



INDUCTION AND PRODUCTION OF CHEMOKINES IN THE CNS BY VIRUS-INFECTED CELLS

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ABSTRACT

Chemokines are proteins that regulate cell migration, especially that of immune cells, which increase during infection and inflammation. They are activated by G protein-coupled receptors (GPCRs) and the Gi protein, to participate in various intracellular pathways involved in cytoskeletal reorganization and chemotaxis. In the central nervous system (CNS), chemokines contribute to neuroinflammation, while during infections, they coordinate leukocyte recruitment through integrin activation and the phases of rolling, adhesion, diapedesis, and chemotaxis, linking microorganism recognition to the inflammatory response. Cells in the brain recognize viral genetic material through innate immune receptors, activating pathways such as NF- κ B, mitogen-activated protein kinase (MAPK), and AP-1, which induce the production of chemokines that attract specific immune cells and coordinate the antiviral response. CD8⁺ lymphocytes are activated by T-cell receptor (TCR)/major histocompatibility complex class I (MHC-I), costimulation, and cytokines, to proliferate and reach infected tissues thanks to chemokines, where they eliminate infected cells via perforin, granzymes, or FAS-FASL and produce interferon gamma (IFN- γ), promoting the antiviral response, the expression of MHC-I, and the activation of macrophages. Virus-infected cells in the brain produce type I IFNs and pro-inflammatory cytokines that induce chemokines such as CXCL10, CCL2, CXCL9, and CCL5. These chemokines attract lymphocytes, natural killer (NK) cells, and monocytes/macrophages to the CNS, contributing to infection control and neuroinflammation. In neurodegenerative diseases and during brain damage, chemokines activate microglia and astrocytes and can cause inflammation, oxidative stress, and alterations in the blood-brain barrier (BBB). Chemokines can induce neurodegeneration and neuronal damage, but in some cases, they also promote repair, neuronal survival, and neuroprotection, depending on the chemokine, receptor, cell type, and disease stage.

KEYWORDS: *Chemokine, virus, infection, CNS, immune cell*

INTRODUCTION

Chemokines are small proteins involved in cell migration and attraction that primarily affect immune cells (1) They are produced by various cells, including endothelial cells, immune cells, and fibroblasts (2). Neurotropic viruses that infect the central nervous system (CNS) can activate an immune response in which chemokines play a key role (3).

Viruses are recognized by the CNS and induce the production of cytokines and chemokines that recruit immune cells and cause neuroinflammation and cellular degeneration (3). In inflammatory processes, cell damage, and infections,

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chemokines increase their production and bind specifically to their receptors (2). It is known that CXC chemokines primarily attract neutrophils, whereas CC chemokines are chemotactic for lymphocytes and macrophages. Chemokines activate G proteins, causing a conformational change in the receptor. Activation of the G α i protein reduces the activity of adenylate cyclase and activates various intracellular pathways (1). The main signalling pathways activated by chemokines are PI3K/Akt, PLC β /Ca $^{2+}$, Ra/MAPK, and the activation of Rho, Rac, and Cdc42, which are important for the cytoskeleton (1).

Chemokines are essential for cellular chemotaxis, resulting in the directional migration of the target cell toward the source of the chemokine. The cell forms a "leading edge" facing the generation of the chemokine and rearranges actin via Rac and Cdc42 and forms cellular protrusions (4). In addition, the cell establishes adhesion to the substrate, contracts the trailing edge via Rho/ROCK and myosin, advancing towards the gradient (4). Chemokines cause leukocyte recruitment in inflammatory processes by coordinating immune cell trafficking and intervening in both the cellular and humoral immune responses, where they guide immune cells circulating in the peripheral blood (5,6).

Chemokines are produced in inflamed tissue and presented on the endothelial surface. Neutrophils possess chemokine receptors and come into contact with selectins present on the endothelium. Chemokines act on G protein-coupled receptors (GPCRs) (1,2). In microbial infections, macrophages, fibroblasts, dendritic cells, endothelial cells, and others produce IL-1, TNF, IL-6, and other inflammatory cytokines, causing tissue damage (7,8) (Fig.1). In particular, chemokines bind to their receptors by activating the G α i protein which activates PI3K/PLC and mitogen-activated protein kinase (MAPK) (1). These reactions lead to an increase in intracellular Ca $^{2+}$, PIP $_3$, activation of AKT and Rac/Rho/Cdc42. Rac/Rho/Cdc42 are involved in the reorganization of the cytoskeleton, causing cell wall concentration and directional movement (4). In addition, chemokines transform leukocyte integrins, making them more high affinity (5,6) The integrins LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) bind to ICAM-1/ICAM-2 molecules, allowing the rolling phase with subsequent activation, adhesion, diapedesis, and chemotaxis (6). In infections, chemokines are important because they link microorganism recognition to leukocyte migration to the site of inflammation (9).

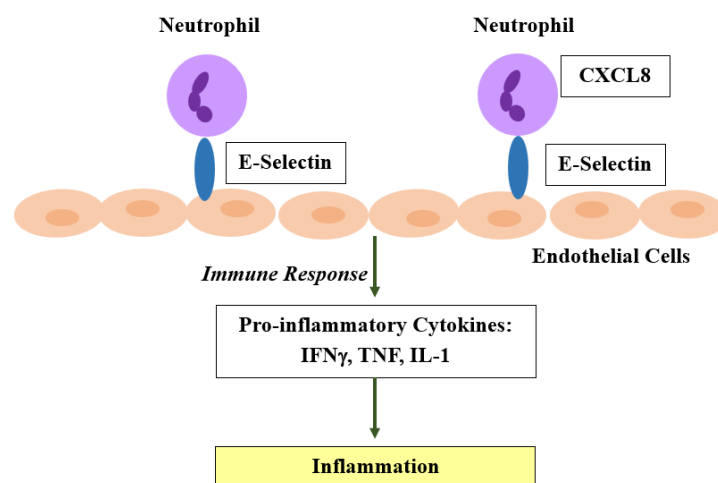


Fig. 1. Neutrophils produce chemokines that bind endothelial cells through E-selectin which induces an immune response with the release of pro-inflammatory cytokines, leading to inflammation.

DISCUSSION

Cells in the brain, such as microglia, astrocytes, and endothelial cells, recognize viral RNA or DNA via innate immunity receptors (10). After a pathogenic virus infects tissue, immune cells rush to the area and recognize pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs) (11). Toll-like receptor (TLR) activation on the cell membrane stimulates NOD1/NOD2 in the cytoplasm and RIG-1/MDA5, which induces viral RNA and cGAS-STING, which binds DNA and leads to the production of inflammasomes with caspase-1 activation (10,11). After several reactions, TLR activation leads to the generation of NF- κ B and, in parallel, TAK1 with activation of MAPK and AP-1 (9). These molecules enter the nucleus and increase chemokine transcription (9). Each specific chemokine binds to its receptor and recruits specific immune cells (12) (Table I).

Table I. *Some chemokine ligands with their corresponding receptors.*

<i>Ligand</i>	<i>Receptor</i>
CXCL8	CXCR1, 2
CXCL11, 12	CCR7
CXCL16	CXCR6
CXCL13	CXCR5
CXCL12	CXCR4
CX3CL1-CCL26	CX3CR1
CXCL1, 5, 7	ECRF3
CCL2, 3, 4, 5	US28
CCL2,3,4,5	UL12
CCL3, 4, 5, 7, 14, 15, 16	CCR1
CCL2, 7, 8, 12, 13	CCR2
CCL5, 7, 11, 13, 14, 15, 24, 26	CCR3
CCL2, 3, 5, 17, 22	CCR4
CCL3, 4, 5, 8, 14	CCR5
CCL20	CCR6
CCL19, 21	CCR7
CCL1, 4	CCR8
CCL25	CCR9
CCL27, 28	CCR10

Chemokines can mediate bacterial and viral infections, inflammation, the Th1 response, the antiviral response, and both B and T cell responses (13). For example, chemokines act against a broad spectrum of viral pathogens through the activation of naive CD8⁺ T cells (9). CD8⁺ T cells perform exceptionally well in viral infections and against intracellular bacteria (14). In viral infections, CD8⁺ cells recognize and initiate migration (15). After contact with the infected cell, they kill it and activate immune memory (14).

The virus-infected cell produces viral proteins that are degraded by the proteasome into small peptides that activate transporter associated with antigen processing (TAP) in the endoplasmic reticulum and major histocompatibility complex class I (MHC-I) (16). The peptide binds to MHC-I and is displayed on the cell surface (17). It is subsequently recognized by the CD8⁺ cell, activating the T-cell receptor (TCR) and forming the viral MHC-I peptide (17).

In the first signal, CD8⁺ activation occurs through TCR signals plus MHC-I peptide that activates LCK, resulting in the formation of PLDg1 and the production of PLP2, IP3 and diacylglycerol (DAG) (18). IP3 increases intracellular Ca²⁺, while DAG activates PKCq (18). At this point, three transcriptional programs are activated: Ca²⁺ leading to calcineurin and NAFT, DAG leading to PKCq, and NF-kB and Ras/MAPK inducing AP-1 (18). NAFT, NF-kB plus AP-1 induce the expression of genes important for the T-cell immune response (18).

In the second signal, the CD8⁺ cell exchanges with the APC cell (CD80/CD86) which activates PI3K, AKT and mTOR, promoting cell survival, metabolism, proliferation and the production of IL-2 (also called TCGF) (18). During viral infection, in the third signal, cytokines such as IL-12 and type I interferon (IFN) are produced which promote the differentiation of CD8⁺ T cells towards an effector phenotype (19). IL-2 allows the clonal duplication of CD8⁺ cells (20).

Upon contact with a specific antigen, CD8⁺ cells proliferate, forming a specific cytotoxic clone that produces perforin, granzymes, IFN-γ, and TNF (21). During infection, tissues generate chemokines such as CXCL9, CXCL10, CDCL11, and CXCR3, which exert a chemotactic effect on CD8⁺ lymphocytes in virus-infected tissue (15). The release of cytotoxic molecules by CD8⁺ cells activates caspase-3/7 and induces apoptosis (14). Another mechanism involves FAS ligand

(FASL), expressed by CD8⁺ cells, which binds to FAS (CD95), expressed by the target cell (14). FAS-FASL binding leads to the formation of caspase-8 and -3, inducing apoptosis (14).

In addition to killing the infected target cell, CD8⁺ T cells also produce IFN- γ , activating signal transducer and activator of transcription 1 (STAT1), which participates in an antiviral transcriptional program (10). In addition, IFN- γ increases MHC-I expression, facilitating antigen presentation, macrophage activation, and inhibition of viral replication (9).

Virus-infected brain target cells primarily induce type I IFNs (IFN- α/β) and other antiviral molecules, including pro-inflammatory cytokines (10). These molecules further stimulate the expression of numerous chemokines, such as CXCL10 (IP-10), which recruits T lymphocytes and natural killer (NK) cells via CXCR3 and CCL2 (MCP-1), which promote the recruitment of monocytes/macrophages via CCR2, CXCL9, and CCL5 (RANTES), which recruit T lymphocytes and other immune cells (22).

Chemokines guide immune cells to the site of infection, causing neuroinflammation (22). Viral invasion is controlled by neuroinflammation, which, when excessive and long-lasting, can cause edema and neuronal degeneration, oxidative stress, and alteration of the blood-brain barrier (BBB) (10). Therefore, chemokines have a protective function because they attract immune cells to eliminate the virus, but they are potentially harmful because they induce neuroinflammation (22). This is demonstrated in viral encephalitis, where increased levels of CXCL10 and CCL2 contribute to the influx of lymphocytes and monocytes into the CNS, which can cause inflammatory pathology (22).

In Alzheimer's Disease, Parkinson's Disease, multiple sclerosis, amyotrophic lateral sclerosis, and cerebral ischemia, neuronal damage activates microglia and astrocytes, producing chemokines (23). Chemokines attract immune cells to the nervous system tissue, activating microglia, and promoting an inflammatory response (24). They induce the production of pro-inflammatory cytokines and reactive oxygen species and alter the BBB (25) (Fig.2). However, in some cases, they can also contribute to repair, neuronal survival, and neuroprotection (24). For example, the chemokine CX3CL1 binds to its receptor CX3CR1 and enables communication between neurons and microglia (24). Additionally, in neuroinflammation, CCL2 binds to CCR2 and participates in the recruitment of immune cells that induce inflammation (26). However, the effect of chemokines on cells can depend on the specific chemokine, the receptor, the cell type, and the stage of the disease (24).

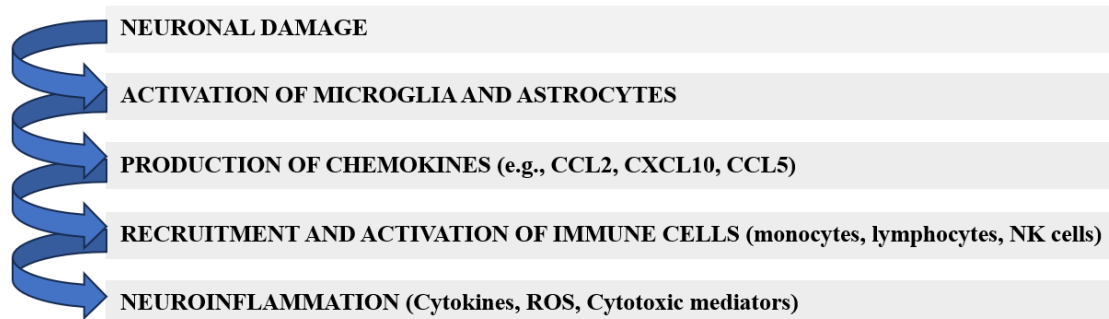


Fig. 2. Neuronal damage caused by viral infection can cause neuroinflammation.

CONCLUSIONS

Virus-infected cells in the brain can activate an immune response in which chemokines intervene. Chemokines play a fundamental role in the immune response, coordinating leukocyte migration and the antiviral response in the CNS, but they can also contribute to neuroinflammation and neuronal damage. Their effect can therefore be protective or detrimental depending on the chemokine, the receptor involved, the cell type, and the stage of the disease, participating both in infection control and, in some cases, in repair and neuroprotection.

Conflict of interest

The authors declare that they have no conflict of interest.

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