INFLAMMATION AND ACUTE PHASE RESPONSE

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ABSTRACT: Inflammation caused by infection takes place by the cooperative cascade of cytokines and leukocytes. Tumor necrosis factor, interlukin-1, and interlukin-6 play important roles as proinflammatory cytokines to mediate local inflammation and activate other inflammatory cells e.g. neutrophils, monocytes, and macrophages. At least 15 different low molecular weight cytokine are secreted by activated leukocytes and are responsible for triggering acute phase response in the form of fever, leukocytosis, increased secretion of adreno corticotropic hormones, and production of acute phase proteins. Acute phase proteins are produced in liver under the influence of cytokines, which through blood stream passes to the site of inflammation and kill the pathogens by opsonization and activating complement pathways. The changes in the concentrations of positive acute-phase proteins and negative acute-phase proteins are due to the changes in their production by liver. Three of the best known acute phase proteins are C-reactive protein, serum anyloid A, and haptoglobin. Some disease states are casually related to acute phase proteins. C-reactive protein mediated compliment activation has a key role in some forms of tissue alteration such as cardiac infarction. Elevated S amyloid A levels are seen in chronic arthritis and tuberculosis. Other acute phase proteins show more moderate rise, usually less than fivefold.

KEYWORDS*:* Acute phase response, acute phase proteins, inflammation, cytokines.

INTRODUCTION

Inflammation is the major and complex reaction of the body against infection upon tissue injury. It consists of recruitment and activation of leukocytes and plasma proteins at the site of infection to eliminate the infectious agent (Kindt, et.al. 2004). The infectious microorganisms, after gaining bodily access to the site of injury, cause local inflammation (Lundberg, 2010). The local inflammatory response is later accompanied by a prominent systemic response known as acute phase response {APR} (Male D, et.al. 2006). This response is marked by the induction of fever, anorexia, solmonescence, lethargy, increased synthesis of hormones such as adrenocorticotropic hormone {ACTH} and hydrocortisone, (Willey J M, et.al. 2008) increased leukocytosis and altered production of large number of proteins in liver (Zheng H, et.al. 1995). Those proteins whose levels change during inflammation are termed acute phase proteins {APP} (Gabay C, 1999).
Many bacterial components and products such as peptidoglycans, lipoteichoic acid, exotoxins, lipoproteins and glycolipids can initiate the local inflammatory processes (Paul W.E, 2008). Subsequent to the bacterial invasion, many cell types residing in the mucosa or skin may produce molecules important in controlling infections (Baumann H, et.al. 1994). Among the important resident host cells are the mast cells, popularly known for their stores of histamine, serotonin (Moshage H, 1997) and also for containing preformed tumor necrosis factor-α {TNF} and various cytokines(Arnett HA, et.al. 2010). On exposure to various bacterial products mast cells release these proinflammatory cytokines, which are essential for the recruitment of neutrophils to the site of inflammation (Abbas, et.al. 2007). Major three of these cytokines are interlukin-1{IL-1}, interlukin-6{IL-6}, and TNF-α, which have a profound behavioral, neuroendocrine and metabolic effect (Rich R, et.al. 2008). The concentration gradient of various tissue products released activates the vascular system and the cells of inflammation. These responses in turn are associated with production of more cytokines and other inflammatory mediators which diffuse to the extracellular fluid compartment and circulate in the blood (Ceciliani F, et.al. 2002). Furthermore, apart from the cytokine mediated rise of clinical symptoms, a series of changes occur such as change in concentration of several APPs, activation of complement cascades, increased value of ACTH and glucocorticoids, and decreased serum levels of calcium , zinc, iron, vitamin A, and α-tocopherol(Moldawer LL, et.al. 1997). Acute phase proteins opsonize microorganisms and activate complement components, while others scavenge cellular remnants and free radicals or neutralize proteolytic enzymes (Nairn R, et.al. 2002).

At the site of injury, proinflammatory cytokines are released from damaged tissue. Activation of complement cascade forms complement products that act as chemotactic agents for the recruitment of neutrophils (Finckh A, 2009). Complement anaphylatoxins (C3a, C5a) induce local mast cells degranulation with release of histamine, causing vasodilation and smooth muscle contraction (Gonda TA, et.al. 2009). Leukocytes, kallikrein and bradykinin move out through blood vessels causing swelling. Bradykinin then binds to nearby capillary cells and stimulates the production of prostaglandins which then binds to free nerve endings making them to start pain impulse (Quinton L J, et.al. 2009).

INITIAL PHASE OF INFLAMMATION AND RECRUITMENT OF LEUKOCYTES

These all in turn lead to the rise of classical signs of inflammation: redness, increased heat,swelling, pain, and loss of function.

Under the influence of proinflammatory cytokines and mediators like histamine and erotonin, the vascular endothelium is activated to express "Cellular Adhesion Molecules" in increased amount. Leukocytes are recruited at the site of inflammation through the process "Extravasation" (Sciacca FL, et.al. 1994). To accomplish extravasation leukocytes recognize inflamed endothelium and adhere to it strongly enough so that they are not swept away by the flowing blood. In response to microbes and cytokines produced by cells e.g. Macrophages, endothelial cells lining postcapillary venules at the site rapidly increase surface expression of proteins called Selectins (Kerfoot SM, et.al. 2005). Selectins bind to mucin like cellular adhesion molecules on leukocyte membrane. Resulting leukocytes repetitively detach and bind, and thus roll along the endothelial surface (Firrell JC, et.al. 1989). Process of inflammation is slow enough to allow leukocyte interaction with chemokines bound by heparin sulfate glycosaminoglycan on luminal surface of endothelial cells (Johnston B, et.al. 1997). Leukocytes express a family of adhesion molecules, integrins, which binds to chemokines. This binding provides a degree of specificity to the recruitment of white blood cells at the site (Dings Z, et.al. 2001). Leukocytes transmigrate through the interendothelial spaces along the chemical concentration gradient without breaking the integrity established with endothelial barriers. It accomplished by binding of protein CD31, which is expressed on leukocytes with Platelet Endothelial Cell Adhesion Molecule-1 {PECAM-1} on the endothelium (Alvarez A, et.al. 2004).

Neutrophils are the first cell type to bind to inflamed endothelium and extravasate into the tissues (Kubes P, et.al. 2003). When selectins are released from the endothelial cells, neutrophils express L-selectin and mucin like P-selectin glycoprotein ligand {PSGL-1} to mediate the rolling on inflamed endothelium. Rolling neutrophils are activated by various chemoattractants released by endothelial cell surface or secreted locally by cells involved in inflammatory response (Birner U, et.al. 2000). Two chemokines are envolved in activation process are IL-8 and macrophage inflammatory protein-1β {MIP-1β}.

Monocytes from the peripheral home reach at the site of infection much later than neutrophils, because of late expression of its receptor vascular cell adhesion molecule-1 {VCAM-1}, complementary to Intercellular adhesion molecules-1 {ICAM-1} on the inflamed endothelium. Monocytes are lured to the area of infection by chemoattractants such as bacterial peptide fragments and complement fragments (Mulligan MS, et.al. 1998). Receptors expressed on monocytes for complement fragments are CR3; consisting of the integrins CD11b/CD18, and CR4. These neutrophils at the site of inflammation phagocytose invading pathogens and release mediators that continued to inflammatory response (Jones MR, et.al. 2006). Among the mediators are the MIP-1α, MIP-1β, chemokines that attract macrophages to the site of inflammation. These activated macrophages exhibit increased phagocytosis and increased release of mediators and cytokines that contribute to the inflammatory response.

Macrophage activation leads increased synthesis of reactive oxygen intermediates and nitric oxide {NO}, which are potent microbicidal agents that are produced within the lysosomes of macrophages and kill the ingested microbes (Janeway, 2005). Reactive oxygen intermediates, NO and lysosomal enzymes may also be released into adjacent tissues where they kill extracellular microbes and may also cause damage to normal tissue. Macrophages secrete three cytokines namely IL-1, IL-6 and TNF-α also a short lived lipid mediators platelet activating factor {PAF}, prostaglandin, leukotrienes that induce localized inflammation (Gameel AA, et.al. 1974). All three cytokines act locally inducing coagulation, increased expression of adhesion molecules on vascular endothelial cells. IL-1 and TNF-α act back upon macrophages and endothelial cells to induce production of chemokines (Sarraf P, et.al. 1997). Additionally, interferon-γ {IFN} activates macrophages and neutrophils promoting increased phagocytic activity and increased release of lytic enzymes into tissue spaces (Dogra N, et.al. 2007). Cytokines released from the site of inflammation facilitate both the adherence of immune cells to vascular endothelial cells and their migration through the vessel wall into tissue spaces.

CYTOKINES

Cytokines are polypeptide produced in response to microbes and other antigens that mediate and regulate immune and inflammatory reactions. Actions of cytokines are often pleiotropic and redundant (Dinarello CA, 1997). From the site of infection local tissue cells release some proinflammatory cytokines TNF, IL-1 and chemokines, which mediate many of the effector functions of innate immunity and also the principle mediators of acute inflammatory response.TNF is secreted by activated mononuclear phagocytes, natural killer {NK} cells and local mast cells while IL-1 is secreted also by neutrophils, endothelial cells and epithelial cells (Wolf M, et.al. 1996). Lipopolysaccharides potently stimulate the production of TNF and IL-1. Both the proinflammatory cytokines induce the expression of adhesion molecules (ICAM-1, VCAM-1) for leukocytes. They also stimulate macrophages to secrete chemokines that enhances affinity to leukocyte integrins for their ligands (Moldawer LL, 1997).

TNF and IL-1 when secreted in large amounts, exerts endocrine effects, by causing fever, chachexia and increased synthesis of APP. Chemokines act as a chemoattractants for leukocutes and are produced by endothelial cells, epithelial cells, fibroblasts, leukocytes and other cytokines (Rollins BJ, 1997). Chemokines act cooperatively in the process of leukocute migration towards chemical gradient. They are classified into two major families; CC and CXC family. Each family having distinct receptors on leukocytes. IL-6 works both in innate and adaptive immunity. It is synthesized in response to microbes and other cytokines such as IL-1 and TNF. It stimulates the synthesis of APP by hepatocytes, production of white blood cells and thus contributes to the efforts of inflammation (Bernardini G, et.al. 1998).

ACUTE PHASE RESPONSE

The acute-phase response consists in a large number of behavioural, physiologic, biochemical, and nutritional changes involving many organ systems distant from the site, or sites, of inflammation. Cytokines conduct the specific immune response of the stressed organism against foreign antigens. The proinflammatory cytokines are responsible for the induction of mentioned fever and muscle catabolism, activate white blood cells precursors in the bone marrow growth of inflammatory tissue fibroblast and macrophages (Baumann H, et.al. 1994).

The fever induced augments the host defense by stimulating leukocytes so that they can destroy the microorganism, it enhances the specific activity of the immune system and also enhances microbiostasis by decreasing available iron to microorganism (Dinarello CA, 1997). Inflammatory reactions, which consume leukocytes, also elicit the production of new leukocutes (Chrousos GP, 1995). Colony stimulating factors are kind of cytokines responsible for differentiation and expansion of bone marrow progenitor cells. IL-6 similarly acts as a growth factor for neoplastic plasma cells and many myeloma cells, which grow autonomously and secrete IL-6 as an autocrine growth factor (Kopf M, et.al. 1994).

Within 12-24 hours of the onset of an acute inflammatory response, increased level of IL-1, IL-6, TNF-α and oncostatin-M induce production of acute phase proteins by hepatocytes. The redundancy in the ability of at least five cytokines induces production of acute phase proteins (Kindt, et.al. 2004). Acute phase proteins are known for whose plasma concentration increase or decrease by at least 25 percent during inflammatory disorder, and are synthesized by the cytokine mediated induction of the common transcription factor, nuclear factor-IL6 {NF-IL6}. Amino acid sequence of NF-IL6 show high degree of sequence identity with a liver specific transcription factor CCAAT/ Enhancer binding protein {C/EBP} and have inverse relationship with it. TNF-α and IL-1β binding to their receptors results in the activation of IkB kinase, the inhibitor associated to NF-kB in cytoplasm. IkB-P is then degraded by the ubiquitin-proteasome pathway, thus allowing the free NF-kB to translocate to the nucleus and promotes transcription of acute-phase genes (Ceciliani F, et.al. 2002).

CLASSIFICATION OF ACUTE PHASE RPOTEINS

These are large and varied group of glycoproteins in serum released into blood stream in response to a variety of stressors. All the up-regulated proteins have been called *positive* APP, in order to differentiate them from the so-called *negative* APP, that are down-regulated (Ceron JJ, et.al. 2005). Positive APP is represented by large number of proteins which may be divided into three classes based on their normal plasma concentrations [Table I]. Concentration of some proteins like C reactive protein {CRP}, Serum amyloid A {SAA}rise as early as 4 hours after inflammatory stimulus and attain their maximum levels within 24 to 72 hours and also decline very rapidly. Class II APP begin to increase 24 to 48 hours and reach to their maximum level in about 7 to 10 days, about two weeks are required to return to their normal levels (Petersen HH, et.al. 2004). Elevated expressions of APP differ widely from species to species and their pattern often depends upon sex.

Table I: Best studied Human Acute Phase Proteins

Group	Proteins	Normal Plasma Concentration(mg/l)
I (concentration may increase by50%)	Ceruloplasmin	150-600
	Complement C3	800-1700
	Complement C4	150-650
II(concentration may increase two to five fold)	AGP	550-1400
	PI	2000-4000
	ACT	300-1600
	Hp	400-1800
	FIBRINOGEN	2000-4500
III (concentration may increase up to 1000 fold)	CRP	<5.0
	SAA	<10.0

AGP, α1-acid glycoprotein; PI, α1-protease inhibitor; ACT, α1-antichymotrypsin; Hp, Haptoglobin; CRP, C-reactive protein; SAA, Serum Amyloid A.

BIOLOGICAL FUNCTIONS OF APP

Positive APPs are regarded as having major functions in opsonisation and trapping of microorganisms and their products, in activating complement system, in binding cellular remnants, in neutralizing enzymes, scavenging free hemoglobin and radicals, and in modulating the host's immune response (Kravitz MS, et.al. 2005). Table II shows list of APPs and their functions during inflammation.

CRP, was the first acute phase protein to be described and is a sensitive systemic marker of inflammation and tissue damage. CRP belongs to pentraxin family and named for its specific binding with the C- polysaccharide of Streptococcus pneumonia. CRP exhibits planar pentagonal structure, made up of five identical, non covalently bound subunits.

Table II: List of APP and their functions during inflammation

Protein	Function
alpha-1 antichymotrypsinogen	protease inhibitor
alpha-1 antitrypsin	protease inhibitor resolution of emphysema
Alpha-2-Macroglobulin	inhibitor of several serum proteases and other functions
Antithrombin-3	modulation of coagulation cascade
Apolipoprotein H (β-2-Glycoprotein 1)	complement component
C1 inhibitor	negative control of complement cascade
C2	complement component
C4	complement component
C4	complement component
C4 binding protein	complement component
C5	complement component
C9	complement component
C-reactive protein	binding to membrane phosphorylcholine complement activation and opsonization interaction with T-cells and B-cells
Ceruloplasmin	Copper transport protein
Factor VIII	clotting formation of fibrin matrix for repair
Factor-B	complement component
Ferritin	iron transport protein
Fibrinogen	clotting formation of fibrin matrix for repair
Fibronectin	fibrin clot formation
Haptoglobin	hemoglobin scavenger
Heme oxygenase	heme degradation
LPS binding protein	Macrophage cell activation
Mannose-binding protein	serum lectin
Plasminogen	proteolytic activation of complement, clotting, fibrinolysis
Plasminogen activator inhibitor-1	protease inhibitor
Prothrombin	clotting formation of fibrin matrix for repair
Serum amyloid A	cholesterol and HDL scavenger
Serum amyloid-P	formation of IgG immune complexes

CRP bind with highest affinity to phosphocholine residues in a calcium dependent manner, it also binds to variety of other autologous and extrinsic ligands, histone proteins, small nuclear ribonucleoprotein particles and apoptotic cells, glycans ,somatic components of bacteria, fungi and parasites. CRP activates the classical complement system when bound to one of its ligands and can also bind to phagocytic cells, initiating the elimination of target cells (Cermak J, et.al. 1993).

SAA is an apolipoprotein of high density lipoprotein, and influence cholesterol transport. It has different isoforms and differs from the inflammatory isotypes (SAA1, SAA2, and SAA3). In tissues it attracts inflammatory cells and inhibits the respiratory burst of leukocytes and modulates the immune response. Human SAA4 (an isotype) is normally present in serum. Prolonged or repeated inflammatory conditions associated with high serum levels of SAA can cause amyloidosis. From the enzymatic degradation of SAA protein, amorphous amyloid fibrils are formed (Malle E, et.al. 1996).

Ceruloplasmin {Cp} is an alpha2-globulin that contains approximately 95 percent of the total serum copper, giving it a blue color. Its primary physiological role involves plasma reduction and oxidation reactions. Cp is vitally important in regulating the ionic state of iron in particular, oxidizing Fe^{2+} to Fe^{3+} and thus permitting incorporation of the iron into transferrin without the formation of toxic iron products (Giurgea N, et.al. 2005). Cp also has an important role as a ferroxidase and superoxide scavenger.

ACUTE PHASE PROTEINS AND PATHOLOGY

Earlier researches suggested a prognostic association between increased APP production and some diseases. Laboratory studies have demonstrated that inflammation plays a patho -physiological role in atherogenesis and may promote the development of atherosclerotic plaques in coronary arteries (Haverkate F, et.al. 1997). CRP mediated complement activation has a key role in some forms of tissue alterations such as cardiac infarction and its elevated serum levels are associated with cardiovascular risk factors and obesity (Koenig, et. al. 2006). Levels of SAA are elevated in synovial fluid during inflammatory joint disease which may be used for diagnostic and prognostic purposes as well as for monitoring effect of treatment. Mastitis causes increases in SAA levels in milk (Scheinberg IH, et.al. 1952). Although low Cp levels are seen in malnutrition, malabsorption, severe liver disease, nephrotic syndrome and Menkes syndrome, their levels in infectious diseases has not been correlated so far. CRP, SAA, Hp and some other APPs are useful for assessing health in human patients (Banka CL, et.al. 1995).

CONCLUSION

Acute phase response is generated during inflammation. In the response, serum levels of various acute phase proteins change. The positive acute phase protein levels may increase up to 1000 folds while that of negative APPs decline from their respective normal values. The major inducers of acute phase proteins are IL1, IL6, and TNF. Although the defensive roles of many acute phase proteins are yet to be traced out, some well known APPs have the disease prognosis importance and even are very helpful in diagnosis when correlated with the clinical symptoms of the patients. In the case of *E. coli* lung infection, loss of either IL-6 or early-response cytokine signaling significantly reduces acute pulmonary inflammation, despite relatively normal expression of inflammatory cells, chemoattractants and other proinflammatory mediators. Acute phase proteins are also being evaluated for their utility in postmortem meat and poultry inspection as part of the Hazard Analysis Critical Control Point {HACCP} program.

APR during pneumonia, by two different pathogens, E. coli and S. pneumoniae, elicit very different responses in the lungs, with different requirements for host defense mediators and distinct mechanisms of virulence and pathophysiology. Acute-phase changes reflect the presence and intensity of inflammation, and have long been used as a clinical guide to diagnosis and management. The purpose of this review is to gain attention to explore research for the better understanding of the role of APPs in infectious diseases.

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REFRENCES

Abbas, Lichtman, Pillai (2007) Cellular and molecular immunology, 6th edition. India: Saunders Elsevier.

Alvarez A, Nicolas MC, Nabah YNA, Mata M, Issekutz AC, Panes J, Lobb RR, Sanz MJ (2004) Direct evidence of leukocyte adhesion in arterioles by angiotensin II. Blood 104: 402-408.

Arnett HA, Viney JL (2010) Gatekeepers of intestinal inflammation. Inflamm Res 59. 1-14.

Banka CL, Yuan T, de Beer MC, Kindy M, Curtiss LK, de Beer FC (1995) Serum amyloid A (SAA): influence on HDL-mediated cellular cholesterol efflux. J Lipid Res 36: 1058-1065.

Baumann H, Gauldie J (1994) The acute phase response. Immunol Today 15: 74-80.

Bernardini G, Hedrick J, Sozzani S, Luini W, Spinetti G, Weiss M, Menon S, Zlotnik A, Mantovani A, Santoni A, Napolitano M (1998) Identification of the CC chemokines TARC and macrophage inflammatory protein-1 beta as novel functional ligands for the CCR8 receptor. Eur J Immunol 28: 582.

Birner U, Issekutz TB, Walter U, Issekutz AC (2000) The role of {alpha} 4 and LFA-1 integrins in selectin-independent monocyte and neutrophil migration to joints of rats with adjuvant arthritis. Int. Immunol 12: 141–150.

Ceciliani F, Giordano A, Spagnolo V (2002) The systemic reaction during inflammation: The acute phase proteins 9. 211-223.

Cermak J, Key NS, Bach RR, Balla J, Jacob HS, Vercellotti GM (1993) C-reactive protein induces human peripheral blood monocytes to synthesize tissue factor. Blood 82: 513-520

Ceron JJ, Eckersall PD, Martinez-Subiela S (2005) Acute phase proteins in dogs and cats: current knowledge and future perspectives. Vet Clin Path 34: 85-99.

Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332: 1351-1362.

Dinarello CA (1997) Cytokines as endogenous pyrogens. In Mackowiak PA editors. Fever: basic mechanisms and management. 2nd edition, Philadelphia: Lippincott-Raven. 87-116.

Dings Z, Xiong K, Issekutz TB (2001) Chemokines stimulate human T lymphocyte transendothelial migration to utilize VLA-4 in addition to LFA-1 J. Leukoc. Biol. 69 : 458–466.

Dogra N, Warburton C, McMaster WR (2007) Leishmania major abrogates IFN-{gamma} induced gene expression in human macrophages on a global scale. Infect Immun 75: 3506-15.

Finckh A (2009) Early inflammatory arthritis versus rheumatoid arthritis. Current opinion in rheumatology 21: 118-123.

Firrell JC, Lipowsky HH (1989) Leukocyte Margination and Deformation in Mesenteric Venules of Rat. American Physiological Society 22: 1167-1674.

Gabay C, Kushner I (1999) Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 340: 448–454.

Gameel AA, Tartour G (1974) Hematological and Plasma-Protein Changes in Sheep Experimentally Infected with Corynebacterium- pseudotuberculosis. J Comp Path 84: 477-484.

Giurgea N, Constantinescu MI, Stanciu R (2005) Ceruloplasmin - acute-phase reactant or endogenous antioxidant? The case of cardiovascular disease. Med. Sci. Monit. 11: 48–51.

Gonda TA, Tu S, Wang TC (2009) Chronic inflammation, the tumor micro-environment and carcinogenesis. Cell cycle 8:2005-2013.
Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB (1997) Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 349: 462-466.
Janeway (2005). Immunobiology 6th edition. New York: Taylor and Francis Group; Garland Science.
Johnston B,Walter U M, Issekutz A C, Issekutz T B, Anderson D C, Kubes P (1997) Differential roles of selectins and the alpha4-integrin in acute, sub acute, and chronic leukocyte recruitment in vivo. J Immunol 159: 4514-4523.
Jones MR, Quinton LJ, Simms BT, Lupa MM., Kogan MS, Mizgerd JP (2006) Roles of interleukin-6 in activation of STAT proteins and recruitment of neutrophils during Escherichia coli pneumonia. J Infect Dis 193: 360–369.
Kerfoot SM, Kubes P (2005) Local coordination verses systemic disregulation: complexities in leukocyte recruitment revealed by local and systemic activation of TLR4 in vivo. J. Leukoc. Biol. 77: 862–867.
Kindt, Goldsby, Osborne (2004). Kuby Immunology, 6th edition. Newyork: W.H Freemann and Company.
Koenig, Wolfgang (2006). C-reactive protein – a critical cardiovascular risk marker. Crit Care 12:412–419.

Kopf M, Baumann H, Freer G, Freudenberg M, Lamers M, Kishimoto T, Zinkernagel R, Bluethmann H, Kohler G (1994) Impaired immune and acute-phase responses in interleukin-6-deficient mice. Nature 368: 339–342.

Kravitz MS, Pitashny M, Shoenfeld Y (2005) Protective molecules— C-reactive protein (CRP), serum amyloid P (SAP), pentraxin3 (PTX3), mannose- binding lectin (MBL), and apolipoprotein A1 (Apo A1), and their autoantibodies: prevalence and clinical significance in autoimmunity. J Clin Immunol 25: 582–591.
Kubes P, Heit B, Marle GV, Johnston JB, Knight D, Khan A, Power C (2003) In Vivo Impairment of Neutrophil Recruitment during Lentivirus Infection. J Immunol 171: 4801-4808.
Lundberg AM, Hansson GK (2010). Innate immune signals in atherosclerosis. Clin Immunol 134. 5-24.
Malle E, De Beer FC (1996) Human serum amyloid A (SAA) protein: a prominent acute-phase reactant for clinical practice. Eur J Clin Invest 26:427-435.
Male D, Brostoff J, Roitt B D (2006) Immunology, 7th edition. Canada: Mosby Elsevier.
M Sherwood, Woolvertin C J (2008) Microbiology 7th edition. Boston: Mc Graw-Hill.
Moldawer LL, Copeland EM III (1997) Proinflammatory cytokines, nutritional support, and the cachexia syndrome: interactions and therapeutic options. Cancer 79: 1828-1839.
Moshage H (1997) Cytokines and the hepatic acute phase response. Journal of Pathology 181: 257-266.
Mulligan MS, Lentsch AB, Ward PA (1998) In Vivo Recruitment of Neutrophils: Consistent Requirements for L-Arginine and Variable Requirements for Complement and Adhesion Molecules. Inflammation 22: 327-339.
Nairn R, Helbert M (2002) Immunology. London: Elsevier Mosby.
Paul W.E (2008) Fundamental Immunology 6th edition. Philadelphia: Lippincott Williams and wilkins.
Petersen HH, Nielsen JP, Heegaard PMH (2004) Application of acute phase protein measurements in veterinary clinical chemistry. Vet Res 35: 163-187.
Quinton L J, Jones M R, Robson B E, Mizgerd J P (2009) Mechaninsm of hepatic acute phase response during bacterial Pneumonia. Infec Imm 77: 2417-2426.
Rich R. R (2008) Clinical Immunology, 3rd edition. China: Mosby Elsevier.
Rollins BJ (1997) Chemokines. Blood 90: 909-928.
Sarraf P, Frederich RC, Turner EM (1997) Multiple cytokines and acute inflammation raise mouse leptin levels: potential role in inflammatory anorexia. J Exp Med185: 171-175.

Scheinberg IH, Gitlin D (October 1952) Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). Science 116: 484–5.
Sciacca FL, Sturzl M, Bussolino F, Sironi M, Brandstetter H, Zietz C, Zhou D, Matteucci C, Peri G, Sozzani S, Benelli R, Arese M, Albini A, Colotta F, Mantovani A (1994) Expression of adhesion molecules, platelet activating factor, and chemokines by Kaposi's sarcoma cells. J Immunol. 153: 4816.
Wolf M, Bohm S, Brand M, Kreymann G (1996) Proinflammatory cytokines interleukin 1 beta and tumor necrosis factor αinhibit growth hormone stimulation of insulin-like growth factor I synthesis and growth hormone receptor mRNA levels in cultured rat liver cells. Eur J Endocrinol 135: 729-73.
Zheng H, Fletcher D, Kozak W (1995) Resistance to fever induction and impaired acute-phase response in interleukin-1 ß-deficient mice. Immunity 3: 9-19.

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