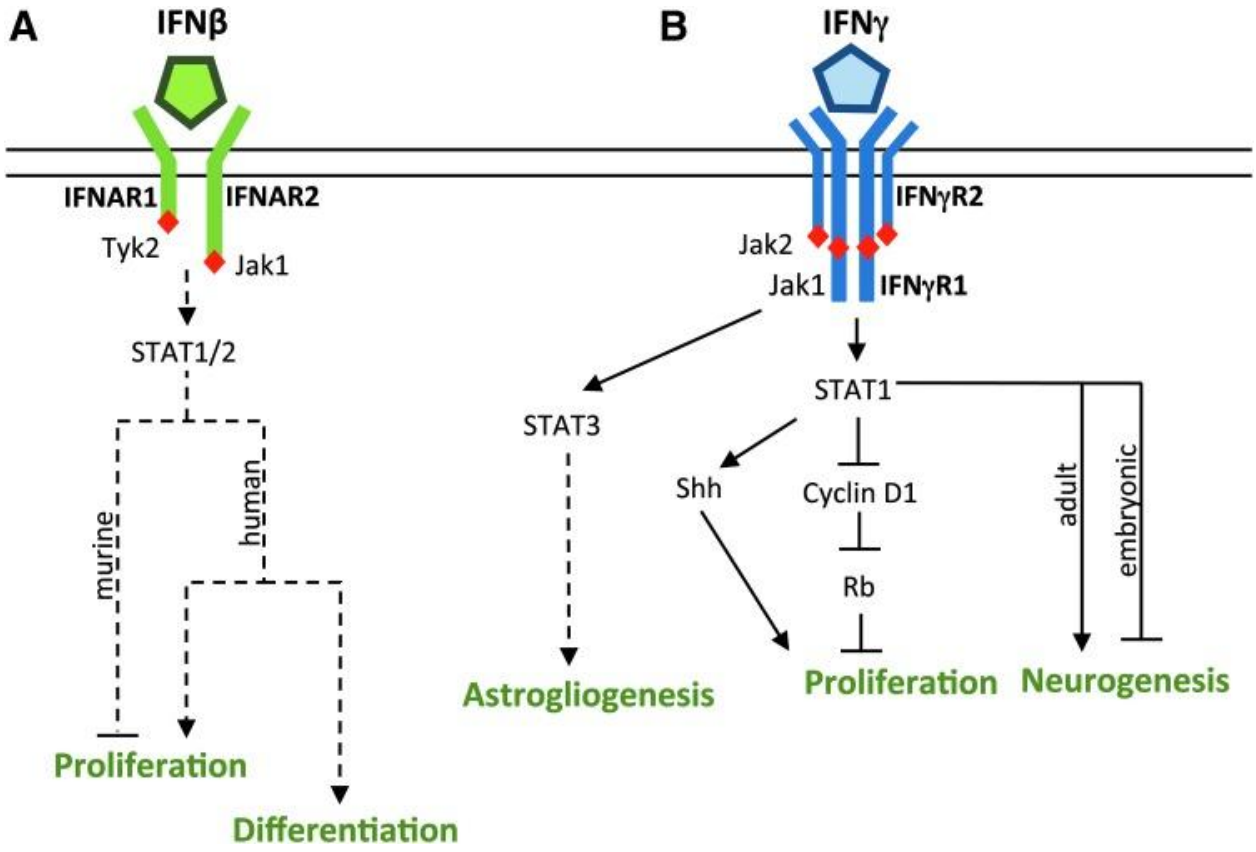

Figure 2: Whilst interferon-beta ultimately plays a role in neuroprotection, the activation of Type I Interferon-based signalling cascades were shown not to bring a considerable influence upon the rates of neurogenesis, whilst restricted Type II Interferon-based signalling cascades are associated with increased rates of neurogenesis and astrogliogenesis (M. N. Chandwani et al., 2019).

Likewise, it is probable that a single or a few sessions of a low-dose nasal administration of Type I (IFN-alpha-2b, -epsilon, -omega, and perhaps IFN-beta, -delta and -kappa) and Type III Interferons (IFN-lambda1, 2 and 3) will help the fetuses be pronouncedly more immunologically prepared against pathogens of medium and high significance, whilst experiencing very low risks of developing adverse reactions, short or long-term. The earlier the activation of the first-line immune defences, the significantly lower the chance of developing significant forms of disease are. Both the mucosal and the systemic immune systems contain cells that produce and signal Interferon I and III to cells containing Interferon-Stimulated Cells, such as epithelial cells, fibroblasts, plasmacytoid dendritic cells, macrophages and parenchymal cells (Swiecki et al., 2011). Furthermore, given that a regulated activation of the C5a complement-related pathway is associated with a robust and regulated Type I and Type III Interferon-based signalling, will the addition of a prophylactic agent preventing an exaggerated C5a complement activation to the interferon approach bring a more efficient and stronger protection against problematic infectious diseases, and will there be any risks of adverse reactions in the mother and/or the foetus? It is important to deep-analyse the associations between developmental immunity and developmental neurology, as well as the common pathways that are responsible for immunisation and neurogenesis.

Methods

We searched peer-reviewed scientific papers on PubMed.gov, by utilising the [MeSH] algorithm and utilising key words, such as “maternal infectious disease”, “natural killer cells”, “adaptive lymphocytes”, “neurogenesis”, “immune evasion” and “immunisation”. We collected essential data to analyse the extent of impact on the incidence of neurodevelopmental disease by the onset of significant maternal infectious diseases

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and by the extent of adaptive immune memory gain. We analysed the dual activity of promotion and inhibition of neurogenesis by the majority of immune cells and inspected its relationship with the intensity of their activities. Afterward, we referenced the relevant results accordingly and we performed statistical significance calculations in order to attempt the determination of a higher resolution of details with regards to the relationship between maternal infectious diseases, innate immune activation, adaptive immune memory gain and the incidence of neurodevelopmental disease in offspring.

Results

After an extensive search and study of relevant peer-reviewed scientific papers and articles, we determined that there is a statistically significant probability of the existence of a firm association between the onset of maternal infectious disease, the gain of immune memory and the higher incidence of neurodevelopmental disease in offspring, and the very likely factor is the critical stage of neurological development in the fetus, given that the maternal neurological state is unaffected by the infection. There is a significantly weaker link between first-line immune signalling and excessive neurogenesis alone, and it is perhaps a more broad level of immune activation (i.e. natural killer cell, antigen-presenting cell and T-lymphocyte-related) that may bring more significant influences on the rates of neurogenesis. Furthermore, we determined that the link between the immune system and the nervous system lies solely upon the developmental side, and not upon the whole mental health spectrum, although affected neurological developmental rates can ultimately affect the entire spectrum of mental health. We determined that the gain of adaptive immune memory, at least for more than one or two pathogenic agents, within the first two years of life, is also associated with developed probabilities that the infant will experience diverse forms of neurodevelopmental disease, and that such probabilities grow exponentially with the number of pathogens of concern that the infant immune system has been trained for. We also found that the administration of one or a couple of rounds of low-dose Interferon I and III-based nasal sprays within the first two years of life probably has considerably lower neurogenesis-stimulatory effects than the administration of seventeen vaccine doses for seven pathogenic agents in such a timeframe. Overall, we determined that the link between maternal infectious diseases and a higher incidence of neurodevelopmental delays is profound enough to threaten the integrity and safety of a few important areas of traditional vaccinology (i.e. pathogen-based) as well.

Discussion

Immune evasion represents a key factor that led to the onset of problematic infectious diseases in the previous centuries. Viruses built an counter-evolutionary response against the ability of toll-like receptors to detect pattern-associated molecular patterns in the viral genome, the ability of interferon-encoding genes to become fully expressed, as well as against the ability of certain products of Interferon-Stimulated Genes to lyse the genetic material of viruses. They also built features that make them capable of preventing the synthesis and secretion of qualitative antibodies and the repairing process of certain mutated or damaged host DNA. In other words, viruses developed mechanisms of action that would directly tackle important activities in both the innate and the adaptive immune system and, one important result is the increased incidence of the onset of autoimmunity. Such a process of collective "immune confusion" led to a more pressurised development of the immune systems in foetuses, which in turn contributed to an excessive rate of neurogenesis, and this process likely resulted in suppressed neurogenesis in other key areas of the foetal brain. Likewise, the matter of viral evolution and immune evasion may represent a foundational problem, as it seems to be a significant factor of multiple distinct natures of pathogenesis. As a result, the need for immunology and vaccinology to change the general course of research and innovation has now likely reached an essential level, given the fine bridge between immune development and neurogenesis rates. Just as Type

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I and III Interferons have a "double-edged sword"-like nature, so it is with Natural Killer Cells and T-Lymphocytes and their relation with rates of neurogenesis. Limited extents of immune activation via natural killer cells, circulatory monocytes, tissue-resident macrophages, as well as B- and T-Lymphocytes tend to increase the rate of neurogenesis, whilst exacerbated activities of such immune cells tend to decrease the rate of neurogenesis. It may be that there is a sequence of dysregulated rates of neurogenesis (i.e. deficitary rates, followed by excessive rates and then deficitary rates again etc.) that play a significant role in the onset of neurodevelopmental delays, rather than a fixed pattern of excess/deficitary neurogenesis. In the case of immunisation, concerns about possible decreased rates of neurogenesis as a direct result can be ruled out without pressure, given the lack of pro-inflammatory responses in the vast majority of the cases. Immune evasion represents an important factor of the development of significant maternal infectious disease and fetal neurodevelopmental disease due to the increased extent of pro-inflammatory chemokine (i.e. CXCL1, CXCL10, CCL2 and CCL3) and cytokine (i.e. IL-1beta, IL-6, IL-18 and TNF-alpha) activation, leading to the large-scale recruitment of natural killer cells and inflammatory monocytes and macrophages, as well as the increased signalling rates of interferon-gamma.

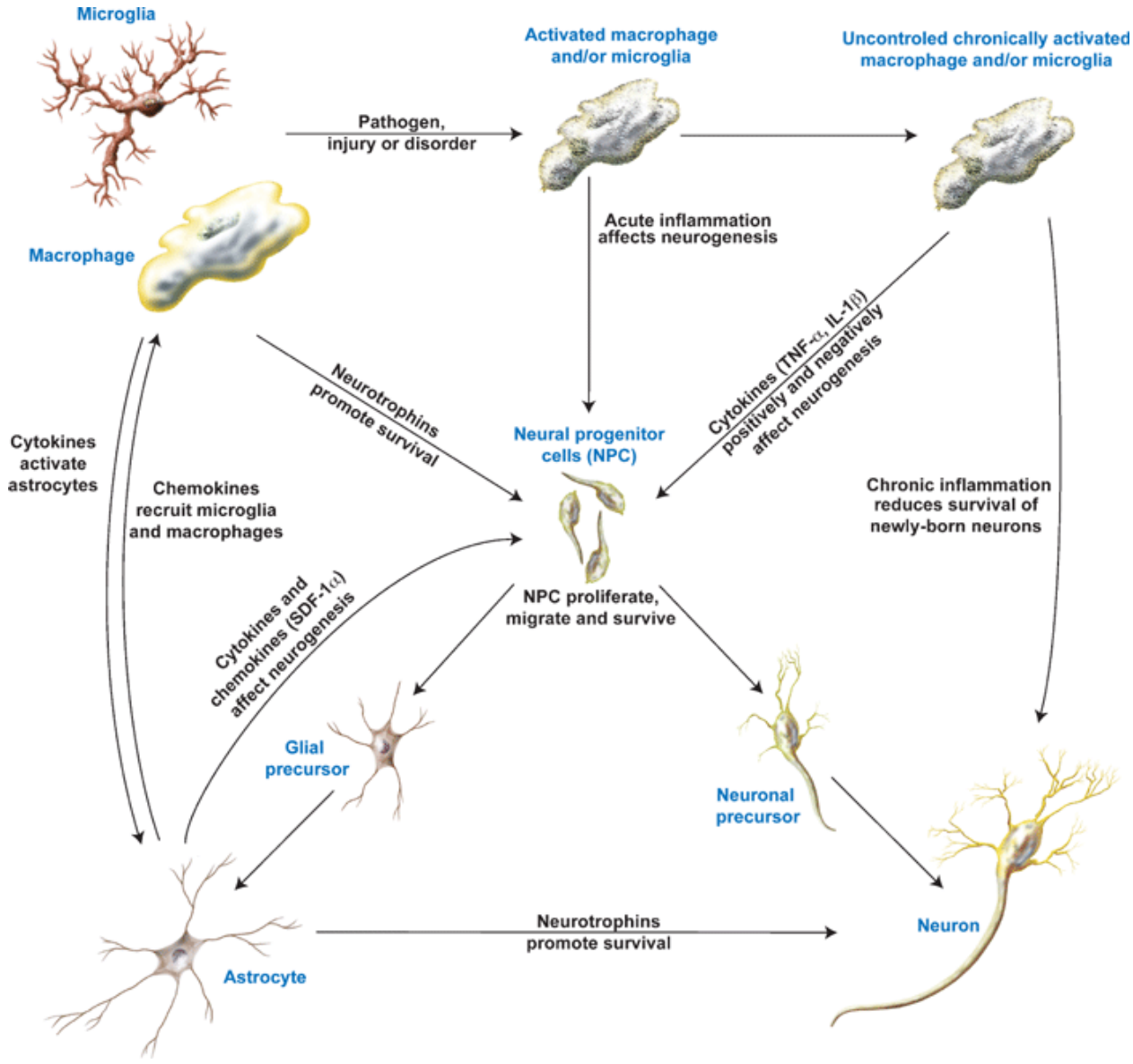

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Figure 3: A diagram displaying the interdependent relationship between chemokines, cytokines, inflammatory macrophages, microglia and neuronal production and maintenance (N. P. Whitney et al., 2009)

The extent of activity by numerous chemokines and cytokines also influence the rates of neurogenesis in a bidirectional manner and, for example, the onset of cytokine storm in the pregnant mother most likely results in an inhibited rate of fetal neurogenesis. Hence, this is the difference between maternal immune activation-related and excedentary immunisation-related neurodevelopmental disease; the first is resulted from a direct impairment of neurogenesis, whilst the second is resulted from an indirect impairment of neurogenesis. Likewise, the concern in the situation of excessive immunisation is the excessive rate of neurogenesis that results particularly from repeated sessions of immunisation during critical neurodevelopmental stages. Forms and extents of immunisation that do not significantly influence rates of neurogenesis are actually associated with increases in the general levels of IQ and EQ as the years pass. Likewise, the objective of the vaccinology-related research community is to innovate methods of immunisation that do not particularly address the neuro-immunological links and offer the immune system the weak form of the antigen, but rather to sensitise first-line immune defences and make them sense and lyse pathogenic genomes faster than the evolutionary ability of pathogens to silence them. In both excessive immunisation and maternal infectious disease situations, there could be similar implications with regards to the rise of the neurodevelopmental delay incidence and intensity of the disease.

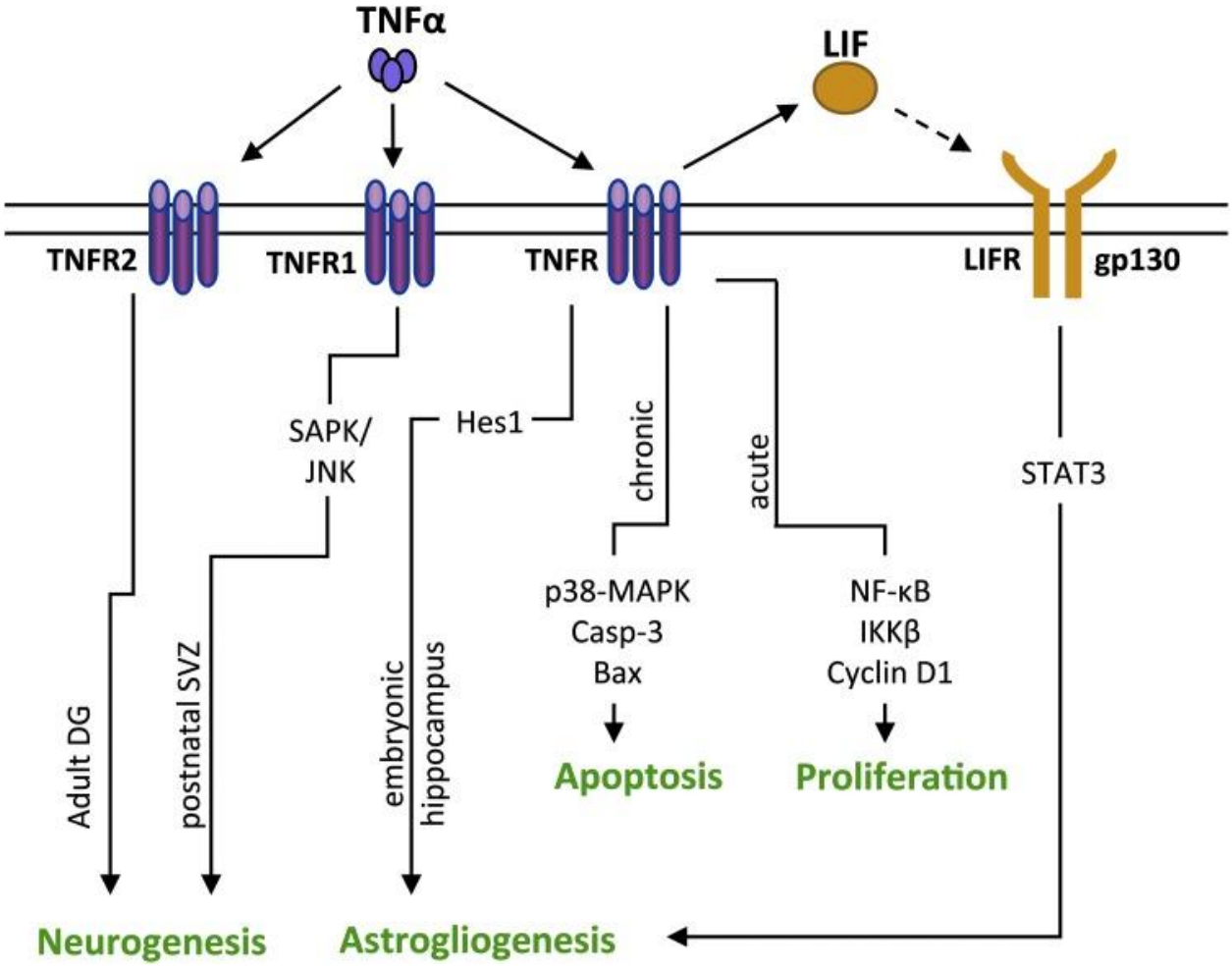

Figure 4: Restricted extents of induced TNF-alpha-based intracellular signalling cascades are associated with stimulated rates of neurogenesis and astrogliogenesis, whilst a restricted extent of LIF-induced STAT3 intracellular signalling cascades is associated with astrogliogenesis only (M. N/ Chandwani et al., 2019).

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The difference between such an Interferon I and III-based maternal approach and traditional methods of vaccination is the indirect training of the immune system to fight off pathogens by means of sensitisation, rather than of a prior gain of immune memory against pathogens of concern, which may have significantly lower neurodevelopmental stimulatory implications. Alternatively, newborns could be offered low dose Interferon I and III-based nasal sprays to train their natural immunity, although further research is likely required in order to rule out risks of inflammatory adverse reactions. This change of approach would also tackle the modern-day challenge of increased viral evolution over cellular immune signalling, as well as adaptive immune evasion, alongside playing important roles in the prevention of tumourigenesis and spread of cancer cells. Moreover, Type I and III Interferons have recently been indicated to play preventive roles against the onset of neurodegenerative diseases, due to their deep, but not that direct, immuno-stimulatory roles upon cells like CD4+ T-helper lymphocytes and microglia to locate and decrease the quantity of aggregated protein throughout the encephalon. Overall, this change of approach could also have positive implications upon the average human lifespan, as it would play a preventive role in the pathogenesis of many kinds of human disease and it would likewise promote lower rates of unnecessary metabolic energy consumption at the intracellular level, given the decreased demand of energy production as a result of pathogenesis.

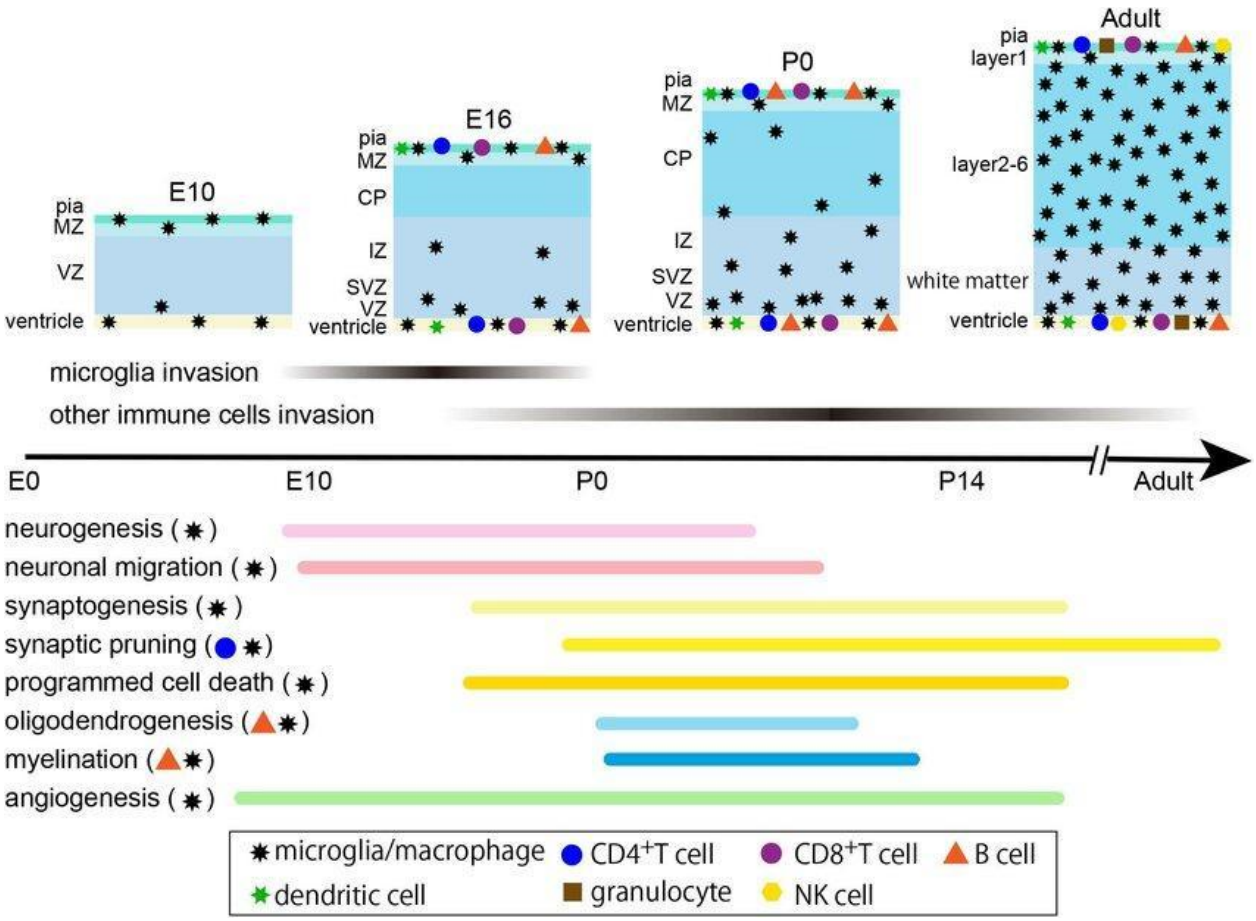

Figure 5: The presence of specific immune and neuronal cells that is contributing to neuronal development and that marks a co-dependence of the two kinds of cells, from early embryonic stages to early adulthood (Morimoto et al., 2019)

The presence of various important kinds of immune cells (i.e. natural killer cells, dendritic cells, macrophages, CD4+ T-lymphocytes and B-lymphocytes) within areas of the central nervous system and during important stages of mass neurogenesis displays the voluminous co-dependence between the nervous system and the immune system, which

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is rather similar to the symbiotic relationship between mitochondria and eukaryotic cells. As a result, infectious during critical stages of neuronal development may have implications upon the rate of neuronal genesis and maturation, and whilst acknowledging the criticality of protecting human life against potentially life-altering and life-threatening infectious diseases, caution should also be rather attentively practiced whilst developing novel methods of immunisation and inoculation for a higher number of concerning pathogens, especially if the patients are in important stages of neurological development. Interestingly, autoimmunity, and specifically a considerable presence of autoantibodies in the organism of the patient, constitute an important immunological marker of autism in the offspring of mothers who experienced significant infectious disease during pregnancy.

Previous research highly indicated an association between the onset of neurodevelopmental disease and higher risks of eventually developing epileptic seizures. What mechanisms in the central nervous system might be at fault, and are there any common genes whose loss or gain-of-function leads to both neurodevelopmental delay-like and epileptic traits?

More significant neurodevelopmental delays automatically may cause forms of neurological damage, and some forms of neurological damage can result in the onset of cognitive and neurological disorders; from attention-deficit hyperactive disorder, obsessive-compulsive disorder and bipolar disease to epilepsy. Moreover, significant neurodevelopmental delays, which result in the onset of autistic spectrum disorder, are also referred to as forms of "inflammation of the brain" and "brain blindness" due to certain symptomatologic expressions that imply greater irritability and loss of general awareness respectively. And the fact that there is a significantly higher incidence of Irritable Bowel Syndrome and Irritable Bowel Disease in autistic people represents an important sign of this, given the considerable associations between the gut health and microbiome, and the encephalon. Autism and epilepsy are known as complex diseases, as they have both genetic and epigenetic factors, and there seems to be an interesting association between outstanding levels of intelligence and increased risks of developing a few or more epileptic seizures. Moreover, before the onset of an epileptic seizure, the patient often goes through a brief process of depersonalisation, when he loses contact with reality, and people on the autistic spectrum also go through such a process from time to time. Perhaps, people on the autistic spectrum are genetically and epigenetically more predisposed to developing epileptic seizures, and it is perhaps immunological inflammation that plays a degree of role in the pathogenesis of both autism and epilepsy.

Conclusion

The associations between the onset of maternal infectious disease and a higher incidence of fetal neurodevelopmental disease may be deeper than previously projected, and if this is the situation, then there is a potential negative impact upon the efforts of vaccinology performed especially in the past half century to tackle several paediatric infectious diseases of concern. The degree of interdependence between the two, particularly via the activation of adaptive immune responses that are more directly implicated in tackling the pathogenic agent, represents a topic that not only deserves further attention, but requires it in an immediate manner. Safety against pathogenic agents of concern is crucial and this is how vaccinology was invented, and what is essential for safety to stay in place long-term is unlimited critical thinking and a full receptivity to all sides of the scientific debate by means of taking note of all points that may contribute to analysis and problem resolution. During an age of high uncertainty with regards to the occurrence of further epidemics and pandemics, we find ourselves to be in critical stages of research and innovation to potentially save millions of lives long-term and overall preserve the general wellbeing of humanity worldwide. Both the COVID-19 pandemic and the recent discoveries of the depths of association between maternal immune activation and excessive fetal neurogenesis have potentially brought us a final opportunity to reform or even to revolutionise vaccinology to preserve its integrity and credibility in the world.

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