

**FACTORS RESPONSIBLE FOR THE RELEASE OF CYTOKINES IN THE MODIFIED  
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**ABSTRACT**

Cytokines are small proteins that are important for cell signaling. They affect the activity of other cells. They also help in autocrine signaling. Cytokines are produced from immune cells like macrophages, B-lymphocytes, T lymphocytes and mast cells. 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 include lymphokine, monokine, chemokine and interleukin. The main function of cytokines is that help in signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines play a main role in the natural or innate response by means of the direct action of mechanism against the invading agent during the early stages of the infection, or by means of immune modulatory mechanism which activate NK cells and monocytes macrophages, which then induce the release of cytokines.

**KEYWORDS:** Cytokines, Oxidised Low Density Lipoprotein, Oxysterols, Lysophosphatidylcholine.**INTRODUCTION  
CYTOKINES**

- Cytokines are a diverse group of non-antibody proteins which act as mediators between cells.
- They are identified as products of immune cells that act as mediators and regulators of immune processes.
- Many cytokines are now known to be produced by cells other than immune cells and they can have effects on non-immune cells as well.
- Cytokines are currently being used clinically as biological response modifiers for the treatment of various disorders.

The basic factors for the release of cytokines are divided into two that are following:

**PRIMARY FACTORS**

- Bioactive Lipid Mediators
- Oxidized Low-Density Lipoprotein
- Oxysterols
- Lysophosphatidylcholine
- Platelet activating factor

**SECONDARY FACTORS**

- Heat shock proteins
- Immune Complexes
- Infectious Agents
- Defective Clearance of apoptotic cells

- Mechanical factors
- Other factors

**PRIMARY FACTORS****Bioactive Lipid Mediators**

This factors induce the cytokines release due to the hepatic tissue injury and inflammation in liver which is because of the chemical agents that can lead in causing toxicity. The macrophages initiate the cytokines release during liver fibrosis and also in chronic hepatitis. The cytokines and bioactive lipid are the mediators which regulates the cutaneous immune system that initiate the rapid immune responses with the controlled inflammation followed by efficient resolution. Skin is characterized by the bioactive lipid metabolism and also by fatty acids which plays a major role in both structural integrity and functionality particularly when they transformed to bioactive mediators.<sup>[1]</sup>

**Oxidized Low-Density Lipoprotein**

- It initiates the cytokines release during atherosclerosis. It has been recognized that through the receptor mediated pathways the vessel wall components in vitro and in vivo internalize ox-LDL. This receptor-mediated pathway involves scavenger receptors (SRs) family, such as class A macrophage scavenger receptor type I/II(SR-AI/II), class B macrophage scavenger receptor type I(SR-BI),

CD36, macrophage receptor with a collagenous structure (MARCO) and macrosialin, for smooth muscle cells and monocyte/macrophages and also fibroblast.

- These SRs are the first line cells which are affected by the ox-LDL. Since endothelial dysfunction is the early step that takes place in atherogenesis, binding (and subsequent endocytosis) of ox-LDL to endothelial cells, these SRs are present in very small amount in vascular endothelial cells and these are also undetectable,
- There is an increasing evidence that LDL plays a important role in pathology of osteoarthritis. This ox-LDL play an essential role in atherosclerosis development which involve in the processes of synovial inflammation, cartilage destruction and bone deformation.<sup>[2]</sup>

### Oxysterols

Oxysterols are the cholesterol derivatives that are the oxidized, which are important in biological processes, which includes cholesterol homeostasis, sphingolipid metabolism, platelet aggregation, apoptosis, and also in protein prenylation. These initiates the release of cytokine during atherosclerosis and alzheimers disease. Serum oxysterols levels are the suitable biomarkers for neurological disease like multiple sclerosis.<sup>[3]</sup>

### Lysophosphatidylcholine

Lysophosphatidylcholine (lyso-PC), a polar phospholipid which are highly present in atherogenic lipoproteins and atherosclerotic lesions, which has been shown to transcriptionally induces the expression of endothelial genes relevant to atherogenesis, lyso-PC is a prooxidant by product of phospholipase A2 activity which can modulate function and maturity of dendritic cells.<sup>[4]</sup>

### Platelet activating factor

This factor is also known as a PAF, PAF-acether or AGEPC (acetyl-glycerol-ether-phosphorylcholine) which is a potent cytokine activator and mediator for many leukocyte functions, that are including platelet aggregation and degranulation, inflammation, and anaphylaxis. It is also involved in vascular permeability changes, the oxidative burst, chemotaxis of leukocytes, and in phagocytes augmentation of arachidonic acid metabolism. It is produced in response for specific stimuli by a variety of cell types, which includes neutrophils, basophils, injured tissue, monocytes/macrophages, platelets, and endothelial cells. PAF and cytokines like interleukin, tumor necrosis factor and other plays a major role in inflammatory process which involves gastrointestinal disorder such as crohn's disease, ulcerative colitis e.t.c.<sup>[5]</sup>

## SECONDARY FACTORS

### Heat shock proteins

Heat shock proteins are secondary activator of cytokines especially in cancer and myocardial infarction. They activate cytokines in antigen presenting cells {dendritic

cells} in cancer. Heat shock protein factor such as Hsp60, Hsp70, Hsp90, Hsp96 which are capable in production of proinflammatory cytokines by the monocyte-macrophage system and their activation and maturation of dendritic cells. The cytokine effect of heat shock protein is due to the LPS and LPS –associated molecule contamination.<sup>[6]</sup>

### Immune complexes

Immune complexes include all interleukins and chemokines. They activate cytokines in almost all processes including wound healing. Levels of induced cytokines which are correlated by complement activation and autoantibody profile by systemic lupus erythematosus. Increased levels of immune complexes that induced cytokines which can leads in increasing the both classical complement activation and occurrence of anti-sjogren's syndrome A (SSA) and anti-SSB but not others.<sup>[7]</sup>

### Infectious agents

All infective pathogens that including many number of viruses and bacteria which initiate the cytokines release.

### Defective clearance of apoptotic cells

- The accumulation of apoptotic cell remnants is due to the inefficient clearance of dying cells. Defective clearance of apoptotic cell is considered an intrinsic defect which can cause the permanent presence of cellular debris that is responsible for the initiation of systemic autoimmunity (cytokines) during systemic lupus erythematosus diseases.

### Mechanical factors

Mechanical factors such as high blood pressure, disturbance in menstrual flow, release of angiotensin etc. leads to the activates the cytokines release. When the blood pressure reaches 170/95 which leads to the cytokines release activation in myocardial infarction. Angiotensin II, also known as hypertensin, which initiates the cytokines release in hypertension. Disturbances in menstrual flow initiates the cytokines release in especially during the presence of tumors in uterus.

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