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# Cytokines and their roles in pathological conditions

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**Abstract:** Cytokines mediate the innate immune response and if their actions sustained and/or dysregulated, pathological conditions resulted. Among cytokines, interleukins (ILs) which bind to specific receptors for intercellular communication between leukocytes. Virally infected cells can be recognized and destroyed by natural killer cells but sometimes, Epstein Barr Virus (EBV) proteins interfere this mechanism. The respond for infection with EBV is by rapid production of copious cytokines. Deaths in case of EB viral infection is mainly due to a hemophagocytic lymphohistiocytosis (HLH) because of hypercytokinemia which means cytokine storm syndrome (CSS). Interleukin (IL)-6 is produced as a response to infections and tissue injuries as a host defense. IL-6 moves to liver to induce acute phase proteins like C-reactive protein (CRP), serum amyloid A (SSA), fibrinogen, haptoglobin as well as α1-antichymotrypsin. IL-6 participates in the regulation of serum iron in addition to zinc levels by controlling their transporters. IL-6 is essential for differentiation of Th17 from naïve $CD4^+$ T cells. EBV viremia levels correlate with IL-6. However, IL-6 can induce malignant B cells. IL-6 able to inhibit insulin receptor (IR) signal transduction and action of insulin. IL-6 increased due to elevation of cortisol as a response for stressor. There is a correlation between cytokines, vitamin D concentration and EBV load. Detection for different genes, their coupled messenger RNAs (mRNAs) as well as their coupled proteins for EBV is recommended to know which of them have sequence and functional homology with the host proteins that may have roles in CSS production. Also, retrospective studies for the previously diagnosed RNA viruses including COVID-19 and comparing their sequences with mRNAs transcribed on the different genes of EBV to exclude fallacy in their detection is recommended. Moreover, detection for if there is relation between EB viral infection, IL-6 and Alzheimer (as a result of abundancy of amyloid A production) is recommended. Finally, excessive production of monoclonal antibodies and/or nanobodies (prepared in camelids) against IL-6 receptor is recommended.
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**Keywords**: cytokines, IL-6, EBV, cancer, cytokine storm syndrome.

## Introduction

In our review we through light on different cytokines and highlight their roles in many pathological conditions such as Epstein Barr Virus (EBV) which can induce immune dysregulation(1). Unfortunately, EBV has proteins of sequence and functional homology with many proteins of human. These proteins have importance in control of infected cells with EBV(2).

## EBV and cytokine production:

EBV codes cytokines that very important in modulating the immune system to allow persistent infection(3). Cytokines mediate the innate immune response and if their action sustained and/or dysregulated, pathological condition resulted such as severe chronic active EBV (CAEBV) that means clonal expansion of Tor natural killer (NK) cytotoxic cells and patients have elevated levels of pro and anti-inflammatory cytokines as interleukin-1 beta (IL-1β), interferon gamma (IFN-γ), IL-13, IL-15, tumor necrosis factor alpha (TNF-α) in addition to transforming growth factor beta (TGF-β)(4). Moreover, symptoms of infectious mononucleosis (IM) are due to cytokine secretion such as IFN-γ and IL-2 as well as activated cytotoxic T cells where peripheral lymphocytosis, lymphadenopathy and splenomegaly are expressions of these proliferated T ($CD8^+$ cytotoxic T) cells(2).

Immune cells possess special functional capacities characteristically have certain surface receptors and cytokine profiles as well. Examples of these cells are CD4 and CD8 T cells, B cells, innate lymphoid cells (ILCs), NK cells and dendritic cells (DCs)(5).

During systemic and local inflammation, cytokines are secreted to produce some responses in the patient such as fever, anorexia even shock in severe cases(6). However, interplay between pro and anti-inflammatory cytokines characterizes inflammation (7)

Among cytokines, interleukins (ILs) which bind to specific receptors for intercellular communication between leukocytes. ILs distributed in families according to their sequence homology, similarity in receptor chain or functions (5)

Examples for proinflammatory cytokines are IL-1, TNF, IFN-γ, IL-12, IL-18 and granulocyte-macrophage colony stimulating factor but IL-4, IL-10, IL-13, IFN-α and transforming growth factor-beta are known as anti-inflammatory cytokines. However, a cytokine can act as a pro and an anti-inflammatory cytokine (7).

Important factors for cytokine properties are the amount of the cytokine, target cell nature, nature of the activated signal, produced cytokine nature, timing, cytokine action sequence in addition to the experimental model (7).

**EBV-IM and cytokines:**

Virally infected cells can be recognized and destroyed by NK cells but sometimes, EBV proteins interfere this mechanism and early viral control failure with NK and/or invariant NK (iNK) T cells can result in IM or fulminant primary viral infection. However, the respond of NK and iNK T cells for infection with EBV is by rapid production of copious cytokines like IL-2, IL-15 and IFN-γ which lead to activation of NK cells and enhancement for expression, activation as well as cytotoxic functions of CD 8 T cells(8).

Acute IM characterized by increasing the number of total peripheral blood T cells of 5 to 10-fold above that for asymptomatic carriers but in latent infection, this response is reduced by 10-fold(9). Also, EBV-specific CD4 T cells showed a lower response as 1% in IM patients and 0.1% in latent infections from the all circulating CD4 T cells (10). CD4 T cells possess specificity for the viral antigens to control EBV infection but its response less than CD8 T cells response. Although the strong T cell response, no complete clearing of EBV-infected B cells and about 1 per 10,000 to 1 per 100,000 memory B cells remain infected for the individual life (11) and the virus from these cells reactivates periodically resulting in infectious virions release to reinfect additional cells.

IM patients have atypical lymphocytosis in peripheral blood (>50% lymphocytes and >10% atypical forms). CAEBV (severe primary EBV infection that lasting more than 6 months) patients have raised anti-EBV titers (>1:5120 anti-VCAIgG as well as >1:640 anti-EA but low <1:2 anti-EBNA). These patients also, have high EBV in peripheral blood and/or tissues which are infected where raised EBV DNA levels are present in CD4 T cells and NK cells and not in B cells in addition to reduced activities of cytotoxic T cells and NK cells. Deaths in case of EB viral infection is mainly due to a hemophagocytic lymphohistiocytosis (HLH) because of hypercytokinemia which means cytokine storm syndrome (CSS) that reveals an aberrant activation for NK cells as well as macrophages resulting in hypercytokinemia that leads to cellular damage, dysfunctions of organs and death (11).

**EBV-HLH and cytokines:**

EBV-HLH characterized by ranging course from multiorgan failure which developed in hours to persistent or IM symptoms with recurring that lasts months. At the beginning, there is atypical lymphocytosis, which is followed by cytopenia, dysfunction of liver, failure of multiple organs showing high infiltration with activated CD8 T cells and macrophages. Also, central nervous system is involved(12). HLH patients reveal fever, splenomegaly, cytopenia, hyperglyceridemia or hypofibrinogenemia and secondary lymphoid organs show hemophagocytosis which are followed by absent or low activity of NK cells, elevated levels of serum ferritin and soluble CD25 (receptor with high affinity to IL-2)(13).

Immune effectors (mainly CD8 T cells, CD4 T cells. NK/INK T cells, neutrophils and monocytes) as well as immune targets (mainly infected B cells in addition to epithelial cells) secrete large amounts of cytokines as EBV response where type 1 interferons (IFN-α and IFN-β) are secreted by NK cells and B cells within 24 hours of infection. IL-6 expression and TNF inhibition induced if EBV binds to surface of monocytes. Also, IL-8, macrophage inflammatory protein-1α and granulocyte macrophage colony stimulating factor (GM-CSF) are induced when EBV binds to macrophages surface. However, due to the innate stage against the viral infection, IL-1 α and β are produced by NK cells and monocytes where levels of IL-1, IL-2, IL-6 in addition to IFN-γ in serum are highly elevated in case of acute or chronic EBV infection in symptomatic patients (11).

**Characteristic features of CSS:**

Cytokine storm is considered a hallmark for all HLH-EBV where deaths is rapid and there is extremely elevated cytokine levels in serum such as IFN-γ that exceeds 100U/ml (normal <1.0 U/ml), SCD25 (that exceeds 10,000 U/ml) (normal <2000

U/ml) in addition to significant rise of IL-6, IL-10 and IL-18 levels (11).

Increasing in the levels of proinflammatory and immunoregulatory cytokines are associated with the increase in the number of cells producing cytokines, for example: IFN-γ, TNF, IL-6 IL-10 and TGFβ(14).

**Cytokines and IL-2 inducible T cell kinase:**

Patients have deficiency in IL-2 inducible T cell kinase (ITK) develop elevated levels of EBV viremia. This viremia produced due to activation and proliferation of T cells hence disability for infection control. Deficient T cells in ITK show abnormalities in production of cytokines. An example of ITK role in cytokine production regulation by Th17 cells (CD4 effector T cell) which in response to IL-6 and TGF-β can differentiate and express the proinflammatory cytokines IL-17A and F, IL-21 as well as IL-22 (11).

**Selenium and cytokine relationship:**

Serum selenium was detected to be inversely associated with IL-6 in elderly (Tseng et al., 2013)(15). Also, concentration of selenium in serum appeared statistically lower in liver cirrhotic patients but IL-6 and growth differentiation factor 15(GDF-15) concentrations are higher than in control group(16).

**Magensium and immune system upregulation:**

Magnesium transporter 1 which is a x-linked gene and very important for regulation of ionized (free) magnesium which must be in flow for NK stimulatory receptor expression upregulation on NK in addition to CD8 T cells for EBV control (11).

**Examples of ILs:**

**IL-1**: IL-1 is essential for Th 17 cells development as well as inflammation initiation (17). IL-1β is potential stimulator for hypercortisolism due to its interaction for all HPA axis levels(18).

**IL-2**: IL-2 is a pleiotropic effect cytokine on the immune system by regulating lymphocytes(19).

**IL-13**: IL-13 is essential for IgE synthesis, especially if IL-4 production is low or absent(20). It also modulates resistance against organisms present intracellularly. Moreover, it regulates eosinophilic, mucous secretion in addition to hyperresponsiveness for airway and it considered as potent mediator for tissue fibrosis as well(21).

**IL-17/IL-23**: IL-17/IL-23 is linked with psoriasis, arthritis as well as ankylosing spondylitis(22, 23). Th17 cells are CD4 (+) helper T-cell which produce IL-17A and IL-17F where IL-17A has very important role in responses of allergy, for example: delayed hypersensitivity type, contact hypersensitivity in addition to allergic inflammation of the airway (17). Moreover, more production of IL-17A is noticed in the peripheral blood of CAEBV pathophysiology(24).

**IL-6 (a major cytokine):**

IL-6 is a soluble mediator of pleiotropic action on inflammation, immune response as well as hematopoiesis. According to its biological activity, it takes name, such as; 1)B-cell stimulating factor 2 (BSF-2) due to its ability to induce differentiation of the activated B cells to be antibody-producing cells(25) ;2) hepatocyte-stimulating factor (HSF) due to its action for acute phase protein synthesis in hepatocytes ;3) hybridoma growth factor (HGF) due to its enhancement for growth of fused cells between plasma cells and myeloma cells and 4) interferon (INF)-β2 because of its IFN antiviral activity(26).

IL-6 is produced as response to infections and tissue injuries as a host defense within stimulation of acute phase response, hematopoiesis in addition to immune reactions. Its expression is controlled by transcriptional as well as posttranscriptional processes. if it deregulated by continual synthesis, it would affect pathologically to give chronic inflammation and autoimmune states as well(27).

**Substances induced by IL-6:**

IL-6 is synthesized in the local area of the initial inflammation, followed by its movement to the liver by blood stream to rapidly induce acute phase proteins like C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin as well as α1-antichymotrypsin(28) but it reduces fibronectin, albumin and transferrin production (28).

Persistent elevated levels of SAA for long time, many chronic inflammatory diseases will result from the generation of amyloid A amyloidosis(29) leading to amyloid fibril deposition to cause in organs a progressive deterioration.

**Regulation of iron and zinc by IL-6:**

IL-6 participates in the regulation of serum iron in addition to zinc levels by controlling their transporters. IL-6 induce production of hepcidin that blocks iron transporters ferroportin 1 action on gut causing reduction in levels of serum iron(30). So, IL-6 hepcidin axis is responsible for hypoferremia as well as anemia accompanying chronic inflammation. Hypozincemia noticed in inflammation resulted from action of IL-6 which enhances expression of zinc importer ZIP14 on hepatocytes(31).

**Action of IL-6 to produce platelets:**

IL-6 when reaching bone marrow, it promotes maturation of megakaryocytes and platelets are produced(32). So, evaluation of the severity of inflammation could be obtained for the routine of

clinical laboratory examination according to results of acute phase protein levels as well as counts of red blood cells and platelets.

**$CD4^+$ T cells promotion by IL-6:**

IL-6 promotes naive CD4+ T cells specific differentiation to perform link between innate and acquired immune response. With transforming growth factor (TGF)-β, IL-6 is essential for differentiation of Th17 from naïve CD4+ T cells(33). Also, IL-6 inhibits TGF-β-induced Treg differentiation(34). Therefore, Th17/Treg balance upregulation has responsibility for immunological tolerance disruption and presence of autoimmune and chronic inflammation(35).

**Induction of B cells differentiation by IL-6:**

IL-6 due to its name BSF-2, it can induce activated B cells differentiation into Ab-producing plasma cells. So, continuous over synthesis of IL-6 leads to hypergammaglobulinemia and antibody production. Moreover, IL-6 promotes differentiation of T-follicular helper-cell and production of IL-21(36), that regulates synthesis of immunoglobulin (Ig) especially IgG4.

**Other actions of IL-6:**

IL-6 induces CD8+ T cells differentiation into cytotoxic cells(37). Also, generation of IL-6 in stromal cells of bone marrow stimulates the RANKL(38), which is very important for osteoclasts differentiation as well as activation leading to bone resorption and osteoporosis(39).

IL-6 induces excess production of VEGF and angiogenesis enhancement which leads to increase in the vascular permeability that is considered as pathological mark for the inflammatory lesions such as synovial tissues of the rheumatoid arthritis and edema of remitting synovitis with pitting edema (RS3PE) syndrome(27).

IL-6 helps keratinocyte proliferation(40) or collagen generation in dermal fibroblast and abnormalities in skin may result as in case of systemic sclerosis(41).

IL-6 dysregulation and expression could be induced by EBV in peripheral blood mononuclear cells in vitro via deoxyuridine triphosphate nucleotidohydrolase (duTPase)(1). However, EBV viremia levels correlate with IL-6(42).

Interactions between IL-6, EBV and B cells can result in tumorigenesis where IL-6 could be induced from B cells by EBV. Also, IL-6 can modulate control of EBV-infected B cells by T cells. However, IL-6 can induce malignant B cells by acting as growth factor for myeloma or EBV-transformed B cells. Therefore, IL-6 inhibition provides preventive or therapeutic mean against EBV-induced lymphoproliferative disease (LPD), a B cell neoplasm where IL-6 has essential role in its pathogenesis(43). However, infected B cells produce IL-6 which drives survival proliferation and maturation(11).

IL-6 which is the most known to be major inflammatory cytokine is also a strong activator for STAT3 (Signal transducer and activator of transcription 3). This developed IL-6 /STAT3 response, its mediation is through over expression of IL-6 receptor. Therefore, IL-6 expression was detected abundantly in the stromal cells of nasopharyngeal carcinoma (NPC, its characters are EBV infection in addition to high inflammatory stroma as well as metastatic nature). Also, elevated levels of IL-6 were found in the sera of patients having advance-staged NPC(44).

Type 2 diabetes and insulin resistance syndrome can represent an acute phase response because of correlation between local as well as circulating proinflammatory cytokines (TNF-α, IL-1, INF-γ and IL-6) elevations and insulin resistance. IL-6 able to inhibit insulin receptor (IR) signal transduction and action of insulin and this inhibition depends on IL-6 exposure duration. However, IL-6 shows 2 to 3-fold elevation in obesity and type 2 diabetes patients who become having increased blood glucose via hepatic glucose output elevation, decrease glucose tolerance as well as decreased insulin sensitivity. IL-6 can be considered as glucoregulatory hormone where its increase binds with hepatic glycogen synthase inhibition, glycogen phosphorylase activation in addition to lipolysis as well as increased triglyceride production. IL-6 produced by macrophages and peripheral mononuclear cells in addition to adipose tissue and muscle tissue where adipose tissue produces 10 to 35% of IL-6 in resting persons which increase if adiposity increase. Also, circulating IL-6 increases by exercise due to increased production by muscle tissue(45).

Although cortisol action on the immune system was known to be immunosuppressive, it can act as immunomodulatory. However, chronic or severe stressor exposure induces prolonged HPA axis activation leading to cortisol release in excess which can participate to inflammation due to impairment in the function of glucocorticoid receptors such as downregulation, reduced expression or nuclear translocation(46).

IL-6 in physiological levels induce anti-inflammatory response more than causing inflammatory response which without dependance on INF-α enhance levels of IL-1 receptor agonist (IL-1 ra) as well as IL-10 in addition to induction of increased cortisol(47).

An example is the increase in IL-6 in the morning due to elevation of cortisol in evening for firefighters stressed by sleep restriction conditions. Immune-endocrine interactions alteration binds with health outcomes such as coronary artery diseases and depression. Due to abnormalities in glucocorticoids receptors, the immune system's ability for responding to cortisol and lowering inflammation is reduced(46).

**Correlation between EBV, cytokines and vitamin D concentration:**

EBV infected patients with significantly high EBV DNA load showed a clear transcriptional signature with mRNA levels of CD74, IL-6, IL-23, IFN-γ, TNF-α, IL-15, IL-28 as well as IL-17 significantly high. These patients have inverse correlation between vitamin D concentration and EBV load. So, correlation between biomarker, EBV replication and vitamin D was obviously presented(48).

**Recommendation:**

Detection for different genes, their coupled mRNAs as well as their coupled proteins for EBV is recommended to know which of them have sequence and functional homology with the host proteins that may have roles in CSS production. Also, retrospective studies for the previously diagnosed RNA viruses including COVID-19 and compare their sequence with mRNAs transcribed on the different genes of EBV to exclude fallacy in their detection is recommended. Moreover, detection for if there is relation between EB viral infection, IL-6 and Alzheimer (as result of abundancy of amyloid A production) is recommended. Finally, excessive production of monoclonal antibodies and/or heavy chain (nanobodies; prepared in camelids) antibodies against IL-6 receptors is recommended.

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