



Pathophysiological Features of Cytokine Storm

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Inflammation involves a set of biologic mechanisms that evolved in multicellular organisms to contain invasive pathogens and resolve injuries by activating innate and adaptive immune responses. The immune system is expected to recognize foreign invaders, respond proportionally to the pathogen burden, and then return to homeostasis.

This response requires a balance between sufficient cytokine production to eliminate the pathogen and avoidance of a hyper inflammatory response in which an overabundance of cytokines causes clinically significant collateral damage. Cytokines play a key role in coordinating antimicrobial effector cells and providing regulatory signals that direct, amplify, and resolve the immune response. Cytokines have short half-lives, which normally prevents them from having effects outside lymphoid tissue and sites of inflammation. Although typically considered to be pathologic, sustained production of cytokines that leads to elevated circulating levels may be necessary to appropriately control some disseminated infections. At increased levels, cytokines can have systemic effects and cause collateral damage to vital organ systems.

Immune hyper activation in cytokine storm can occur as a result of inappropriate triggering or danger sensing, with a response initiated in the absence of a pathogen (e.g., in genetic disorders involving inappropriate inflammasome activation or idiopathic metacentric Cattleman's disease); an inappropriate or ineffective amplitude of response, involving excessive effector immune-cell activation (e.g., in cytokine storm due to CAR T-cell therapy), an overwhelming pathogen burden (e.g., in sepsis), or uncontrolled infections and prolonged immune

activation (e.g., in HLH associated with Epstein-Barr virus [EBV]); or failure to resolve the immune response and return to homeostasis (e.g., in primary HLH). In each of these states, there is a failure of negative feedback mechanisms that are meant to prevent hyper inflammation and the overproduction of inflammatory cytokines and soluble mediators.

The excessive cytokine production leads to hyper inflammation and multiorgan failure. Regulatory cell types, decoy receptors for proinflammatory cytokines such as IL1RA, and anti-inflammatory cytokines such as interleukin-10 are important for antagonizing inflammatory-cell populations and preventing immune hyperactivity.

Given the lack of a unifying definition for cytokine storm and disagreement about the distinction between cytokine storm and a physiologic inflammatory response, we propose the following three criteria for identifying cytokine storm: elevated circulating cytokine levels, acute systemic inflammatory symptoms, and either secondary organ dysfunction (often renal, hepatic, or pulmonary) due to inflammation beyond that which could be attributed to a normal response to a pathogen (if a pathogen is present), or any cytokine-driven organ dysfunction (if no pathogen is present). Improvement in outcomes with cytokine neutralization or anti-inflammatory agents further supports the pathologic role of excessive cytokines and the classification of a condition as a cytokine storm.

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