NeuroView: Breaking boundaries in neural-immune interactions

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Abstract

For the past 60 years, the central nervous system has been considered immunologically-privileged. Yet results from diverse fields show clear and convincing evidence of bidirectional communication between the nervous and immune systems.

The observations that immune responses are blunted in the central nervous system (CNS) and that the blood-brain barrier (BBB) prevents infiltration of immune cells and molecules into the CNS originally established the belief that the nervous and immune systems were isolated with little interaction except during disease and/or trauma. This dogma was generally accepted for many years and immune responses within the CNS were studied almost exclusively in response to injury and in a handful of "immune-mediated" diseases. Recently, however, a true paradigm-shift in our understanding of neural-immune interactions has occurred due to the convergence of unexpected results from diverse fields showing clear and convincing evidence of bidirectional communication between these systems. Although pioneers in this field still meet resistance from both the traditional neuroscience and immunology communities, interest in this new frontier in neuroscience is accelerating at a dizzying pace and has become a source of great expectations for future discoveries that will allow us to better understand and treat conditions that have thus far eluded explanation.

The classical view that immune responses occur in the CNS exclusively following brain injury received support for decades. Until recently, the BBB was thought to be an impermeable barrier to immune cells and most diffusible factors produced in the periphery. In response to insult, glial cells in the brain produce diffusible factors called cytokines, a large and diverse family of proteins that cross the compromised BBB and signal recruitment and activation of immune cells (see Deverman & Patterson, this issue). In response, blood-derived monocytes migrate through the compromised BBB into the CNS and aid microglia in causing neural inflammation, degeneration, and cell death. The detrimental effects of immune cell infiltration into the CNS have been well-documented, especially in the context

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of autoimmune disorders (see Bhat & Steinman, this issue), and are the focus of drug development to prevent this infiltration.

The dogma of CNS immune-privilege began to break-down with the realization that immune cell infiltration into the CNS may be more common than previously believed. Indeed, many neurological diseases, including Alzheimer'''s and Parkinson'''s disease, are accompanied by neuroinflammation and anti-inflammatory drugs can dramatically reduce the risk for Alzheimer'''s and Parkinson'''s disease (see Lucin & Wyss-Coray, this issue). Despite these exciting findings, the role of the immune system in neurodegenerative disease remains unclear. Is this neuroinflammation the result of increased immune cell infiltration into the CNS, increased levels of cytokines within the brain, or microglial activation caused either by peripheral stimuli or by local immune responses to protein aggregates that form early in the progression of many of these diseases? Once the cause of the increased neural inflammation is identified, it should be possible to design drug therapies that specifically target the altered immune response at distinct stages of these diseases (see Yong & Rivest, this issue).

In addition to brain injury and neurological disease, there is now growing evidence that neural-immune crosstalk may even occur in non-disease conditions, including in the healthy brain. BBB permeability can change as a result of many factors including sub-clinical infection, exposure to environmental toxins, addictive drugs, extreme stress, and possibly from some medications. Some bacteria and viruses have even become adept at breaching this barrier. Finally, it has recently been suggested that the BBB becomes more permeable with healthy aging. Consistent with this observation, healthy aging is accompanied by increased immune activation, expression of genes related to cellular stress and inflammation, and immune cell infiltration into the CNS (see Lucin & Wyss-Coray, this issue). Finally, microglia may become senescent with age, leading to inefficient clearance of toxic protein aggregates in neurodegenerative disease.

Remarkably, it is not just immune cells that participate in neural-immune crosstalk; larger immune proteins, such as antibodies, also appear to infiltrate the brain at times of increased BBB permeability. Such infiltration has been well-documented in autoimmune diseases. For example, autoantibodies produced in systemic lupus erythematosus cross the BBB and may contribute to the cognitive impairments in this disease (see Bhat & Steinman review, this issue). In human development, maternal antibodies (IgG) are passed to the fetus during gestation to provide passive immunity where they serve a protective role until the child'''s immune system matures. A growing body of evidence suggests that some mothers of children with autism produce detrimental antibodies that target brain proteins in their infants (reviewed in Enstrom et al. 2009). While the role of these antibodies in autism is currently unknown, animal models assessing behavioral consequences of prenatal exposure to antibodies from mothers of children with autism showed significant increases in behavioral changes in the offspring that mimic autism endophenotypes (Enstrom et al., 2009).

Increased BBB permeability during gestation suggests that elevated and/or abnormal peripheral immune responses could have profound effects on the developing brain. In fact, several groups have reported a potential link between infections during pregnancy and neurodevelopmental disease in the offspring. The development of a mouse model of

maternal infection has added strong support for a link between maternal immune activation, elevated cytokines, and changes in brain development (see Deverman & Patterson review). Moreover, specific haplotypes of MHCI molecules correlate with increased incidence of schizophrenia and autism, and a growing number of genes encoding immune proteins have been reported to be dysregulated in autistic and schizophrenic brains (see Boulanger, this issue). Ultimately, large-scale epidemiological studies are required to elucidate the true contribution of maternal infection to these disorders (see Ellman & Susser, this issue). Determining if, and how, immune dysregulation contributes to the development of any of these neurodevelopmental disorders is of paramount importance because that information will guide future therapies.

A prevailing hypothesis in this field is that neural-immune crosstalk is often detrimental, mediated by cytokines that cross the BBB and signal a peripheral immune response in the CNS. However, cytokines are also normally produced in the healthy brain where they play critical roles in stem cell renewal, cell fate decisions, neuronal differentiation, and synaptic plasticity required for learning and memory (see Deverman & Patterson, Carpentier & Palmer and Boulanger, this issue). Because cytokines are involved in both normal neuronal function and in mediating the effects of neural inflammation and disease, they appear to be critical effectors that could translate the immune status of an individual into changes in cognition. Cytokines generally fall into two categories: pro-inflammatory cytokines cause destruction of neural pathways whereas anti-inflammatory cytokines are neuroprotective. However, recent evidence suggests that cytokines can exert both neuroprotective and destructive roles, depending on the context and timing. Thus, it is the balance between the protective and destructive roles of cytokines altered in the brain that determines their effects on neural function and has profound implications for drug therapies that target specific cytokines.

The final proverbial nail in the coffin of CNS immune-privilege came about 10 years ago with the observation that classes of "classic" immune molecules, such as major histocompatibility complex (MHCI) molecules, putative MHCI receptors, and components of the complement cascade play important roles in many aspects of neural development and function (see Boulanger, this issue). These immune molecules are clearly present on neurons and glia in the brain and emerging evidence suggests that MHCI molecules, their putative receptors, and members of the complement cascade play important roles in neural plasticity as well as in information processing in the olfactory system (Restrepo et al., 2006). Despite growing evidence supporting roles for immune molecules in many aspects of neural development and plasticity, these observations have been so antithetical to the dogma of CNS immune-privilege that this rapidly growing and exciting new field of research still meets resistance from the basic neurobiology community.

In contrast, many immunologists seem to have embraced the idea that there are functional similarities between the immune and nervous systems. About 10 years ago, it was proposed that specialized contacts between immune cells might be similar to synaptic contacts between neurons; these contacts were called immune synapses. Synapses in either system are defined as stable adhesions between two distinct cells that allow for information transfer through directed secretion. Neuronal synapses are asymmetric structures that use

neurotransmitters to transmit information from the presynaptic axon terminal to receptors on the postsynaptic cell. The immunological synapse (IS) is an asymmetric contact between two cells (e.g. a T cell and an antigen-presenting cell (APC)) that allows controlled secretion of molecules between the engaged cells to effect immune activation. Interestingly, for both neuronal and immune synapses, many of the same cell adhesion molecules regulate the specificity of synapse formation and interact with networks of cytoplasmic scaffolding and signaling proteins to regulate synapse function (reviewed in Yamada and Nelson, 2007).

Recent advances in understanding a less well-known kind of immunological synapse—the natural killer (NK) cell immunological synapse (NKIS)—may have especially interesting implications for our understanding of the plasticity of neuronal synapses. NK cells determine the health of other cells by recognizing the balance of activating and inhibitory ligands expressed by each target. NK cells form transient adhesions to nearby cells and detect the presence, or absence of MHCI molecules on them. A lack of MHCI on the target, caused by viral infection or tumorigenesis, favors formation of an activating IS using mechanisms similar to those described for T cell-APC synapses. Conversely, the presence of MHCI on the target results in binding of MHCI to NK inhibitory receptors, including PirB and Ly49 receptors, which initiates dominant inhibitory signaling and prevents the formation of the NK cell activation synapse (reviewed in Krzewski & Strominger, 2008). Because both PirB and Ly49 NK inhibitory receptors are present in the CNS, it is possible that these receptors mediate the effects of MHCI on synaptic refinement (see Boulanger, this issue).

Although there has been much recent focus on immune molecules present at neural synapses, there is equally exciting data showing that proteins traditionally studied at neural synapses play important roles in immune function (reviewed in Habibi et al. 2009). Perhaps the most compelling example in this literature is the role for glutamate receptors on several types of immune cells. Glutamate receptors are expressed on peripheral blood mononuclear cells (PBMC) and T-cells, where they are believed to be involved in immune development, activation, response, and survival. In addition, GABA receptors on PBMCs also appear to modulate immune responses (Habibi et al., 2009). Thus, it is possible that a genetic defect in a common receptor pathway, such as either of these receptors, may manifest in changes in both neuronal and immune function.

Taken together, these data indicate that "immune proteins" play integral roles in neural development, function and plasticity, and "neural proteins" play equally important and interesting roles in the immune system. Do these molecules play similar or distinct roles in the two systems? If they play similar roles, and if there is truly open dialogue between the two systems, then peripheral immune responses might affect shared proteins in the nervous system, altering neural development and/or function either transiently or pathologically during systemic infection or disease. Interestingly, illnesses accompanied by high levels of systemic pro-inflammatory cytokines are often associated with cognitive problems, perhaps due to disruption of normal cytokine functioning in synaptic plasticity (see Boulanger, this issue). Moreover, a mouse model that lacks a functional immune system (severe combined immunodeficient; SCID mice) shows impairment in the acquisition of cognitive tasks, and acute depletion of adaptive immunity in normal adult mice impairs their learning behavior

(Brynskikh et al., 2008). Finally, our immune responses might be altered not just in disease, but even by major events in our lives. Increased levels of pro-inflammatory cytokines and neural inflammation, stimulated by chronic stress (see Sorrells & Sapolsky, this issue), likely also contribute to the altered synaptic plasticity and long-term cognitive changes in depression. Thus, in addition to investigating whether neural-immune crosstalk could and should be targeted in therapies for neurodevelopmental and neurodegenerative diseases, perhaps even subtle psychiatric changes could be improved with directed manipulation of immune signaling within the brain.

These dynamic new discoveries could be taken as evidence that immune responses within the CNS are always deleterious. But such extreme interpretations of this field are overly-simplistic, and potentially more harmful to human health than the altered immune responses in the brain themselves. Our understanding of crosstalk between the immune and nervous systems is still in its infancy and a better understanding of both the neuroprotective and destructive roles of the immune response within the CNS is essential for major advances in treating diseases with an immune component. We also need a much better understanding of both the roles and balance of immune responses in the healthy brain during neural development and aging. Can we alter this balance to better and more subtly control the immune response and neural inflammation in typical development and aging, as well as during disease? The development of more specific therapeutic interventions will require defining precise roles for immune molecules and cells in the CNS at specific ages, and the balance between protective and destructive responses in the CNS in specific disease contexts. Given the rapid progress in this very young field of neuroimmunology, it is possible that we could even devise ways to protect the functions of immune molecules on neurons that mediate neuronal growth and plasticity while allowing other important, but less destructive aspects of the CNS immune response to occur.

Finally, neural-immune crosstalk also has profound implications for public health policy. Growing evidence that maternal immune activation could increase the incidence of autism or schizophrenia in offspring suggests that health-care providers should revisit the pros and cons of using anti-inflammatory drugs in pregnancy with the goal of developing drugs that prevent a pro-inflammatory response in the CNS without damaging the fetus. Another issue for society right now is whether, and when, pregnant mothers should be given the seasonal flu and H1N1 vaccines. While the flu can be extremely harmful to pregnant women, the effects of stimulating the immune response with two flu vaccines during pregnancy are unknown. Absent the luxury of waiting for large-scale study results, recommendations that pregnant women receive both vaccines may be valid based on current knowledge of the dangers of natural flu infection during gestation. However, since the negative effects of immune stimulation during pregnancy are likely determined by susceptibility factors, our understanding of factors that cause aberrant baseline immune responses in some pregnant women must be improved, and better methods for susceptibility screening developed soon. Finally, it is important to note that neural-immune crosstalk could also be affected by the current schedule of childhood immunizations. Although there is some epidemiological evidence that immunizations are not likely to have a direct role in the ontogeny of autism (Institute of Medicine, 2004), it is still possible that responses to the number and combinations of vaccinations given at some visits could contribute to cognitive changes in

children who may already have altered immune responses. However, natural infections in an individual with a dysfunctional immune system might have an equally deleterious effect. Thus, a better understanding of the effects of immune activation during gestation and early postnatal development, especially in the context of increased disease-susceptibility, will be critical to either validate our current health policies or modify them for specific populations of individuals.

Although at this point the relationship between the neural and immune systems is still emerging, the long-lasting impact of current studies may be profound. A whole-systems approach is becoming critical to the successful study and treatment of both neurodevelopmental and neurodegenerative disorders. We have now come to realize that beyond its traditional role in host defense, the immune system can be considered as a diffuse sensory organ, which works in concert with the nervous system to achieve and maintain homeostasis throughout the body. One could imagine that in the future, evaluation of immune function may be essential to understanding and treating many neurological and psychiatric disorders. Breaking down the boundaries between the fields of immunology and neuroscience is not only intellectually exciting, but the future of our health may depend upon it!

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