



# Alzheimer's & Parkinson's Disease: Open Access

## Editorial

# Cytokines in Chronic Neurodegenerative Diseases -

**Marcella Reale<sup>1\*</sup>**

*Department of Medical, Oral and Biotechnological Sciences, University "G. d'Annunzio" Chieti-Pescara, 66100 Chieti, Italy*

**\*Address for Correspondence:** Marcella Reale, MD, Department of Medical, Oral and Biotechnological Sciences, University "G. d'Annunzio" Chieti-Pescara, 66100 Chieti, Italy

**Submitted:** 25 November 2015; **Approved:** 28 December 2015; **Published:** 31 December 2015

**Citation this article:** Reale M. Cytokines in Chronic Neurodegenerative Diseases. *Alzheimers Parkinsons Dis Open Access*. 2015;1(1): 004-006.

**Copyright:** © 2015 Reale M. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

There has been an increasing interest in the role of inflammation as a common mechanism of disease in a several medical disorders including cardiovascular and neurodegenerative diseases, diabetes and cancer [1-3]. Indeed, epidemiological studies found that inflammation biomarkers may help to predict the development and progression of these illnesses. In the brain, the inflammation is generally beneficial and drives the brain responses to dangerous stimuli. Unfortunately, this beneficial process sometimes gets out of balance and the neuroinflammatory process persists. Therefore, it has been possible to associate the progression of damage in several neurodegenerative diseases to uncontrolled chronic neuroinflammation, based on levels and pathophysiology of pro-inflammatory cytokines [4].

Neurodegenerative diseases are defined as hereditary and sporadic conditions which are characterized by progressive degeneration and/or death of nerve cells. This causes problems with movement and mental functioning often associated with atrophy of the central or the peripheral nervous system. Common neurodegenerative diseases including Alzheimer's disease and Parkinson's disease such as multiple sclerosis (MS) and Huntington's disease (HD), are associated with chronic neuroinflammation. It has been associated a strong link between pro-inflammatory cytokines and neurodegeneration, both in clinical data and bench research [5].

Cytokines are soluble mediators of cell communication that are critical in immune regulation and bidirectional communication between cells of the nervous and immune systems. T cells can pass through the blood-brain barrier, it means that they probably can be responsible for releasing inflammatory mediators in brain during neurodegeneration. Systemic inflammatory cytokines circulate in the blood and communicate with neurons in the brain or diffuse from the blood into the brain parenchyma.

The main reason why it's important to examine cytokines in neurodegenerative disease is the ease with which their expression can be documented in disorders associated with inflammation.

Alzheimer's disease (AD) is the most common age-dependent neurodegenerative disorder resulting in a progressive impairment in memory, judgement, decision-making, orientation to physical surroundings and language. In AD brain, high expression of inflammatory mediators has been highlighted in the neighbour of Amyloid peptide deposits and neurofibrillary tangles. Activated microglia showed increased levels of cytokines that could increase the loss of neurons that are damaged by the Amyloid or by disruption of their cytoskeleton and axonal transport due to accumulation of tau [6]. Exposure of microglia or PBMC to Amyloid beta (A $\beta$ 42) deposits increases production of pro-inflammatory cytokines [7]. In AD brains the increase of chemokines was localised in neurons, astrocytes and plaques. High levels of pro-inflammatory cytokines, such as tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ), interleukin (IL) 1 $\beta$ , IL-6 and the colony stimulating factor, have been found in the brain and cerebrospinal fluid. Increased peripheral blood levels of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , TGF- $\beta$ , and IL-18 suggest that AD may be associated with a more widespread inflammatory state [8-10]. A cerebrospinal fluid (CSF) cytokine and receptor profile was proposed as a marker of the conversion of MCI to AD. Through the examination of mouse models of AD, have been identified cytokines involved in the maintaining of inflammatory environment [11-12]. Cytokines associated with the biochemical diagnostic tools currently used for AD diagnosis, could be particularly interesting for early diagnosis of AD or for patients

presenting ambiguous profiles.

MS is the most common chronic inflammatory disorder of the central nervous system (CNS), which leads to focal inflammatory demyelinated lesions with secondary neurodegeneration, and which causes disability in young adults. The immune activation plays a key role in MS, environmental and genetic factors too are involved in the MS pathogenesis [13]. The infiltration of T helper (Th)1 cells into the brain represents the crucial event in the inflammatory processes and the formation of demyelinating lesions via the secretion of Interferon gamma (IFN $\gamma$ ) and TNF $\alpha$ . IFN $\gamma$  and IL12 are increased in the brain, the cerebrospinal fluid (CSF) or peripheral blood of MS patients, particularly when acute exacerbations come to light. IL-18, that acts as an important link between innate and adaptive immune responses, participates too in the pathogenesis of MS. In contrast, cytokines produced by Th2 cells such as IL-4 and IL-10, downregulating Th1 cells exert antiinflammatory functions and may be beneficial. Studies in the experimental model of MS (experimental autoimmune encephalomyelitis, EAE), suggested that IL17 producing cells (Th17) plays a crucial role in the pathogenesis of the disease. IL-23 is critical in EAE pathogenesis promoting the expansion of Th17 cells [14-15]. Thus, the modulation of Th1/Th2 and Th17/Th2 balance is aetiologically important during MS progression. Since cytokines are easily measured and reflect the underlying immunopathology in the periphery (blood) and/or the CNS, they are proposed as useful biological markers of MS and potential prognostic markers of treatment responses [16].

Evidence of chronic inflammatory reactions in the brain of PD patients is shown by numerous studies [17-18]. Neuroinflammatory responses in the brain involve cells of the immune system, resident cells of CNS and protein such as adhesion molecules, chemokines and cytokines. Microglial activation in the PD brain results in increased expression of pro-inflammatory cytokines. Expression of pro-inflammatory cytokines have been demonstrated in the brain of PD patients and high levels of the same cytokines were detected in cerebrospinal fluid as well as in serum [19]. It has been reported that even in peripheral blood mononuclear cells that come from patients with PD there is an altered production of inflammatory cytokines [20]. In PD patients it has been evidenced a strong correlation between pro-inflammatory cytokine levels and Hoehn-Yahr scores as well as disease duration. This correlation supports the idea that a chronically systemic inflammation state plays a role in the progression of PD. Multiple studies indicated that there is a cross talk between systematic inflammation and neuronal damage also in PD [21,22]. Increased expression of cytokines is been noted in multiple PD animal models, following administration of 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Lentiviral therapy with a dominant-negative TNF two weeks after 6-OHDA lesion also prevented the progressive degeneration of DA neurons and microglial activation, confirming a key role for cytokine signaling in models of PD [23].

Huntington's disease (HD) is an autosomal dominantly progressive neurodegenerative disorder with no available cure, characterised by motor, psychiatric, and cognitive symptoms.

Several studies have showed microglial activation in the brains of both premanifest HD patients and post mortem. A parallel immune activation in CNS and the periphery has been shown. Furthermore, proteomic profiling of plasma from HD patients has demonstrated that cytokines are increased earliest in the disease course, before

the onset of neurological symptoms. Recently, it was showed that, in HD patients, IL-6, IL-8 and TNF- $\alpha$  inflammatory cytokines were elevated both centrally and peripherally and increased with disease progression. Similarly, serum levels of cytokines, were elevated in several mouse models of HD [24,25].

Numerous studies have confirmed the theory that cytokines and chemokines and their receptors profile analysis and interaction between the sympathetic nervous system (SNS) and pro-inflammatory cytokine production both centrally and peripherally are important for detailed understanding of the pathological mechanisms associated with the neurodegeneration. In addition, cytokines may represent a viable target to improve therapeutic options such as neutralizing antibodies or receptors antagonist in the treatment of neurodegenerative disorders. Although, caution must be taken in this approach because cytokines and chemokines may have key roles in neurodegeneration and too in neuroprotection. Inflammation should not only be considered as responsible of the mechanisms underlying neurodegeneration, but it often shows a protective role in the CNS.

Further studies are needed to fully understand the conditions that promote cytokine-mediated neuronal degeneration over survival and they should place particular emphasis on the effects of SNS activity on local microglial and peripheral responses as well as the contribution of the peripheral immune system to neurodegeneration.

To consider cytokines and cytokine antagonists as novel therapeutic approaches, it is necessary improve their effectiveness developing more effective methods of administration, the better combination with other treatments, improve their effectiveness and minimize their toxicities, extend their biological activity. The copiousness of studies that link pro-inflammatory cytokine involvement to neurodegeneration makes this an exciting field of study with particular clinical relevance.

## REFERENCES

- Baune BT. Inflammation and neurodegenerative disorders: is there still hope for therapeutic intervention? *Curr Opin Psychiatry*. 2015; 28(2):148-54
- Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002; 420(6917):860-7.
- Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Research and Clinical Practice*. 2014; 141-150.
- Ramesh G, MacLean GAG, Philipp MT. Cytokines and Chemokines at the Crossroads of Neuroinflammation, Neurodegeneration, and Neuropathic pain. *Mediators of Inflammation*. 2013 Article ID 480739.
- Alam Q, Alam MZ, Mushtaq G, Damanhoury GA, Rasool M, et al. Inflammatory Process in Alzheimer and Parkinson's Diseases: Central Role of Cytokines. *Curr Pharm Des*. 2016;22(5):541-8.
- Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. *Ann Transl Med*. 2015;3(10):136.
- Reale M, Kamal MA, Velluto L, Gambi D, Di Nicola M, et al. Relationship between inflammatory mediators, A $\beta$  levels and ApoE genotype in Alzheimer disease. *Curr Alzheimer Res*. 2012; 9(4):447-57.
- Reale M, Brenner T, Greig NH, Inestrosa N, Paleacu D. Neuroinflammation, AD, and Dementia. *Int J Alzheimers Dis*. 2010 ; ID 974026
- Reale M, Iarlori C, Gambi F, Lucci I, Salvatore M. Acetylcholinesterase inhibitors effects on oncostatin-M, interleukin-1 beta and interleukin-6 release from lymphocytes of Alzheimer's disease patients. *Exp Gerontol*. 2005; 40(3):165-71.
- Iarlori C, Gambi D, Gambi F, Lucci I, Feliciani C, et al. Expression and production of two selected beta-chemokines in peripheral blood mononuclear cells from patients with Alzheimer's disease. *Exp Gerontol*. 2005; 40(7):605-11
- Yang SH, Kim J, Lee MJ, Kim Y. Abnormalities of plasma cytokines and spleen in senile APP/PS1/Tau transgenic mouse model. *Sci Rep*. 2015 Oct 27;5:15703.
- Gabbita SP, Johnson MF, Kobritz N, Eslami P, Poteskhina A, et al. Oral TNF $\alpha$  Modulation Alters Neutrophil Infiltration, Improves Cognition and Diminishes Tau and Amyloid Pathology in the 3xTgAD Mouse Model. *Harris-White ME. PLoS One*. 2015;10(10):e0137305
- Dendrou CA, Fugger L, Friese MA. Immunopathology of multiple sclerosis. *Nat Rev Immunol*. 2015;15(9):545-58.
- Reale M, de Angelis F, di Nicola M, Capello E, di Ioia M, et al. Relation between pro-inflammatory cytokines and acetylcholine levels in relapsing-remitting multiple sclerosis patients. *Int J Mol Sci*. 2012; 13(10):12656-64.
- Cheng W, Chen G. Chemokines and chemokine receptors in multiple sclerosis. *Mediators Inflamm*. 2014;2014:659206
- Sankowski R, Mader S, Valdés-Ferrer SI. Systemic inflammation and the brain: novel roles of genetic, molecular, and environmental cues as drivers of neurodegeneration. *Front Cell Neurosci*. 2015; 9:28.
- Tufekci KU, Meuwissen R, Genc S, Genc K. Inflammation in Parkinson's disease. *Adv Protein Chem Struct Biol*. 2012;88:69-132.
- Ferrari CC and Tarelli R, Parkinson's Disease and Systemic Inflammation. *Parkinson's Disease*2011, ID 436813
- Pessoa Rocha N, Silva de Miranda A, Antônio Lúcio Teixeira A T Insights into Neuroinflammation in Parkinson's Disease: From Biomarkers to Anti-Inflammatory Based Therapies. *BioMed Research International*. 2015
- Reale M, Iarlori C, Thomas A, Gambi D, Perfetti B, et al. Peripheral cytokines profile in Parkinson's disease. *Brain Behav Immun*. 2009;23(1):55-63
- Wang Q, Liu Y, Zhou J Neuroinflammation in Parkinson's disease and its potential as therapeutic target. *Transl Neurodegener*. 2015; 4:19.
- Reale M, Iarlori C, Feliciani C, Gambi D. Peripheral chemokine receptors, their ligands, cytokines and Alzheimer's disease. *J Alzheimers Dis*. 2008;14(2):147-59
- Nagatsu T, Mogi M, Ichinose H, Togari A. Cytokines in Parkinson's disease. *J Neural Transm Suppl*. 2000;(58):143-51
- Chang KH, Wu YR, Chen YC, Chen CM. Plasma inflammatory biomarkers for Huntington's disease patients and mouse model. *Brain Behav Immun*. 2015;44:121-7.
- Nguyen HP, Björkqvist M, Bode FJ, Stephan M, von Hörsten S. Serum levels of a subset of cytokines show high interindividual variability and are not altered in rats transgenic for Huntington's disease. *PLoS Curr*. 2010.