New Progress in Cytokine Research: Effects on Alzheimer and Inflammatory Bowel Disease

Adina Hadade, MD,

Abstract— Multiple types of mediators and signaling pathways can trigger inflammatory responses. For example, interleukins are cytokines which regulate inflammatory responses and are accountable for the communication between leukocytes. Other examples are chemokines, small cytokines promoting chemotaxis, and interferons having antiviral effects. Additionally, these molecules are implicated in both innate and adaptive immunity, having an important physiological role in lymphoid tissue ontogenesis, organogenesis, vasculogenesis and tissue repair. We summarize here the progress in cytokine research with special focus on Alzheimer and Inflammatory Bowel diseases.

Keywords— cytokines, inflammation, neurodegenerative diseases, inflammatory bowel disease

I. INTRODUCTION

Multiple types of mediators and signaling pathways can trigger inflammatory responses. For example, interleukins are cytokines which regulate inflammatory responses and are accountable for the communication between leukocytes. Other examples are chemokines, small cytokines promoting chemotaxis, and interferons having antiviral effects. Additionally, these molecules are implicated in both innate and adaptive immunity, having an important physiological role in lymphoid tissue ontogenesis, organogenesis, vasculogenesis and tissue repair.[1-3]

The chronic alteration of these molecules results in the occurrence of various diseases. Cytokine and chemokine deregulation can particularly support the onset of diseases related to chronic inflammation, the production or formation of tumors and autoimmunity. The importance of examining multiple systemic chemokines and cytokines lies in the understanding of the complex mechanism of immunological changes detected in patients with inflammatory and autoimmune pathologies.[4] Nevertheless, the assessment of the significance of cytokine and chemokine modulation in pathological conditions requires knowledge of the physiological range of these molecules in healthy subjects. Furthermore, additional evidence suggesting that there are similar clinical presentations and basic therapeutic algorithms in the onset of these pathologies in children and adults, bearing in mind the fact that children are not miniature adults. Even concerning physiological parameters, the aspects which are specific to children must be considered in case of disease in order to assure an early diagnosis and an adequate medical management. Cytokines and chemokines trigger immune responses and inflammatory processes and their expression, at least for some of these molecules, is clearly supposed to vary with age, as the immune system gradually attains full maturation.[5-7]

II. THE IMPACT OF CYTOKINES ON INFLAMMATORY PROCESSES IN ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) was first defined by Alois Alzheimer and it is today the most common cause of dementia in older people. This disease affects more than 4 million people in the United States[8-10] About 27 million people are estimated to be suffering from AD in the world.[11] Together with the increase in life expectancy, the number of people suffering from AD is believed to increase three times by 2050.[12] The initial cause of cell damage and the necrotic cells and tissues caused by it are fought by inflammation. When it doesn’t restore tissue health, inflammation turns into a chronic disease that increasingly injures the neighboring tissue. In such a situation, tissue damage and restoration progress at the same time. The slow injury of the surrounding tissue can sometimes be asymptomatic for many years. This can result in severe tissue damage.[13] Among the pathological indications of AD is brain inflammation. Nevertheless, the typical inflammatory characteristics like swelling, heat and pain, do not occur in the brain. Thus, it is a matter of chronic and not of acute inflammation.[14] Among the basic features of chronic inflamed tissues is the high number of monocytes and tissue macrophages derived from monocytes, namely microglia cells in the central nervous system (CNS). The clear inflammation occurs in pathologically exposed regions of the AD brain, with higher expression of acute phase proteins and pro-inflammatory cytokines that are scarcely obvious in the healthy brain.[15]
The inflammatory reaction is triggered by microglia, astrocytes and neurons. The following are strongly produced by activated cells: inflammatory mediators, namely pro-inflammatory cytokines, chemokines, macrophage inflammatory proteins, monocyte chemo-attractant proteins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, reactive oxygen species (and other radicals), nitric oxide, complement factors, proteases, protease inhibitors, pentraxins, and C-reactive protein.[16]

The intractable nature of the Aβ plaques and tangles is assumed to stimulate a chronic inflammatory reaction in order to eliminate this waste. These plaques consist of dystrophic neurites, activated microglia and reactive astrocytes.[17] The collection of amyloid fibrils and inflammatory mediators secreted by microglia and astrocytes determine neuronal dystrophy. Moreover, chronically activated glia release exceptionally toxic compounds (reactive oxygen intermediates, nitric oxide (NO), proteolytic enzymes, complementary factors or excitatory amino acids) and can kill adjacent neurons.[18]

On the other hand, stress and inflammatory mediators enhance the production of Alzheimer Amyloid Precursor Protein (APP) and the amyloidogenic processing of APP in order to trigger the production of amyloid-β-42 (Aβ-42) peptide. Moreover, this can restrict the generation of soluble APP fraction which provides neuronal protection.[19]

In turn, Aβ generates pro-inflammatory cytokine expression in neuroglia in a vicious cycle, activating the complement cascade, as well as inducing inflammatory enzyme systems, namely the inducible nitric oxide synthase (iNOS) and the cyclooxygenase enzyme (COX)-2.[20] There is proof suggesting that all these factors can lead, individually or in association with each other, to neuronal impairment and cell death. Small and nonstructural proteins, cytokines range between 8,000 to 40,000 daltons in molecular weight. They were initially called lymphokines and monokines, indicating their cellular sources, but the term “cytokine” was later used, as almost all nucleated cells can synthesize these proteins and get a response from them. There is no 3D or amino acid sequence motif linking cytokines. In turn, due to their biological functions, cytokines can be grouped into different categories. Both immune (T-lymphocytes, macrophages, natural killer cells), as well as nonimmune cells (Schwann cells, fibroblasts), secrete cytokines. Cytokines have various biological effects, stimulating or inhibiting cell proliferation, cytotoxicity or apoptosis, antiviral activity, cell growth and differentiation, inflammatory responses and upregulation of surface protein expression. The control over T-cell differentiation from undifferentiated cells to T-helper 1 and 2 cells, regulatory T cells and T-helper 17 cells is one of the major cytokine functions.[21] Some of these regulatory proteins are interleukines (ILs), interferons (IFNs), colony stimulating factors (CSFs), tumor necrosis factors (TNFs) and several growth factors (GFs).[22] There have already been reports that most of these cytokines are produced by neurons or glia, some indicating changes in cytokine levels in Alzheimer’s disease brain, blood and cerebrospinal fluid (CF).

Elevated levels of IL-1α, IL-1β, IL-6, TNF-α, granulocyte-macrophage colony-stimulating factor (GMSF), IFN-α, type B of IL-8 receptor (IL-8RB) and the receptor for CSF-1 have been reported in AD brain tissue.[23] There have also been reports of multiple synergies between cytokines and constituents of the AD senile plaques, indicating the possible generation of a vicious circle. Therefore, Aβ plaque protein is reported to enhance IL-6 and IL-8 secretion by IL-1β-activated astrocytoma cells, IL-6 and TNF-α secretion by lipopolysaccharide-(LPS-) stimulated astrocytes and IL-8 secretion by monocytes.[24] The secretion of other proteins found in senile plaques can also be stimulated by cytokines. Additionally, there might be synergistic effects between cytokines and Aβ. For instance, IFN-γ is reported to interact with Aβ, releasing TNF-α and reactive nitrogen species harmful for neurons. Reports also suggest that IL-1 increases the degree of Aβ damage in PC12 cells. Pro-inflammatory cytokines are cytokines promoting inflammation and anti-inflammatory cytokines are cytokines suppressing the activity of pro-inflammatory cytokines. Thus, IL-4, IL-10 and IL-13 are effective B lymphocyte activators, but they are also effective anti-inflammatory agents. As they are able to inhibit genes for pro-inflammatory cytokines, such as IL-1, TNF and chemokines, they are first of all anti-inflammatory cytokines. Another good example of the pleiotropic characteristic of cytokines is IFN-γ. It has antiviral activity, like IFN-α and IFN-β. IFN-γ also activates the pathway disturbing cytotoxic T cells, but it is thought to be a pro-inflammatory cytokine as it enhances TNF activity and generates NO. Cytokine biology and clinical medicine take into consideration the importance of cytokine functions inducing inflammation, as well as suppressing inflammation.[24] The ground for this concept lies in the genetic coding for small mediator molecule synthesis, upregulated throughout the course of inflammation. The “balance” between the consequences of pro-inflammatory and anti-inflammatory cytokines is reported to decide the short term or long term outcome of the disease. In fact, several studies suggested that the equilibrium or expression of either pro-inflammatory or anti-inflammatory cytokines genetically determine disease susceptibility. Nevertheless, the difficulty in interpreting some gene linkage studies should be considered. The production of the inflammatory mediators produced by microglia and astrocytes around Aβ neuritic plaques is enhanced in inflammatory states, regulating the intensity and duration of immune response.[25] There are two agonist proteins in IL-1 family of cytokines, namely IL-1α and IL-1β, inducing cell activation after attaching to specific membrane receptors. Another member is the glycosylated secretory protein of 23 kDa, IL-1ra, neutralizing the activity of interleukin-1.[26] Immune responses are successfully initiated by IL-1, which is of utmost importance in the onset and evolution of a compound hormonal and cellular inflammatory cascade. Both humans and rodents have displayed increased IL-1β levels in the CF and brain parenchyma right after brain injury.[27] The impact of IL-1 in neuronal degeneration has also been reported. In astrocytes, it triggers IL-6 production, triggers iNOS activity and generates M-C SF production. Moreover, IL-1 increases neuronal acetylcholinesterase activity, microglial activation and supplementary IL-1 production.
astrocyte activation and expression of the beta-subunit of S100 protein (S100B) by astrocytes, thus determining a self-reproducing cycle. The multifunctional cytokine, IL-6, is of great importance for host protection system, having significant regulatory effects on the inflammatory response.[28] It is one of the four-helix bundle cytokines called neuropoietin, with direct and indirect neurotropic impact on neurons.[29] Among IL-6 effects are the promotion of astrogliosis, microglia activation and the stimulation of acute phase protein production Castell JV, Andus T, Kunz D, Heinrich PC.[30] Cytokine cascade initiation and regulation during an inflammatory response are strongly influenced by TNF-α. TNF-alpha production as a membrane-bound precursor molecule of 26 k daltons divided by the TNF-α converting enzyme, generates an active cytokine with a molecular weight of 17 k daltons.[31] There are low levels of TNF-α expression in the normal brain, which burdens the determination of its exact impact under physiological conditions. In case of inflammation or illness, TNF-α is predominantly produced by activated microglia together with more pro-inflammatory mediators or neurotoxic chemicals. Even if brain-derived neurotrophic TNF-α is generally combined by glia as a reaction to pathological stimuli, there have been reports of neuronal production of TNF-α.[31] Glial cells produce both TNF-α and IL-1 which in turn initiate further autocrine induction into cytokine production and astrogliosis. Nevertheless, there are reports indicating the neuroprotective properties of TNF-α in Alzheimer’s disease brain.

III. CYTOKINES AND INFLAMMATORY BOWEL DISEASES

Ulcerative colitis (UC) and Crohn’s disease (CD) are immune related types of inflammatory bowel disease (IBD).[32] Comprehensive data indicate that IBD is caused by an inadequate inflammatory response to bacteria in a genetically exposed host.[33] Additional proof indicates that disease development is generated by an impaired dialogue between intestinal flora and components of both inborn and adaptive immune systems. [33] Cytokines strongly influence immune functions. The classical T helper Th1/Th2 example triggering predominant Th1-mediated responses governed by the production of interferon-γ (IFN-γ) in CD and an excessive Th2-like inflammation in UC with enhanced production of IL-13 is joined by extensive information about the function of inborn immunity in IBD pathogenesis.[34] Therefore, recent data have demonstrated that: (1) the Th1 and Th2 immune responses in the mucosa of CD and UC may be in fact subordinated to an impaired inborn immune response; (2) regulatory T cell dysfunction might lead to mucosal immune abnormalities; (3) the newly described Th17 cells also influence the intestinal inflammatory response in both types of IBD. T cell differentiation and survival is based on the amount of key regulatory cytokines produced mainly by macrophages and dendritic cells.[35] When accompanied by IL-12 and IFN-γ, naive CD4+ T cells take up a Th1 phenotype and activate macrophages that release IL-1, IL-6 and TNF-α. This generates a positive feedback circle.[36] When accompanied by IL-4, naive CD4-T cells take up a Th2 phenotype Th17 is generated by IL-6, IL-21, IL-23 and transforming growth factor-β (TGF-β), resulting in the IL-17 cytokine family and IL-22 secretion. Even if there is not enough evidence regarding the function of Th17 cells, the importance of this type of T cell population which expresses IL-23 receptors is not contested. It has been recently proved as an IBD susceptibility gene in genome-wide association studies (GWAS). On the other hand, TGF-β and IL-10 adjust naïve T cell differentiation into T regulatory cell subgroups generating high amounts of IL-10 and TGF-β, being able to inhibit bystander T cell activation.[37] This could be inadequate in IBD.[38] There is a strong relationship between these different cell populations in case of inflammation, such as the negative cross-regulation of Th17 cell differentiation by Th2 cells (IL-4, IL-27) and Th1 cells (IFN-γ). The best therapy for IBD in 2010 was represented by infliximab. But there are some limitations of this chimeric monoclonal antibody against TNF. Firstly, even if it is widely used in IBD, 20% of patients still need surgery.[39] Secondly, approximately 10% of patients don’t usually respond to infliximab and only one-third of IBD patients are in clinical remission at 1 year. Thirdly, there is an annual risk of loss of response of 13% per patient-year.[40] Finally, infliximab treatment can be optimized by combining it with other therapy, considering the high risk of severe infections and lymphoma. All these emphasize the immediate need for new drug classes. One of the most promising future therapies is based on humanized IL-12/23 antibodies. IL-23 is a basic mediator of proinflammatory Th17 cell differentiation and expansion. It increases host susceptibility to IBD in case of IL-23 receptor polymorphism. IL-23 has displayed effective results in a recent randomized, controlled trial, especially when infliximab has been withdrawn. There are ongoing phase III clinical trials in IBD patients. New cytokine pathways have been identified in recent studies in the pathophysiology of IBD, representing potential therapeutic targets. There is ongoing investigation of multiple cytokines: IL-27, produced mainly by dendritic cells, acting in Th1 and Th2 cell differentiation; IL-32, produced by NK cell-activated lymphocytes and epithelial cells, offering a proinflammatory amplification pathway in the inborn immune responses to bacteria.[41] IL-31, preferentially produced by T cells altered towards a Th2 phenotype, influencing acute-phase inflammation by maintaining proliferation of B and T cells. There is need for further studies to completely explore their different functions in human IBD and their biological significance, in order to ultimately determine their therapeutic implications.

References


