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Cytokine Modulation of Microglia in the Brain Can Overcome Vascular Dementia

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Human macrophages are produced by the differentiation of monocytes in adult healthy tissues and then maintained during adult life independently of monocytes. Macrophages distributed in the CNS are microglia. As to immune surveillance, microglia of the healthy brain have for the protection of the CNS would require the production of cytokines. Recently, chronic microglial production of pro-inflammatory cytokines including interleukins (IL-1 and IL-6), tumor necrosis factor (TNF), and interferon (IFN) has received considerable attention for its role in neurodegenerative disorders. Recent findings also suggest that Alzheimer disease (AD) may be associated with a more widespread inflammatory state characterized by increased peripheral blood levels of IL-1, IL-6, TNF-α, TGF-β, and IL-18. The purpose of this review is to outline current evidence regarding how these cytokines may contribute to the process of neurodegeneration and their potential as therapeutic targets in a wide range of central nervous system (CNS) diseases.

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Key Words Macrophage, Microglia, Interleukin-6, Dementia.

Introduction

Macrophages are produced by the differentiation of mononuclear cells, and particularly the host is involved in defending itself from exogenous factors such as bacteria. Macrophages present in the central nervous system are called microglial cells and their functions are the same as macrophages.[1,2] Microglial cells monitor the well-being of their environment, being able to respond to signs of homeostatic disturbance with a program of supportive and protective activities, to safeguard innate defense mechanisms, or to assist in specific immune reactions.[3-6] The substance that is produced to complete the self defense mechanism of these microglial cells is cytokine. Cytokines serve cellular communication[7] and produced for autocrine and paracrine signaling, or occasionally carrying biological information through body fluids, these small proteins regulate cell growth, survival, differentiation, and activities. Several cytokines and their receptors have been found to be present and functional in the CNS.[8,9] These studies might be useful to central position within the CNS and distinguish microglia from other macrophages. Here, we will briefly discuss the definition of functional clarity of phenotypically similar macrophage and microglia cells. We will also briefly describe how the cytokines produced by microglia in the brain are related to vascular dementia.

Characterization of Macrophage

Human macrophages are produced by the differentiation of monocytes in tissues. Macrophages that reside in adult healthy tissues either derive from circulating monocytes or are established before birth and then maintained during adult life independently of monocytes.[1,2] These cells together as a group are known as the mononuclear phagocyte system. Each type of macrophage, determined by its location, has a specific name (Table 1).

They can be identified using flow cytometry or immunohistochemical staining by their specific expression of proteins such as CD14, CD40, CD11b, CD64, F4/80 (mice)/EMR1 (human), lysozyme M, MAC-1/MAC-3, and CD68.[10]

Function of Macrophage and Microglia

The macrophage and microglia cells share essential features.[4] Macrophages are highly specialized in removal of dying or dead cells, immediately respond against several pathogens such as bacteria in tissue. As the resident macrophage cells, they act as the first and main form of active immune defense in the central nervous system (CNS).[11] Macrophages distributed in the CNS are microglia. Microglia are considered the resident macrophages

Table 1. Type of macrophages

Cell name	Anatomical location
Adipose tissue macrophages	Adipose tissue (fat)
Monocytes	Bone marrow/blood
Kupffer cells	Liver
Sinus histiocytes	Lymph nodes
Alveolar macrophages (dust cells)	Pulmonary alveoli of lungs
Tissue macrophages (histiocytes) leading to giant cells	Connective tissue
Microglia	Central nervous system
Hofbauer cells	Placenta
Intraglomerular mesangial cells	Kidney
Osteoclasts	Bone
Epithelioid cells	Granulomas
Red pulp macrophages (sinusidal lining cells)	Red pulp of spleen
Peritoneal macrophages	Peritonal cavity
LysoMac	Peyer's patch

of the brain given that they are the only myeloid cells present in the CNS parenchyma.[3] Microglial cells monitor the well-being of their environment, as a cell of macrophage potential, microglia need appropriate stimulation to enter a stepwise transformation for developing features and functions of a macrophage.[4] As to immune surveillance, microglia of the healthy brain can have occasional contact to cellular components of the immune system and their release products[5] and microglial activation aims at CNS protection.

Microglia Produce Cytokines

The protection of the CNS would require the production of cytokines. Microglial cytokine production is demonstrated *in vitro* and *in vivo* (Table 2).[6] Cytokines comprise a broad category of ~5−30 kDa small polypeptides possessing tremendous diversity in their potential actions.[12,13] Cytokines may include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors, which are important cell signaling molecules. Most cytokines act at very low concentrations of Pico molar to Nano molar, and signal in either an autocrine or paracrine fashion to modulate local cellular activities including survival, growth, and differentiation. Cytokines are also rapidly upregulated in response to disease, injury, and infection and serve an important role in tissue repair in these acute pathologic states. These cytokines have typically been classified as either pro-inflammatory or anti-inflammatory based on their actions in peripheral tissues. They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, and reproduction (Hopkins et al. 1995). These macrophages produce several major cytokines including interleukin 1 (IL-1), IL-6, IL-8, IL-12 and tumor necrosis factor (TNF).[14] Recently, chronic microglial production of pro-inflammatory cytokines including interleukins (IL-1 and IL-6), tumor necrosis factor (TNF), and interferon (IFN) has received considerable attention for its role in neurodegenerative disorders.

Table 2. Cytokines and chemokines with microglial synthesis

Abbreviation	Full name
GROα	Growth regulated oncogene α
IL-1α/-1β	Interleukin-1α/-1β
IL-1ra	Interleukin-1 receptor antagonist
IL-3	Interleukin-3
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-12	Interleukin-12
IL-15	Interleukin-15
IL-18	Interleukin-18, also interferon-inducing factor (IGIF)
IP-10	Gamma interferon inducible protein-10
MCP-1	Monocyte chemoattractant protein-1
M-CSF	Macrophage colony stmulating factor
MDC	Macrophage derived chemokine
MIP-1α/-1β	Macrophage inflammatory protein-1α/1β
MIP-2	Macrophage inflammatory protein-2
MIP-3	Macrophage inflammatory protein-3
TGF	Transforming growth factor
TNF	Tumor necrosis factor
RANTES	Regulated on activation, normal T cell expressed and secreted

Cytokine Involvement in Neurodegenerative Disorders

Alzheimer's disease (AD) is the most common form of dementia in the elderly resulting in a progressive decline in a number of cognitive functions including short-term memory. AD have provided extracellular beta-amyloid deposits forming senile plaques and intracellular neurofibrillary tangles made up of the microtubule associated protein tau. Recent findings also suggest that AD may be associated with a more widespread inflammatory state characterized by increased peripheral blood levels of IL-1, IL-6, TNF-α, TGF-β, and IL-18.[15] Recent studies have provided further evidence supporting an association between microglial cytokine production and AD.[16,17]

Cytokines Involvement in Dementia

Inflammatory cytokines have been linked to AD neurodegeneration, but little is known about the temporal control of their expression in relationship to clinical measurements of AD dementia progression. Several cytokines have been associated with AD neuropathology. The level of the pro-inflammatory cytokine IL-6 is increased in the brain, blood, and cerebro-

spinal fluid of patients with AD, and IL-6 has been implicated in the transformation of diffuse to neuritic plaques in the AD brain.[18-24] Injury may release cytokines that are bound to the extracellular matrix but carry latent microglia activating signal character. Microglia could also sense inundating serum proteins that are normally denied CNS.[25-27] Serum factors can also fulfill functions as accessory agents in microglial responses. Examples are LPS-binding protein (LBP) and serum components required for full microglial activation by gram-positive bacteria.[28] Proteins with disease-related production, processing, and aggregation, such as amyloid-β (Aβ) in AD, can reportedly stimulate microglia, including its release properties. In conjunction with other stimuli, Aβ aggregates seem to irritate microglial cells chronically as they concentrate around AD plaques. Clusters of activated microglia then produce factors (such as IL-1, TNF) that can drive neurotoxic cascades that in turn recruit more microglia.[6] IL-6 is an important mediator of fever and responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It is capable of crossing the blood-brain barrier,[29] and also it particularly helps to initiate and regulate acute-phase responses, a complex of adjustments in metabolic and circulating serum components that assist in host defense. Interestingly, IL-6 can have both pro- and anti-inflammatory outcomes. Microglia seems to provide IL-6 especially in early phases of CNS insults. Subsequently, IL-6 may act on astrocytes to involve these cells in the orchestration of attempts for tissue repair.[30,31]

Conclusion

The flood of information about multiple CNS effects of cytokines with recently will affect concepts of initiation, maintenance, termination, and modification of the microglial activation process. While their involvement in the activity of the brain is still poorly understood, it is widely accepted that they control the process and outcome of traumatic, infectious, or degenerative challenges. This may lead to the identification of sensitive targets for pharmacological interference. Potential therapeutic strategies should aim at containment of excessive activation, rather than a depletion of any microglial activity.

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