Neuronal influence behind the central nervous system regulation of the immune cells

Anahí Chavarría†* and Graciela Cárdenas2

1 Laboratorio de Neuroinmunología, Departamento de Medicina Experimental, Facultad de Medicina, Universidad Nacional Autónoma de México, México City, México
2 Departamento de Neuroinfectología, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, México City, México

INTRODUCTION

The central nervous system (CNS) has a highly specialized microenvironment, which has developed several mechanisms to protect itself from immune-mediated inflammation. This microenvironment is sustained by existing physiological and anatomical elements such as the blood-brain barrier (BBB) that limits peripheral immune cells and molecules entry; the afferent nerves of the autonomic nervous system (ANS) that limits systemic neurogenic inflammation; and the resident cells that also limit immune access to the CNS. These cell populations exert a strong role in the regulation of the immune system, favoring an immune-modulatory environment in the CNS. Neurons control glial cell and infiltrated T-cells by contact-dependent and independent mechanisms.

CONTACT-DEPENDENT MECHANISM FOR IMMUNE MODULATION

Neurons can display an array of membrane molecules in order to control local immune functions; these molecules can target local immune cells like microglia and astrocytes or peripheral immune cells present in the CNS. When BBB is ruptured, immune privilege is lost and neurons may come in contact with T or mononuclear cells, endangering their survival. However, neurons might modulate these immune cells by several strategies, either indirectly suppressing T-cell activation by restriction of antigen presenting properties of glial cells, directly suppressing T-cell activation, or promoting apoptosis of activated microglia and T-cells (Tian et al., 2009).

MOLECULES INHIBITING GLIAL ACTIVATION

The neuronal cell adhesion molecule (NCAM/CD56) is expressed on the surface of neurons, astrocytes and microglia (Sporns et al., 1995; Krushel et al., 1998; Chang et al., 2000a,b), and has a critical role in cell-cell adhesion, synaptic plasticity, neurite outgrowth, among other processes (Tian et al., 2009). Astrocyte-neuron interactions via NCAM lead to modulate glial scar formation by the inhibition of astrocyte proliferation in vitro and in vivo after performed stab lesions in the striatum, cerebral cortex, or hippocampus (Krushel et al., 1995, 1998). NCAM requires the activation of the glucocorticoid receptor to inhibit growth

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factor-induced mitogen-activated protein kinase (MAPK) activity and therefore preventing astrocytic proliferation (Krushel et al., 1998). NCAM also modulates microglial activation, decreases the production of TNFα and nitric oxide (NO) after glial stimulation with lipopolysaccharide (LPS) by reducing the expression of transcription factors like c-Jun, among others (Chang et al., 2000a,b). For the mediation of glial immune responses the homophilic binding of third Ig domain of NCAM is crucial (Sporns et al., 1995; Krushel et al., 1998).

Another important molecule thought to contribute to the constitutive anti-inflammatory and regulatory environment of the brain is CD200, a highly expressed glycoprotein in the CNS, mainly in neurons (Chitnis et al., 2007; Koning et al., 2009). Neuronal CD200 down-modulates the activation state of perivascular macrophages and microglia trough the CD200 receptor (Hoek et al., 2000). Upon binding to its ligand, the tyrosine residues on the cytoplasmic tail of CD200R are phosphorylated and the downstream signaling leads to inhibition of p38 MAPK, c-Jun N-terminal kinase (JNK), and extracellular-signal-regulated kinases (ERK; Zhang et al., 2004), interfering with the activation of macrophages and microglia. Moreover, IL4 mediated neuronal CD200 expression maintains microglia in a quiescent state and anti-inflammatory/neuroprotective profile (Lyons et al., 2009). Additionally, aging leads to a depressed CD200 expression and microglial activation, favoring a pro-neurodegenerative disease environment (Cox et al., 2012). Also, defects in CD200-CD200R pathway play a critical role in neurodegenerative disease development such as multiple sclerosis (MS), Parkinson’s and Alzheimer’s diseases (Koning et al., 2007; Walker et al., 2009; Zhang et al., 2011).

CD22 is a regulatory sialic-acid-binding molecule that mediates neuron binding to microglia through CD45, inhibiting CD40L-induced microglial activation by suppression of the p38 and p44/42 MAPK signaling pathway and preventing microglial TNFα production after LPS stimulation (Tan et al., 2000; Mott et al., 2004; Zhu et al., 2008).

Neuronal membrane integrin-associated protein (CD47) is specially concentrated on synapses and exerts its neuroimmune functions mainly via two receptors (Tian et al., 2009). CD172 (SIRPa) ligation results in phosphatidylinositol 3-kinase (PI3K) signaling cascade activation, and reduces inflammation severity by increasing TGFβ levels, diminishing phagocytosis TNFα and INFα levels (Reinholt et al., 1995; Smith et al., 2003). Furthermore, decreased levels of CD47 are found in chronic active and inactive MS lesions, possibly favoring persistence of damage by the lack of regulation of activated microglia and macrophages (Koning et al., 2007). CD47 interaction with thrombospondin TSP, a further receptor, leads to T-cell and microglia apoptosis via CD95/CD95L pathway also reducing inflammation (Lamy et al., 2007).

Residential brain cells express CD95L (FasL) constitutively to limit possible damaging inflammatory responses. Neuronal CD95L expression induces apoptosis of infiltrating and autoreactive T-cells (Flügel et al., 2000), as well of activated microglia (Choi and Benveniste, 2004). Additionally, CD95L protects neurons from perforin-mediated T-cell cytotoxicity (Medana et al., 2001).

The expression of chemokine CX3CL1 (fractalkine) and its receptor CX3CR1 is limited to neurons and microglia, respectively (Hughes et al., 2002). CX3CL1 can be found membrane-anchored or secreted both in physiological and pathological conditions such as facial motor nerve axotomy or a toxic model of Parkinson’s disease (Harrison et al., 1998; Cardona et al., 2006). CX3CL1-CX3CR1 interactions lead to the JNK MAPK pathway activation and Nrf2 recruitment suppressing the neurotoxic microglia activity and reducing neuronal death due to inflammation (Zujovic et al., 2000; Mizuno et al., 2003; Cardona et al., 2006; Noda et al., 2011).

**MOLECULES INHIBITING IMMUNE CELLS**

Plexin and semaphorin signaling has revealed that several members of this family are involved in immune cell processes. Among these semaphorins are Sema-3A, Sema-3E, Sema-4D, Sema-4A, Sema-6D, and Sema-7A (Roney et al., 2013). However, only Sema-3A and Sema-7A are expressed by neurons, respectively either as secreted or membrane-bound regulatory proteins that attenuate T-cell activation, proliferation, and function through T-cell receptor (TCR) signaling (Czopik et al., 2006; Lepelletier et al., 2006). Sema-3A exerts its action forming a complex with neuropilin-1 and plexin-A1 that leads to the prevention of immune response over-activation and the inhibition of human monocytes migration through the blockage of actin cytoskeleton reorganization, interfering with TCR polarization and signal transduction events by down-modulation of MAPK signaling cascades (Lepelletier et al., 2006). Also stressed neurons may induce apoptosis of INFγ or LPS activated microglia through Sema-3A secretion recruiting CD95 to lipid rafts next to neuropilin-1 (Majed et al., 2006; Moretti et al., 2008). Sema-7A, a glycosylphosphatidylinositol-linked semaphorin, negatively regulates TCR signaling and avoids activation of the ERK-MAPK pathway decreasing T-cell proliferation.
proliferation. Sema-7A deficient mice present T-cell hyperresponsiveness and hyperproliferation with severe experimental autoimmune encephalomyelitis pathology (Czopik et al., 2006).

Additionally, N- and E-cadherins are highly expressed in the CNS and bind to the killer cell lectin-like receptor G1 (KLRG1) on NK- and T-cells, preventing NK lysis of neurons and suppressing CD8 + T-cells antigenic proliferation and cytolytic activity (Gründemann et al., 2006; Ito et al., 2006).

Only soma and dendrites of neurons express the intercellular adhesion molecule-5 (ICAM-5/telencephalin; Tian et al., 2000). Neurons bind to T-cell through the ICAM-5-CD11a/Cd18 (LFA-1) interaction diminishing TCR dependent T-cell activation and enhancing TGFβ and INFγ expression in naïve T-cells (Tian et al., 2008). Additionally, ICAM-5 can be cleaved by activated T-cell or microglial-secreted matrix metalloproteinases-2 and -9, soluble ICAM-5 may compete with ICAM-1 costimulatory signal necessary for T-cell activation (Tian et al., 2008). Also, soluble ICAM-5 is present in blood and cerebrospinal fluid after hypoxia due to carotid artery ligation in mice and acute encephalitis in humans (Guo et al., 2000; Lindsberg et al., 2002). Moreover, ICAM-5 regulates microglia morphology and function by facilitating cell spreading and increasing CD11a/Cd18 expression (Mizuno et al., 1999).

**NEURON-MEDIATED GENERATION OF REGULATORY T-CELLS**

Regulatory T-cells (Tregs) are important in keeping CNS homeostasis in healthy and pathological conditions, and are also locally induced by glia cells and neurons (Liu et al., 2006; Saenz et al., 2010). Encephalitogenic T-cell production of IFNγ and TNFα leads to neuronal expression of TGFβ1, CD80, and CD86, which induce encephalitogenic CD4 + T-cells to become Tregs, in a cell-to-cell dependent and antigen independent way through the TGF-β1-TGF-βR and TCR signaling pathway (Issazadeh et al., 1998; Liu et al., 2006). Neuron-induced Tregs are able to inhibit progression of experimental autoimmune encephalomyelitis by suppression of encephalitogenic CD4 + T-cells proliferation (Liu et al., 2006).

| Neuronal molecule | Target cell | Receptor | References |
|-------------------|-------------|----------|------------|
| **CADHERIN SUPERFAMILY** | | | |
| E-cadherin | NK-cell, T-cell | KLRG1 | Gründemann et al., 2006; Ito et al., 2006 |
| N-cadherin | NK-cell, T-cell | KLRG1 | Ito et al., 2006 |
| **IMMUNOGLOBULIN SUPERFAMILY MOLECULES** | | | |
| CD22 | Microglia | CD45 | Mott et al., 2004 |
| CD47 | Microglia | CD172a, TSP | Smith et al., 2003; Lamy et al., 2007 |
| CD200 | Microglia | CD200R | Hoek et al., 2000; Rijkers et al., 2008 |
| ICAM-5 | T-cell | CD11a/Cd18 | Mizuno et al., 1999; Tian et al., 2000, 2008 |
| NCAM | Microglia, Astrocyte | NCAM | Sporns et al., 1995; Krushel et al., 1998; Chang et al., 2000a |
| **TUMOR NECROSIS FACTOR FAMILY** | | | |
| CD95L | Microglia, T-cell | CD95 | Choi and Benveniste, 2004 |
| **CYTOKINES AND CHEMOKINES** | | | |
| IL10 | Microglia, T-cell | IL10R | Strle et al., 2001 |
| TGFβ | Microglia, T-cell | TGFβR | Pratt and McPherson, 1997; Liu et al., 2006 |
| CX3CL1 | Microglia | CX3CR1 | Hughes et al., 2002 |
| **NEUROTRANSMITTERS AND NEUROPEPTIDES** | | | |
| GABA | Microglia | GABAAA, GABAB | Färber and Kettenmann, 2005 |
| Dopamine | Microglia, T-cell | D1, D2, D3, D4, D5 | Färber et al., 2005 |
| NE | Microglia, Astrocyte, T-cell | α1A, α2A, β1, β2 | Färber et al., 2005; Gyoneva and Traynelis, 2013 |
| VIP | Astrocyte, T-cell | VPAC1, VPAC2 | Delgado et al., 2004, 2008 |
| **NEUROTROPHINS** | | | |
| NGF | Microglia, Astrocyte | p75, NTR, TrkA | Neumann et al., 1998; Althaus and Richter-Landsberg, 2000; Cragnolini et al., 2012 |
| BDNF | Microglia, Astrocyte | p75, NTR, TrkB | Neumann et al., 1998; Althaus and Richter-Landsberg, 2000 |
| NT-3 | Microglia | p75, NTR, TrkB, TrkC | Neumann et al., 1998; Althaus and Richter-Landsberg, 2000; Tseng and Huang, 2003 |
| **SEMAPHORINS** | | | |
| Sema-3A | Microglia, T-cell | Neuregulin-1 and plexin-A1 | Lepelletier et al., 2006 |
| Sema-7A | T-cell | Plexin-C1, α1β1 integrin | Czopik et al., 2006 |

BDNF, brain-derived neurotrophic factor; ICAM-5, intercellular adhesion molecule-5; GABA, γ-aminobutyric acid; NCAM, neuronal cell adhesion molecule; NE, norepinephrine; NGF, nerve growth factor; NT-3, neurotrophin-3; Sema-3A, semaphorin-3A; Sema-7A, semaphorin-7A; VIP, vasoactive intestinal peptide.
CONTACT INDEPENDENT MECHANISMS FOR IMMUNE MODULATION

Constitutive-secreted neurotrophins, neurotransmitters, and neuropeptides, as well as cytokines provide contact-independent routes for neurons to control microglial and T-cell activities.

Neurotrophins play a critical role in the control of neuronal survival, migration, and differentiation and modulate immune cell functions (Tabakman et al., 2004). Nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) can inhibit MHCII expression in microglia in hippocampal slice cultures via the low affinity p75 neurotrophin receptor (Neumann et al., 1998). NGF also down-regulates the co-stimulatory molecules CD40 and CD86 in microglia (Wei and Jonakait, 1999), is increased in cerebral spinal fluid of MS patients (Laudiero et al., 1992), and NGF treatment delays EAE onset and clinical severity (Arredondo et al., 2007). Nerve growth factor treatment delays EAE onset and clinical severity (Arredondo et al., 2007). Nerve growth factor in experimental autoimmune encephalomyelitis (EAE) ameliorates disease by inhibiting Th1 cytokine production and Th2 cytokine production, as well as inflammatory responses (Bjurstöm et al., 2008; Delgado et al., 2008). Physiological concentrations of GABA activate functional GABA_A channels on encephalitogenic T-cell decreasing cell proliferation, while GABA_B channels activation on microglia attenuates IL6 and IL 12p40 levels after LPS stimulation (Kuhn et al., 2004; Bjurstöm et al., 2008). Functional dopamine receptors D1 and D2 are expressed by microglia and their activation lead to attenuate NO production after LPS stimulation (Kuhn et al., 2004). CNS NE levels are relevant in order to maintain tissue homeostasis since NE loss contributes to neuroinflammatory processes that lead to neurodegenerative diseases, for instance depressed mice with low NE levels respond with higher TNFα production after LPS stimulation while increasing NE levels are necessary to reduce EAE severity (Szelenyi and Vizi, 2007; Simonini et al., 2010). Moreover, NE regulates microglia morphology and motility by microglial processes retraction; in this dynamic process the β2 and α2A receptors are involved in resting cells and activated microglia cells, respectively (Gyoneva and Traynelis, 2013).

CONCLUSIONS

Traditionally glial cells are considered to be responsible for the regulation of immune processes in the CNS. Nevertheless neurons contribute to immune modulation through contact-dependent and -independent mechanisms (Figure 1). Several neuronal secreted as well-membrane associated molecules (Table 1) are implicated in the control of glial and T-cell functions, thus contributing to CNS immune privilege.

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