

Acute phase proteins

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.

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.

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 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 immunoglobulins, with results that are imprecise and sometimes misleading.

Advantages of determination of Acute phase proteins:

1. Acute Phase Proteins levels directly reflect hepatic production and are not influenced by other blood constituents, nor by change in clearance or catabolism.
2. Acute Phase Proteins 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 Acute Phase Proteins, with accompanying clinical implications; thus, Acute Phase Proteins serum concentrations over 100 mg per L are associated with bacterial infection 80–85% of the time.
4. Most laboratories easily and routinely measure Acute Phase Proteins and an international standard is available.
5. ESR values steadily increase with age, while comparable changes are not seen for Acute Phase Proteins. 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.

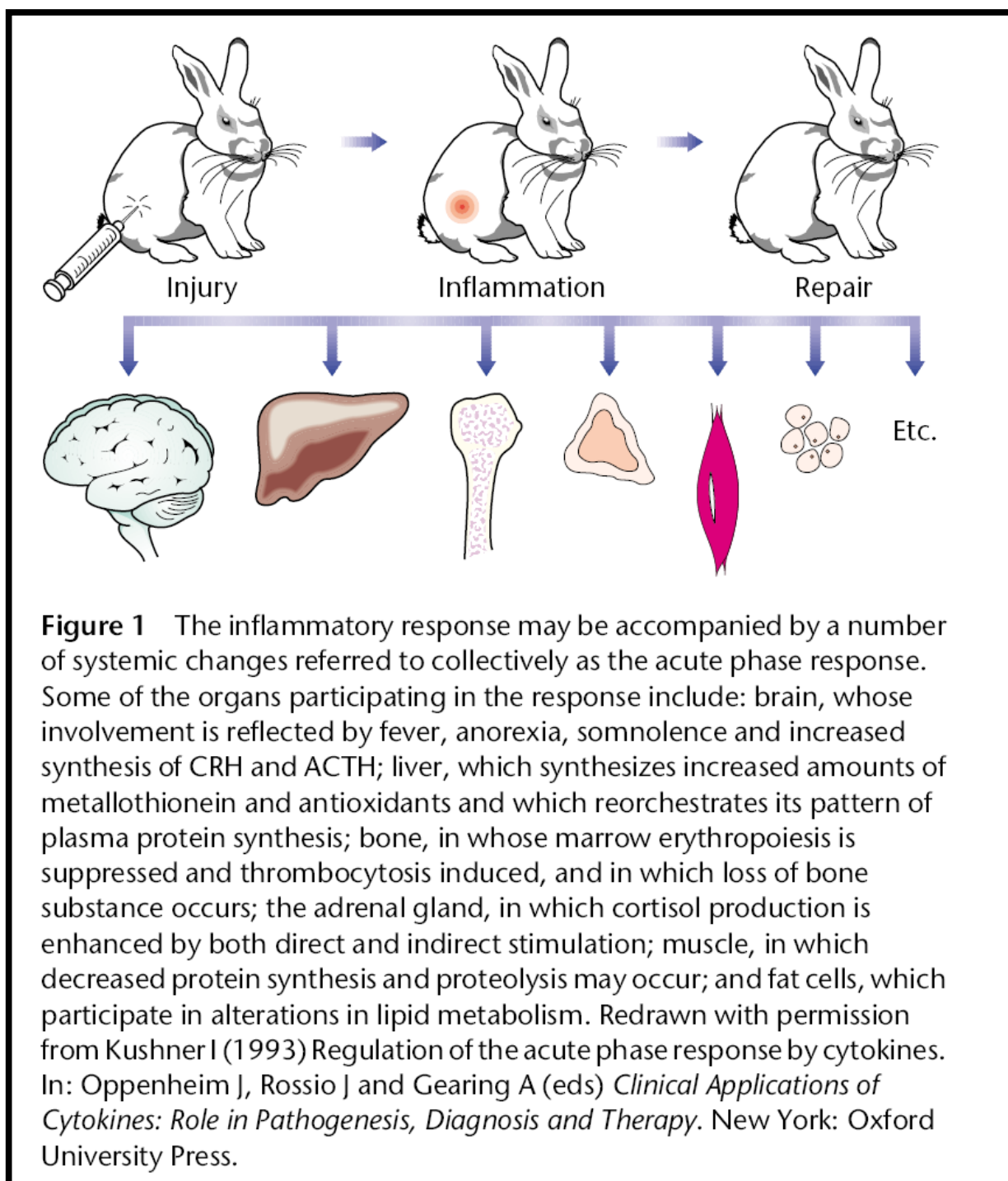
There are two types of acute phase proteins: positive and negative acute phase proteins. During the time of acute inflammation some acute phase protein concentration in serum decreases (negative acute phase proteins). For instance, albumin, transferrin, transthyretin, α -2 HS glycoprotein, α -fetoprotein, T4-binding protein globulin, insulin-like growth factor I and coagulation factor XII.

The serum concentration of acute phase proteins such as C-reactive protein (CRP) and serum amyloid A (SAA) increases during the acute inflammatory responses, are grouped under positive acute phase proteins.

Catogories of acute phase protein based on their normal functions

- 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
- 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 A2, lipopolysaccharide (LPS)-binding protein, and interleukin 1 receptor antagonist (IL-1Ra).

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.



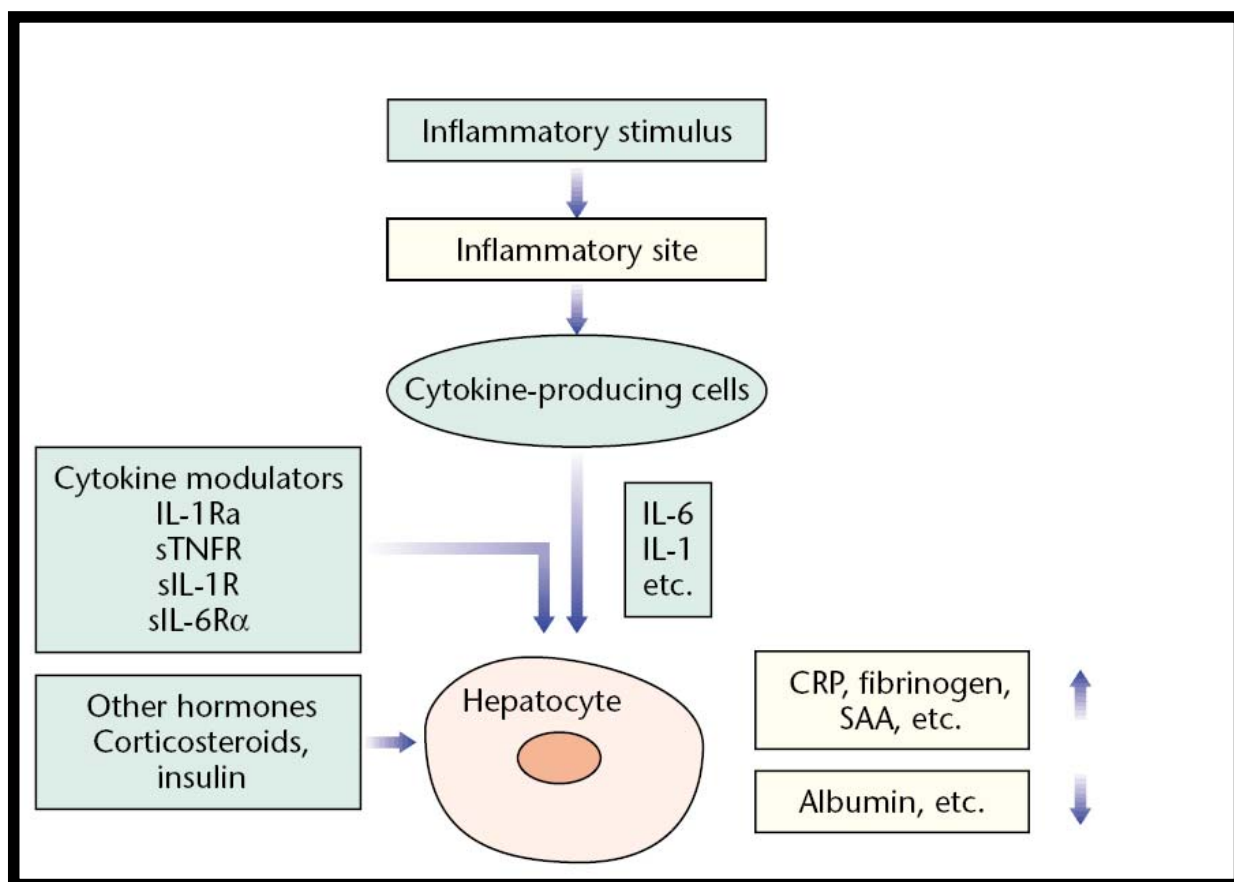


Figure 2: The acute-phase protein response is regulated both directly and indirectly by a complex network of intercellular signalling molecules involving cytokines, cytokine modulators and other hormones. Inflammation-associated cytokines, produced by cells at the inflammatory site and probably by distant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