Acute-phase Proteins

Secondary article

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Acute-phase proteins form part of the systemic acute-phase response which accompanies inflammation. Their synthesis by hepatocytes is primarily regulated by inflammation-associated cytokines and their presumed functions are highly variable and diverse.

Article Contents

Introduction

The discovery of large amounts of C-reactive protein (CRP) in the serum of patients during the acute phase of pneumococcal pneumonia in 1930 focused interest on the plasma protein changes that accompany inflammatory states. CRP and other plasma proteins whose concentrations rose significantly under such circumstances were accordingly referred to as acute-phase proteins (APP). The subsequent realization that concentrations of some other plasma proteins decrease led to their designation as negative APPs, while the earlier recognized APPs are often referred to as positive APPs. It is now appreciated that APP changes are only part of a large number of systemic manifestations, distant from inflammatory sites, that replace normal homeostasis during inflammatory states (**Figure 1**). APP changes are not limited to acute illness, but persist during a great variety of chronic inflammatory states as well, constituting a semantically paradoxical chronic acute-phase response.

A change of approximately 25% in plasma concentration has been suggested as the definition of an APP (Morley and Kushner, 1982). Changes in plasma protein concentrations largely result from alterations in synthesis by hepatocytes in response to circulating inflammation-associated cytokines. While other cells, including macrophages, fibroblasts, epithelial cells and adipocytes can also produce APPs, it is unlikely that synthesis at these sites contributes significantly to plasma concentrations.

In humans, many different stimuli can induce the acute-phase response, including bacterial (and to a lesser extent viral) infection, trauma, surgical procedures, burn injury, tissue infarction, various immunologically and crystal-mediated inflammatory disorders, advanced malignancies, strenuous exercises, childbirth and heatstroke.

Clinical Relevance

Estimation of changes in APP levels can be useful to clinicians, since they generally reflect the presence and intensity of an inflammatory process, although the acute-phase response is nonspecific. Thus, estimation of plasma levels of APPs can be useful as a diagnostic aid, helping to differentiate inflammatory from noninflammatory conditions. Levels of APPs can also be important for management of patients, since they generally reflect the extent and intensity of the inflammatory process and the response to, and need for, therapeutic interventions. Finally, in certain cases, initial or serial measurement of APPs can be of prognostic value.

Currently, the most widely used indicators of the acute-phase response are the erythrocyte sedimentation rate (ESR) and serum CRP concentrations. ESR measures the rate at which erythrocytes fall through plasma. This phenomenon largely depends on plasma concentrations of fibrinogen and certain other APPs. The ESR has the advantage of simplicity, familiarity and the abundant literature compiled about it since its introduction into

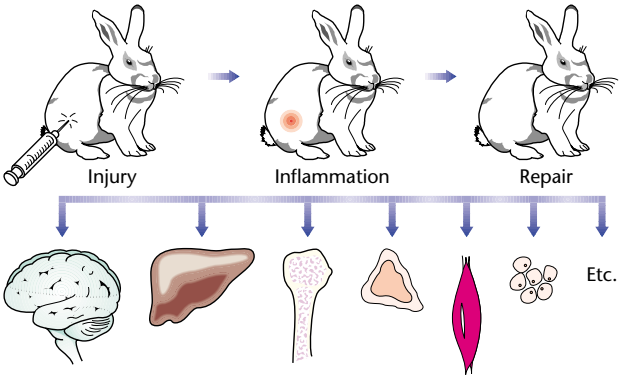

Figure 1 The inflammatory response may be accompanied by a number of systemic changes referred to collectively as the acute phase response. Some of the organs participating in the response include: brain, whose involvement is reflected by fever, anorexia, somnolence and increased synthesis of CRH and ACTH; liver, which synthesizes increased amounts of metallothionein and antioxidants and which reorchestrates its pattern of plasma protein synthesis; bone, in whose marrow erythropoiesis is suppressed and thrombocytosis induced, and in which loss of bone substance occurs; the adrenal gland, in which cortisol production is enhanced by both direct and indirect stimulation; muscle, in which decreased protein synthesis and proteolysis may occur; and fat cells, which participate in alterations in lipid metabolism. Redrawn with permission from Kushner I (1993) Regulation of the acute phase response by cytokines. In: Oppenheim J, Rossio J and Gearing A (eds) *Clinical Applications of Cytokines: Role in Pathogenesis, Diagnosis and Therapy*. New York: Oxford University Press.

clinical medicine about seven decades ago. However, ESR has the disadvantage of being merely an indirect method of assessing acute-phase changes. It is influenced by abnormal size, shape and number of erythrocytes, and by other plasma constituents such as monoclonal immunoglobulins, with results that are imprecise and sometimes misleading.

CRP determination has several advantages compared with ESR: (1) CRP levels directly reflect hepatic production and are not influenced by other blood constituents, nor by change in clearance or catabolism. (2) CRP blood levels have a rapid kinetic profile, with both rapid increase and decrease following the beginning and the resolution of the inflammatory process, respectively. (3) A broad range of variation has been observed for CRP, with accompanying clinical implications; thus, CRP concentrations over $100\,mg\,L^{-1}$ are associated with bacterial infection 80–85% of the time (Morley and Kushner, 1982). (4) Most laboratories easily and routinely measure CRP and an international standard is available. (5) ESR values steadily increase with age, while comparable changes are not seen for CRP. The publication of many studies during the last 15 years has increased familiarity with this test and has decreased one of the historic advantages of ESR.

Among other APPs, plasma levels of serum amyloid A (SAA) vary in parallel with those of CRP. They may constitute a more sensitive inflammatory marker than CRP in instances such as allograft rejection and benign infections (Malle and De Beer, 1996). However, quantitative assays for SAA are not widely available and SAA determination still remains a research tool. Determination of plasma levels of other APPs described below has the potential of also reflecting the acute-phase response. However, these do not offer several of the advantages afforded by CRP, which is only minimally detectable in health, rapidly changes in response to worsening or improvement of disease and manifests a great range of abnormal levels, with corresponding clinical implications.

Blood levels of CRP, determined in population studies of patients with a variety of inflammatory diseases, demonstrate good correlation with the extent and severity of the inflammatory process. However, in some conditions such as systemic lupus erythematosus, scleroderma, Sjögren disease and dermato/polymyositis, CRP (and SAA) concentrations remain normal or only slightly elevated despite the presence of significant inflammation and the presence of elevated ESR values (Pepys *et al.*, 1982). In contrast, patients with systemic lupus erythematosus are capable of mounting a significant CRP response during superimposed bacterial infections as well as in the presence of some clinical manifestations of their disease such as serositis and arthritis. These discrepancies between obvious signs of inflammation and the CRP response in some diseases indicate that the acute-phase response is not globally regulated and that different patterns of APPs may reflect the contribution of different cytokines or cytokine modulators in different diseases or their subsets.

Population studies have shown that the majority of healthy individuals have CRP levels of $2\,mg\,L^{-1}$ or less, but that substantial numbers of apparently healthy individuals have CRP concentrations as high as $10\,mg\,L^{-1}$. The latter observation, attributed to modest acute-phase stimulation secondary to minor inflammation or trivial injury, led to the conclusion that CRP values up to $10\,mg\,L^{-1}$ should be regarded as clinically insignificant. However, attention has recently turned to the possible clinical significance of CRP levels in this range. Levels of CRP below $10\,mg\,L^{-1}$, but significantly higher than in appropriate control populations, have been observed in patients with conditions generally not considered as inflammatory, including osteoarthritis and coronary disease. Elevated CRP levels have been reported in patients with osteoarthritis and radiological signs of progressive joint damage. Similarly, elevated CRP levels have been found predictive of coronary events in patients with stable angina and in a control population, suggesting that low-grade inflammation may be present in osteoarthritis joints and in coronary arteries, or alternatively that CRP itself may have pro-inflammatory or pro-thrombotic effects. Although these findings may provide interesting insight into the pathogenesis of these different conditions, they have no useful clinical value since the mildly elevated CRP levels observed in these studies fall well within the range found in many healthy individuals.

Positive and Negative Acute-phase Proteins

As indicated above, circulating levels of plasma proteins can increase (positive APPs) or decrease (negative APPs) during the acute-phase response. Changes in different proteins occur at different rates and to different degrees. Rapidity of change of plasma APP concentrations generally parallels magnitude of change. Ceruloplasmin and the complement components C3 and C4 exhibit relatively modest acute-phase behaviour (typically about 50% increase). Concentrations of haptoglobin, α_1-acid glycoprotein, α-1 protease inhibitor, α_1-antichymotrypsin and fibrinogen ordinarily increase about 2–5-fold. The two major APPs in humans, CRP and SAA, are normally present in only trace amounts, but may exhibit dramatic increase (1000-fold or more) in individuals with severe infections. In contrast, plasma concentrations of negative APPs such as albumin, transferrin, transthyretin, α-2 HS glycoprotein, α-fetoprotein, T4-binding protein globulin, insulin-like growth factor I and coagulation factor XII, typically decrease during the acute-phase response.

APPs can be classified into different categories based on their functions. Examples of these categories include the

following. (1) Members of the complement system: complement factors C3, C4, C9, factor B, C-1 inhibitor, C4b-binding protein and mannose-binding lectin. (2) Members of the coagulation and fibrinolytic systems: plasminogen, tissue plasminogen activator, urokinase, protein S, vitronectin and plasminogen activator inhibitor 1. (3) Antiproteases: α-1 protease inhibitor, α_1-antichymotrypsin, pancreatic secretory trypsin inhibitor and inter-α-trypsin inhibitors. (4) Transport proteins: ceruloplasmin, haptoglobin and hemopexin. Some positive APPs can play a role as modulators of the inflammatory response. These include secreted phospholipase A_2, lipopolysaccharide (LPS)-binding protein, and interleukin 1 receptor antagonist (IL-1Ra) (Gabay *et al*., 1997). Finally, some APPs cannot be easily classified functionally because their function is still not completely clarified or cannot be included in one typical category. These include CRP, SAA, α_1-acid glycoprotein, fibronectin, angiotensinogen and ferritin.

Some acute-phase protein changes are misinterpreted clinically. Thus, elevated serum ferritin levels occurring as a result of inflammation may be misinterpreted as indicating high iron body stores. Similarly, decreased serum albumin levels, commonly occurring as a consequence of inflammatory states, have been misinterpreted as reflecting malnutrition.

There are significant differences between species in APP expression. A notable example is CRP, which, following inflammatory stimulus, is strongly increased in humans and rabbits, but only minimally induced in mice. Another example is SAA, which is a major APP in virtually all mammals but whose gene product is not expressed in the rat, even though transcription of the gene is sharply induced. Serum amyloid protein (SAP), a member of the same pentraxin family as CRP, is a major APP in mice but not in humans. α_2-Macroglobulin is a major APP in the rat but not in humans, and haptoglobin, only a modest APP in humans, behaves as a major acute-phase reactant in ruminants.

The Acute-phase Response

Most of the data on APP gene regulation are derived from studies in hepatoma cell lines, which may not accurately reflect the changes taking place in normal hepatocytes. Nevertheless, they cast considerable light on what occurs *in vivo*. A number of inflammation-associated cytokines play central roles in regulation of the APP response, including interleukin 6 (IL-6), IL-1, tumour necrosis factor α (TNFα), interferon γ, transforming growth factor β (TGFβ), and, recently described, IL-8. Some of these are commonly classified as pro-inflammatory, while others are regarded as anti-inflammatory. These cytokines can be produced by many different cells, including monocytes, macrophages, neutrophils, lymphocytes, fibroblasts, endothelial cells and epithelial cells. However, it is clear that monocytes and macrophages at the site of inflammation constitute the major source of these cytokines, particularly IL-6, IL-1β, and TNFα.

These cytokines operate both as a cascade and as a network (**Figure 2**). Some cytokines can up- or down-regulate production of other cytokines and cytokine receptors. For example, TNFα may be the main inducer of IL-1 in rheumatoid arthritis and IL-1β is required for IL-6 induction following turpentine injection in mice. In addition, cytokines are components of a large and complex signalling network. The effect of cytokines on hepatocytes and other cells can be influenced by soluble cytokine receptors, receptor antagonists, and autoantibodies to cytokines. Combinations of these different mediators can have additive, synergistic or inhibitory effects. It is unlikely that cells are often exposed to only a single cytokine and likely that it is cytokine combinations and sequences that convey biologically relevant information.

IL-6 is considered to be the major inducer of APP gene expression, since it, either alone or by enhancing the effects of other cytokines, induces virtually all APPs (Gauldie *et al*., 1987). Effects comparable to those induced by IL-6 have been observed in cell culture with other members of the IL-6 family, including IL-11, oncostatin M, leukaemia inhibitory factor, ciliary neurotrophic growth factor and cardiotrophin-1, all of which share the cell surface signal-transducing subunit gp130 with IL-6. However, the role of these IL-6-related cytokines in induction of APPs *in vivo* is still unclear. In addition, a series of observations in mice rendered incapable of expressing IL-1β or IL-6 (knockout

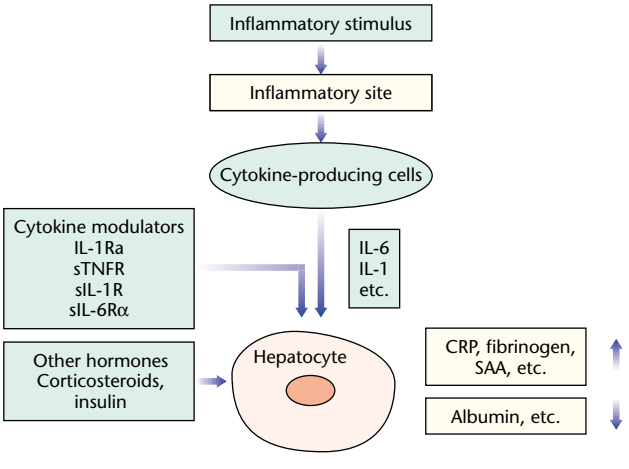

Figure 2 The acute-phase protein response is regulated both directly and indirectly by a complex network of intercellular signalling molecules involving cytokines, cytokine modulators and other hormones. Inflammation-associated cytokines, produced by cells at the inflammatory site and probably by distant cells as well, induce changes in production of acute-phase proteins by hepatocytes.

mice) indicate that the role of IL-6 depends on the nature of the inflammatory stimulus (Fattori *et al*., 1994). APP production was largely inhibited in IL-6 knockout mice following turpentine injection, whereas a virtually intact APP response was observed following bacterial endotoxin (LPS) injection. Similar findings were observed in IL-1β knockout mice, presumably because IL-1β is required to induce IL-6 following turpentine injection.

In addition to IL-6, IL-1 and TNFα both affect the production of a large subset of APPs. Shortly after the important role of IL-6 was appreciated, it was proposed that the APP be divided according to their response to IL-1. However, this classification is not completely satisfactory, because different results are obtained in different model systems and because newly obtained information on the effects of other cytokines and other inflammatory mediators on the regulation of APP is not consistent with such a classification.

TGFβ induces the production of several antiproteases, urokinase and plasminogen activator inhibitor 1, and decrease the synthesis of some negative APPs. Interferon γ is a notable inducer of complement components. IL-8 has been reported recently to induce the production of a number of APPs. Finally, induction of APP is not limited to cytokines. Other inflammatory mediators such C5a, an important member of the complement cascade, can also induce the production of two antiproteases by a hepatoma cell line.

The effects of cytokines can be modulated by other cytokines, soluble receptors, hormones and circulating antibodies to cytokines. IL-4, a cytokine mainly produced by CD4 + T lymphocyte and involved in the T_H2 response, is able to modulate the production of APPs by hepatocytes. IL-1Ra can block the effects of IL-1 on production of APP. Soluble IL-6 receptor α (sIL-6Rα) enhances the effects of its ligand, whereas soluble IL-1 and TNF receptors (sIL-1R and sTNFR) are inhibitory. Autoantibodies to cytokines can also have either enhancing or decreasing effects. Recent findings indicate that hepatocytes can play an additional active role in the acute-phase response by producing cytokines such as IL-1Ra and granulocyte colony-stimulating factor (G-CSF) and by releasing soluble IL-6 receptors alpha into the circulation. Taken together, all these observations indicate that regulation of APP production results from complex interactions between multiple mediators, including cytokines, soluble receptors, other cytokine modulators and hormones.

In most instances studied so far, with the exception of apoferritin, APP gene expression is regulated at the level of transcription. Transcriptional activation is mediated by a number of transcription factors, including nuclear factor-κB (NF-κB), CCAAT/enhancer-binding protein (C/EBP), and signal transducer and activator of transcription (STAT) family members. Interaction between these different transcription factors is usually necessary to fully stimulate the production of APP. NF-κB acts synergistically with C/EBP family members through functional and physical interactions to mediate the effects of IL-1 and IL-6 on APP gene expression (Betts *et al*., 1993) and it is likely that interactions between C/EBP and STAT3 are needed to achieve optimal response of some APP genes to IL-6.

In addition to transcriptional regulation, posttranscriptional and posttranslational mechanisms also participate in the APP response. Apoferritin is translationally regulated by IL-1 in a hepatoma cell line and by IL-4 and IL-13 in macrophages. Secretion of CRP is upregulated during the acute-phase response by mechanisms distinct from those controlling its production. Several changes of APP glycosylation occur during the acute response and are mediated by inflammation-associated cytokines independently of their effects on APP production. Best studied are changes in binding of some APP to concanavalin A, which reflect differences in the number of branches in the antennary structures of the glycan side-chains of these proteins. Concanavalin A binding of acute-phase glycoproteins is increased in several acute inflammatory states, but decreased in a number of chronic diseases, suggesting that different extracellular signals regulate the glycosylation of these APPs in acute and chronic diseases.

Resolution of the Acute-phase Response

While most studies have concentrated on examining the initiation of the acute-phase response, little is known of its resolution. The acute-phase response subsides when the initial stimulus is not present, e.g. when an infectious agent is eliminated. While it is possible that an active mechanism may be required to downregulate overexpressed APP genes, it is at least equally likely that such downregulation could result from cessation of continued stimulation. Due to their short circulating half-lives, blood levels of cytokines and other mediators decrease rapidly in the absence of further stimulation and persistent APP production would depend on the half-life of its mRNA. However, it is conceivable that several cytokines or cytokine modulators produced during the inflammatory response, including IL-1Ra, IL-10, IL-1 and TNF-soluble receptors, could play an active role in the resolution of the acute-phase response.

Biological Significance

The biological significance of the acute-phase response can best be understood in the context of the large number of homeostatic mechanisms that maintain the internal environment during good health (Claude Bernard's 'milieu intérieur'), despite an everchanging environment. Examples are the mechanisms which maintain concentrations of the blood cells, solutes and of temperature in a relatively

narrow range. During inflammatory states, however, new set points – which represent the acute-phase response – replace many of these homeostatic mechanisms, presumably because they contribute to defensive or adaptive capabilities. In addition to alterations in APP production by the liver, many other acute-phase phenomena take place during inflammatory states. The assumption that the plasma protein acute-phase response is beneficial is largely based on the known functional capabilities of many of the acute-phase proteins and logical speculation as to how these many serve useful purposes in inflammation, healing or adaptation to infection or injury.

Inflammation is a complex, highly orchestrated process. It involves many cell types and molecules, some of which initiate, amplify, or sustain the process, some of which attenuate tissue injury by modulating it, and some of which cause it to resolve. A number of APPs have the potential to influence one or another stages of the inflammatory response. CRP, a component of the innate immune system, has been presumed to play a significant role in the clearance of infectious agents, as well as damaged cells, through its ability to bind phosphocholine. CRP can activate the classical complement pathway when bound to one of its ligands and can also bind to phagocytic cells, suggesting that it can initiate elimination of targeted cells or infectious organisms by interacting with both humoral and cellular immunity.

Moreover, CRP can participate in the inflammatory response by inducing production of inflammatory cytokines (Ballou and Lozanski, 1992) and tissue factor. However, recent studies, particularly studies of transgenic mice overexpressing CRP, indicate that CRP can also display anti-inflammatory effects (Xia and Samols, 1997). Such effects may be at least partly explained by the ability of CRP to prevent neutrophil adhesion to endothelial cells by decreasing surface expression of L-selectin (Zouki *et al.*, 1997), to inhibit superoxide anion generation by neutrophils and to induce synthesis of IL-1Ra by mononuclear cells.

SAA proteins comprise a family of acute-phase apolipoproteins that are rapidly associated with high-density lipoprotein (HDL) during inflammation and have the potential to influence cholesterol metabolism during inflammatory states. As with CRP, a single function for SAA is not readily apparent. SAA has been reported to induce adhesion and chemotaxis of phagocytic cells and lymphocytes and may contribute to the inflammation seen in atherosclerotic coronary arteries by increasing low-density lipoprotein oxidation (Malle and De Beer, 1996).

The classic complement components, many of which are APPs, play central pro-inflammatory roles in innate immunity. When activated, they participate in opsonization of infectious agents and damaged cells, in attraction of phagocytes and in plasma protein exudation at sites of inflammation. Pro-inflammatory functions are also implied by the findings that α-1 acid glycoprotein increases tissue factor expression and TNFα secretion by monocytes and that transthyretin, a negative APP, inhibits IL-1 production by monocytes and endothelial cells.

In contrast, many APP may play modulatory or anti-inflammatory roles. Haptoglobin and hemopexin, both antioxidants, are protective against reactive oxygen species. The antiproteases α-1 protease inhibitor and α_1-antichymotrypsin antagonize the activity of proteolytic enzymes produced by phagocytic cells. α_1-Antichymotrypsin also suppresses superoxide anion generation. α-1 Acid glycoprotein is reported to modulate neutrophil function and to protect against TNFα-induced liver failure. C-1 inhibitor modulates activation of the complement cascade and vitronectin can inhibit complement-mediated cell lysis.

In addition to changes in plasma proteins, a very large number of clinically significant behavioural, physiologic, biochemical and nutritional changes, affecting many organ systems, occur during the acute-phase response. All of these phenomena investigated thus far have been found to be induced by inflammation-associated cytokines. Fever is representative of the neuroendocrine changes that take place during inflammatory states. Other neuroendocrine changes include somnolence and anorexia, and increased secretion of corticotrophin-releasing hormone, adrenocorticotrophic hormone (ACTH), cortisol and arginine vasopressin. In addition, increased serum levels of glucagon and insulin are seen, as well as decreased insulin-like growth factor 1 production. Finally, the sick euthyroid syndrome (low thyroid-stimulating hormone (TSH), triiodothyronine (T_3) and tetraiodothyronine (T_4)) is seen, as is increased secretion of adrenal catecholamines.

Haematopoietic changes include the anaemia of chronic disease, leucocytosis and thrombocytosis. Metabolic changes include loss of muscle with negative nitrogen balance, decreased gluconeogenesis, increased leptin production, osteoporosis and cachexia. Many changes in lipid metabolism occur, including increased hepatic lipogenesis, increased lipolysis in adipose tissue, decreased lipoprotein lipase activity in muscle and adipose tissue, increased plasma levels of triglycerides and very low density lipoprotein (VLDL) and decreased plasma levels of cholesterol high- and low-density lipoproteins (HDL and LDL). Intrahepatic changes include increased synthesis of metallothionein, inducible nitric oxide synthase, a haem oxygenase, manganese superoxide dismutase, hepatocyte growth factor activator, glutathione and tissue inhibitor of metalloproteinase 1 (TIMP-1). In contrast, decreased catalase and phosphoenolpyruvate carboxykinase activity occur, as does altered expression of cytochrome P-450s. Changes in nonprotein plasma constituents include hypozincaemia, hypoferraemia and hypercupraemia, as well as increased glutathione and decreased retinol levels.

It is possible to speculate about the functional roles of these nonplasma protein acute-phase phenomena during inflammatory states. Increased hepatic production of the

antioxidant agents haem oxygenase and manganese superoxide dismutase may be required for the limitation of oxidant mediated-tissue injury. TIMP-1 inhibits the tissue destructive effects of metalloproteinases. Somnolence associated with various inflammatory states may reduce demands for energy during illness. Fever may stimulate chemotaxis, cytokine production, complement-mediated opsonization, and T-cell function. Hypercortisolaemia can modulate the immune and inflammatory responses and play a major role in the maintenance of haemodynamic stability in patients with severe illness. The catabolic effects of inflammation-associated cytokines, resulting in increased lipolysis in adipose tissue and in muscle breakdown, finally leading to cachexia, are clearly deleterious. Alterations of lipid metabolism during the acute-phase response may also be beneficial. Increased circulating levels of lipids are redistributed to cells at sites of inflammation, providing nutrients to cells involved in host defence and substrates for regeneration of damaged membranes. In addition, circulating lipoproteins have the ability to bind LPS and decrease its toxic effects, and may play a role in host defence against different microbial agents. Finally, recent findings indicate that leptin may aid in preventing LPS-induced liver injury and death.

As with all inflammation-associated phenomena, however, the acute-phase response is not uniformly beneficial, but bears risks with it. When extreme, cytokine-induced changes associated with the acute-phase response can be fatal, as in septic shock. In addition, persistence of the acute-phase response due to chronic stimulation, as in advanced malignancies and the acquired immune deficiency syndrome (AIDS), can induce metabolic disturbances that affect skeletal muscles, adipose tissue and bone mass, leading to cachexia, the extreme consequence of these metabolic changes. Finally, reactive amyloidosis has long been recognized as a deleterious consequence of chronically clevated SAA levels in some patients with chronic inflammatory conditions.

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