

Lecture-11

Acute Phase Proteins (APPs)

Acute phase proteins (APPs) are defined as proteins that change their serum concentration by >25% in response to inflammatory cytokines (IL-1, IL-6, TNF α). The acute-phase response is considered part of the innate immune system, and APPs play a role in mediating such systemic effects as fever, leukocytosis, increased cortisol, decreased thyroxine, decreased serum iron, and many others. APPs can be categorized as positive (increasing serum concentration) or negative (decreasing serum concentration). Increased production of positive acute phase proteins is a sensitive indicator of inflammation which can occur prior to the development of an inflammatory leukogram.

Positive acute phase proteins

Positive acute-phase proteins increase in plasma concentration in response to inflammation (usually within 1-2 days). Positive APPs are further categorized as major, moderate or minor, depending on the degree of increase.

- **Major APP:** A protein with a low concentration in the serum of healthy animals (often <0.1 $\mu\text{g/dL}$), but upon stimulation will increase over 100 – 1000 fold, reaching a peak 24-48 hours after insult, then rapidly decreasing. An example of a major APP is Serum amyloid A.
- **Moderate APP:** Present in the blood of healthy animals, but increases 5 – 10 fold upon stimulation, peaking around 48 – 72 hours after insult, then decreases at a slower rate than major APPs.
- **Minor APP:** Increase only by 50 – 100% above resting levels and at a gradual rate.

The rapidity and magnitude of the increase in each acute phase protein varies depending on the species. The following table list the acute phase proteins that are major and moderate responders in various animal species.

Protein	Main function
Alpha-1-acid glycoprotein	Antiinflammatory and immunomodulatory agent: has antineutrophil and anticomplement activity and increases macrophage secretion of IL-1 receptor antagonist. Binds to lipophilic and acidic drugs.
C-reactive protein	On bacteria, it promotes the binding of complement, facilitating phagocytosis. Induction of cytokines Inhibition of chemotaxis and modulation of neutrophil function

	Neutralizes deleterious effects of histones
Ceruloplasmin	Copper transport (for wound healing, collagen formation and maturation) Antioxidant Reduces the number of neutrophils attaching to endothelium
Haptoglobin	Binds free hemoglobin (limiting Hb iron availability for bacterial growth) Natural antagonist for receptor-ligand activation of the immune system Inhibition of granulocyte chemotaxis and phagocytosis
Serum amyloid A	Chemotactic recruitment of inflammatory cells to sites of inflammation Induction of inflammatory cytokines (via surface receptors, including Toll like receptor) Inhibition of myeloperoxidase release and lymphocyte proliferation Involved in lipid metabolism and transport immunomodulatory (via the inflammasome)

Negative acute phase proteins

Negative acute phase proteins decrease in plasma concentration by greater than 25% in response to inflammation. This reduction can occur rapidly (within 24 hours) or may decrease gradually over a period of days. The two main negative acute phase proteins are albumin and transferrin. The mechanism by which their concentrations decrease is likely multifactorial, including decreased production by the liver in response to inflammatory cytokines, and possibly increased loss or increased proteolysis.

- **Albumin**

- Reduced production of albumin allows greater increase in the amount of amino acids available for positive APP production.
- Albumin concentration falls gradually and reduction in concentration is more noticeable in chronic inflammatory disease.

- **Transferrin**

- Usually measured to assess iron status.
- Ovotransferrin is the avian analog, but it is a positive acute phase protein.