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Case Report

ROLE OF CYTOKINES IN INFLAMMATORY DISEASES

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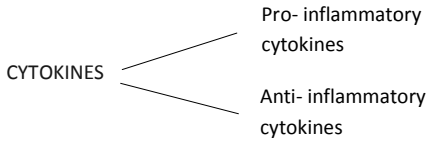
ABSTRACT

Cytokines are small secreted proteins released by cells have a specific effect on the interactions and communications between cells. Cytokine is a general name; other names are lymphokine, monokine, chemokine, and interleukin. Cytokines may act on the cells that secrete them), on nearby cells, or in some instances on distant cells. There are both pro-inflammatory cytokines and anti-inflammatory cytokines. There is significant evidence showing that certain cytokines/chemokines are involved in not only the initiation but also the persistence of pathologic pain by directly activating nociceptive sensory neurons.

INTRODUCTION

Cytokines

Cytokines are small molecules secreted by cells of the immune system that serve to regulate various other components of the immune system, and they play a crucial role in health and disease[1,2]



Types of Cytokines

Pro-inflammatory cytokines	Anti- inflammatory cytokines
Interleukin- 1	Interleukin-4
Tumour necrosis factor	Interleukin- 13
Gamma interferon (IFN-gamma)	Interleukin -10
Interleukin-2	Alpha interferon (IFN- Alpha)
Interleukin-18	Transforming growth factor - beta
granulocyte-macrophage colony stimulating factor	

Alzheimer's Disease- Alzheimer's disease is a very common neurological degenerative disorder. It is the main cause for dementia in elderly people. Brain inflammation is a pathological hallmark of Alzheimer's disease[3].

Pathogenesis of Alzheimer's Disease- Microglia and astrocytes surrounding Aβ neuritic plaques secretes cytokine class of inflammatory mediators which gets increased in Inflammatory states and it functions to regulate intensity and duration of immune response[4].

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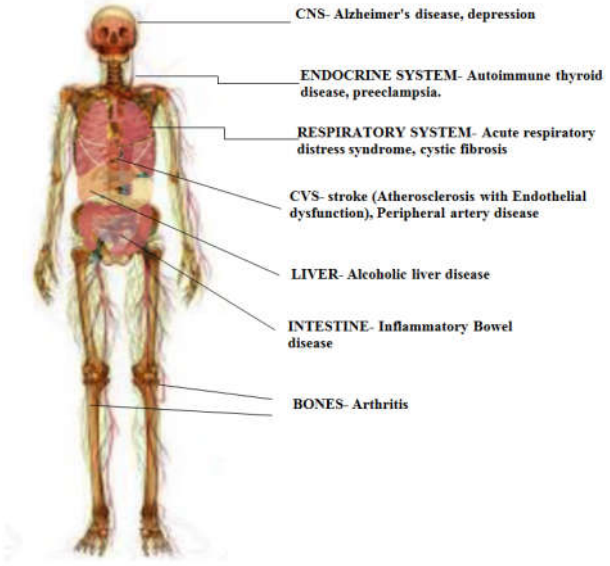
IL-1 group of cytokines is further divided into IL-1 alpha and IL-1 beta which triggers cell activation upon binding with specific membrane receptors. Here IL-1ra which is a glycosylated secretory protein of 23 kDa counteracts IL-1.

Actions of Il- 1β in Other Inflammatory Diseases



Role of IL-1β

IL-1 is the initiator of immune response and IL-beta is found in elevated levels in CSF and brain parenchyma within early hours after brain injury [5,6]. IL-1 causes the onset and development of cellular and inflammatory cascade. IL-1 in the astrocytes induces IL-6 action and stimulates iNOS activity. Additionally IL-1 enhances neuronal acetylcholinesterase

activity and induces the production of MCSF and microglial activation.

Depression

Major depressive disorder (MDD) is a ver common psychiatric illness and it is the main cause of disability worldwide[7,8].

Symptoms

Biological Symptoms

- Disturbed sleep with early morning wakening
- Loss of appetite
- Diurnal mood variation and
- Reduced libido.

Cognitive Symptoms

- Hopelessness
- Helplessness
- Worthlessness
- Poor concentration
- low-self esteem
- Guilt and
- Suicidal ideation.

Pathogenesis of Depression

Innate immune mechanism plays an integral role in depression which determines the type of T helper cells involved whether Th1 or Th 2 cells. In Th1 type of response the macrophages releases pro-inflammatory cytokines IFN-gamma, TNF-alpha, Interleukin-1,2 by the recognition of pathogen, tissue damage or destruction with the help of Toll-like receptors[9,10]. These TLRs activates nuclear factor kappa B which in turn induces the innate inflammatory response by releasing pro-inflammatory cytokines like IL-1, IL-2, IL-6, TNF-Alpha[9,10,11].

Pro-inflammatory cytokines creates a communication peripheral and central immune response. Pro-inflammatory cytokines accesses brain through leaky regions of BBB, active transport across the BBB, a neural pathway involving afferent nerve fibers such as the sensory vagus which relay information through the nucleus tractus solitarius, a humoral pathway, involving volume diffusion from circumventricular organs across the BBB[11,12,13].

Sometimes BBB can be impaired in brain which allows extravasation of leukocyte and up-regulation of intracellular adhesion molecules.

Auto-Immune Thyroid Disease

Autoimmune diseases are a group of heterogeneous disorders which are identified by abnormal lymphocytic activation directed against self-tissue[14,15]. Autoimmune thyroid diseases (AITD) are a set of very common organ-specific autoimmune disorders, among which Hashimoto's thyroiditis (HT) and Graves' disease (GD) are two of the most common clinical forms.

Role of Il-1 in Aitd

T helper cells produces Th cells through TCR engagement and STAT signalling which is caused by IFN-γ binding to its cognate receptor. Phosphorylated STAT4 signalling induces transcription factor-beta to help in differentiation of Th cells into Th1 cells and Th2 cells by transactivating IFN-γ and also the specific subunit of IL-12Rβ2, the receptor for IL-12. Now cell responds to IL-12 produced by the activated macrophages and DCs due to expression of 12Rβ2.

APCs produced by macrophages and DC, create a link between innate and acquired immune response, which in turn produces pro-inflammatory cytokines. Pro-inflammatory cytokines like TNF-Alpha and IL-1β induce adaptive immune response. DCs helps IL-12 to also induce adaptive immune response.

IL-1β has pleotropic effects which induces Cell signalling, migration, and cytokine production, and influence T cell differentiation differently under different conditions[16,17,18]

And facilitating the expansion of Teff which breaks peripheral tolerance causing auto-immune diseases like RA. IL-1β helps in the generation of IL-17 which secretes T helper cells in human. IL-23 along with IL-1β develops and maintains pathogenic Th17 cells which through several immune mechanisms by other inflammatory mediators lead to Graves' disease.

Pre-Eclampsia

Preeclampsia is considered to be a pregnancy-specific syndrome, identified by the new onset hypertension and proteinuria after 20th week of gestation. Preeclampsia occurs in almost 5%-7% of all pregnancies in the world, which is a main cause of the maternal and foetal mortality and morbidity[21].

Pathogenesis of Preeclampsia

Serum inflammatory cytokines were found to be raised in pregnant patients with preeclampsia rather than normal pregnant patients. Inflammatory cytokines like IL-1β, IFN-gamma, IL-2, IL-6 causesharmful Th1 immunity, threatening pregnancy by generating cytotoxic factors that injured maternal endothelium, altered steroid hormones biosynthesisand also affected other factors which were implicated in trophoblast invasion and maternal spiral artery remodelling[22,23]. Cytokine gene regulates the production of inflammatory cytokines, therefore, the cytokines gene polymorphism plays a main role in the development of Preeclampsia.

IL-1β is a pro-inflammatory cytokine, belongs to the IL-1 system, has an important role in mammalian reproduction. It was reported that IL-1β was being implicated in the pathogenesis of preeclampsia [24]. Many researchers found that the plasma level of IL-1β was raised in preeclamptic women[25-28]. And the elevated placental expression of IL-1β was also observed in several researches [26,29].

Diabetes Mellitus

Diabetes mellitus is a group of endocrine diseaseidentified by hyperglycaemia due to lack of insulin or disruptions in insulin signalling. The very common forms of diabetes are type 1 and type 2 diabetes mellitus. Type 1 diabetes mellitus is an autoimmune disease which results in an insulin deficiency, while type 2 diabetes mellitus is determined by peripheral insulin resistance frequently in combination with a dysfunctional insulin production[30].

Pathogenesis of DM

Type2 diabetes is associated with chronic activation of the innate immune system[31-33]. The increased number of islet-related macrophages and elevated expression of interleukin (IL)- 1b was reported in the pancreatic islets from patients with T2D[34,35].Elevated islet IL-1b levels was reported following chronic exposure of human islets to increased glucose,fatty acids, or leptin-3 factors whiich are closely related with T2D[36,37,38]. Moreover, it was recently found that biosynthetic amyloid formation in human islets lead to b-cell dysfunction and death through induction of Fas upregulation and activation of the Fas-mediated apoptotic pathway started by caspase-8, which closely correlates with elevated islet IL-1b level[39,40]. These studies provided evidence that amyloid-induced Fas upregulation is likely mediated by IL-1b. Along with these findings, Westwell-Roper *et al*.[41] have reported b-cell dysfunction associated with increased islet IL-1b expression in high fat–fed transgenic mice with islet amyloid formation. These findings helpsin local IL-1b production, likely created by multiple factors during prediabetic state and/or early stages of T2D, may play a key role in b-cell failure in T2D.

Acute Respiratory Distress Syndrome

The initial acute phase ofARDS is determined by the sudden onset of dyspnea, hypoxemia,respiratory failure, and bilateral infiltrates on chest radio graph which are consistent with pulmonary edema[42]. The sudden onset of respiratory failure usually needs mechanical ventilation.

Pathogenesis And Role of Cytokines In Ards

The inflammatory response in ARDS is started, amplified, and modulated by a complex network of cytokines and other proinflammatory molecules cytokineswhich are produced different cells in the lungs, including fibroblasts, epithelial cells, and inflammatory cells[43]. For (e.g.), tumor necrosis factor (TNF)-a and IL-1 are early response cytokines which are produced mostly by monocytes and macrophages as a result of direct or indirect insult to the lung such as endotoxin or other microbial products[44]. TNF-a and IL-1 acts on other cells, including macrophages, endothelial cells, fibroblasts, and epithelial cells to stimulate production of other cytokines, such as the neutrophil chemotactic factor IL-8. Increased concentrations of IL-8 are present in the alveolar space of patients with ARDS[45].

Nuclear factor kappa-B (NFkB), which is a transcription factor that controls the expression of ICAM-1, IL-1b, IL-6, IL- 8, and TNF-a[46,47].Activation of NFkB, allows the localisation to the nucleus and alter transcription. This nuclear localization of NFkB is a key proximal activation signal in the initiation, amplification and maintenance of the proinflammatory cytokine cascade in ARDS[47].

Cytsic Fibrosis

Airway disease like cystic fibrosis (CF) is determined by a continuous cycle of chronic infection and inflammation which is dominated by a neutrophilic infiltrate. This kind of inflammation is determined by an elevated production of pro-inflammatory cytokines in the lung. This airway inflammation in cystic fibrosis is related with raised production of pro-inflammatory cytokines in the lung. Airway epithelial cells, macrophages, and neutrophils are capable of producing cytokines.

Pathogenesis of Cystic Fibrosis

The inflammatory response happening in cystic fibrosis lung is due to the complex balance prevailing between pro-inflammatory and anti- inflammatory mediators.The epithelial lining fluid of cystic fibrosis patients when compared to healthy controls was found to have reduced levels of anti-inflammatory cytokine IL-10[48], which prevents the production of TNFa, IL-1β, IL-6, and IL-8 by macrophages[49,50]. There are two more anti-inflammatory cytokines namely IRAP and TNFsR. Macrophages produce IRAP due to an inflammatory stimulus[51] and it is a specific antagonist to IL-1a and IL-1β. The pathogenesis of bone resorption and prevention of bone formation is mostly promoted due to the pro-inflammatory cytokines, especially TNFa and IL-1β[52,53,54].

Atherothrombosis- Stroke

Stroke is a very common neurological disorder which is the second main cause of death worldwide [55]. It is determined that by 2030, there would be almost 12 million stroke deaths, 70 million stroke survivors, and also more than 200 million disability-adjusted life-years lost from stroke each year.

Pathogenesis of Stroke AND Role of Cytokines

Interleukin-1 (IL1), is a highly active pro-inflammatory cytokine, which acts as a main regulator of inflammatory process and it triggers a cascade of inflammatory mediators by the activation of the IL1 receptor[56]. There are two associated but individual IL1 genes, IL1A and IL1B, which encodes for IL1α and IL1β, respectively. Experimental results show abnormal levels ofIL1α or IL1β which leads to inflammatory diseases. IL1 is found to involve in the acute and chronic neurodegenerative brain disorders, including ischemic stroke, Alzheimer's disease and Parkinson's disease, even though the cytokine is thought to be involved in the recovery of neurological functions[56,57].

IL6 is a main early mediator of the inflammatory and overall immune response and plays an important role in the development of pathological conditions[58,59]. And it's produced by various kinds of cells which includes monocytes, macrophages, fibroblasts, endothelial cells, keratinocytes, mast cells, T-lymphocytes, and also by microglia and astrocytes. Many experimental studies showed that IL6 plays a key role in the pathogenesis of several ischemic cardiovascular disorders, including ischemic stroke[60]. TNF-α causes the expression of IL1, IL6 and other cytokines. In the acute phase of ischemia, TNF-α and IL1B are the inflammatory factors which cause the speeds upthe inflammatory lesions, and also causes cell necrosis or apoptosis[61].

Peripheral Artery Disease

Peripheral arterial disease (PAD) affects almost 8 million Americans and has more chances to increase its prevalence[62]. The disease is related to severe physical impairment and affects the quality of lifestyle[63-65] many other evidences supports a higher risk of mortality in patients with peripheral artery disease[66,67], specifically from cardiovascular causes[68,69].

Pathogenesis of Pad And Role of Cytokines

IL-1 enhances the expression of cell adhesion molecules on the endothelial surface and has also been deemed to be pro-atherogenic[70]. The potential role of IL-1 in Peripheral artery disease is IL-6 production, an independent predictor of peripheral artery disease progression. But while IL-1 levels was found to be raised in the pericardial fluid of patients having unstable angina[71], plasma levels of IL-1 weren't found to be indicative of Peripheral artery disease[72,73].

Alcoholic Liver Disease

Long term increased consumption of alcohol can result in a list of liver abnormalities, likefrom steatosis or steatohepatitis to fibrosis, cirrhosis, and even liver cancer hepatocellular carcinoma. In its mildest form, fatty liver mostly causes no clinically evident symptoms and is very rarely fatal.

Role of Cytokines In Alcoholic Liver Disease

IL-1 helps in producing inflammatory responses; causes fever; and also stimulates growth and differentiation of immune system cells.Patients with alcoholic liver disease have demonstrated increased serum concentrations of interleukin (IL)-1, tumor necrosis factor- alpha (TNF-α), IL-6, and IL-8[74].

Inflammatory Bowel Disease

Inflammatory bowel diseases (IBD) are chronic infections, determined by active and remission periods. The inflammatory bowel diseases is of three forms

- Crohn's Disease (CD),
- Ulcerative Colitis (UC) and
- Indeterminate Colitis.

In inflammatory bowel disease immune tolerance is usually lost by the intestinal flora which is controlled by various substances, especially cytokines.

Pathogenesis and Role Of Il1β In Ibd (Uc)

Interleukin 1 (IL-1) in combinationwith TNF-α is vital in the pathogenesis of inflammatory bowel disease becauseof its up-regulatory and pro-inflammatory activity. The IL-1 system is subdivided mainly into IL-1α and **IL-1β**, both of which causes the production of type 2 cyclo-oxygenase, phospholipase A and inducible nitric oxide synthase (iNOS)[75]. The tissular level of IL-1 was found to be predominantlyelevated in UC (Ulcerative colitis) patients[76]. The IL-1 system includes antagonists of IL-1 receptors (IL-1Ra), as control mechanism. In UC, IL-1, IL-1Ra and the Transforming Growthfactor β1 (TGFβ1) which controls the size, time extent of the inflammatory process.

Arthritis

Arthritis is chronic autoimmune disease which results in inflammation and deformity of joints. It can cause other systemic problems, also cause inflammation of blood vessels, and rheumatic nodules in various body regions[77].

ROLE OF IL-1β IN ARTHRITIS

Usually inside joint, the pro-inflammatory cytokines co-exist alongside their endogenous inhibitors. This is a a result of ongoing processes in which pro-inflammatory stimuli induce their anti-inflammatory counterparts and the imbalance between the two causes the disease. The very strong pro-inflammatory cytokines, IL-1 stands out as a paradigmatic example of fine-tuned regulation of biological activities through a complicated system of ligands with agonist and antagonist functions, as well as signaling and non-signaling receptor.

CONCLUSION

IL-1beta plays a very important role in the pathogenesis of various systemic diseases. Further research in molecular mechanisms of IL-1 pathogenesis can help to modulate in disease prevention in the near future.

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