Agonists and antagonists an uncertain balance

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Within hours of the upregulation of proinflammatory cyto kines, endogenous cytokine antagonists enter the circulation (e.g. interleukin-1 receptor antagonist [IL-1Ra] and TNF- soluble receptors [TNF-sR-55 and 75]) and act to control the initial proinflammatory response and limit any systemic organ damage caused by it. A complex further series of adaptive c hanges includes the development of a counter-inflammatory response regulated by IL-4, -5, -9 and -13 and transforming growth factor beta (TGF β). Within inflamed tissue the duration and magnitude of acute inflammation as well as the return to homeostasis are influenced by a group of local mediators known as specialised pro-resolving mediators (SPMs), which include essential fatty acid-derived lipoxins, resolvins, protectins and maresins. These endogenous resolution agonists orchestrate the uptake and clearance of apoptotic polymorphonuclear neutrophils and microbial particles, reduce proinflammatory cytokines and lipid mediators as well as enhance the removal of cellular debris. Thus, both at the systemic level (endogenous cytokine antagonists – see earlier) α α and at the local tissue level, the body attempts to limit the inflammatory response, but further tissue damage, sepsis or other complications challenge these processes of resolution. As with the initial inflammatory response to tissue injury , it - appears that the degree of the secondary anti-inflammatory response varies between individuals, probably on a genetic basis. If the anti-inflammatory response dominates or is accentuated and prolonged in critical illness, it is characterised as a compensatory anti-inflammatory response syndrome (CARS), resulting in immunosuppression and an increased susceptibility to opportunistic (nosocomial) infection. Further sepsis, with its associated catabolism, results. CARS can be prolonged by ongoing critical illness as part of an ongoing vicious cycle of chronic critical illness (also known as Persis - tent Inflammation, Immunosuppression and Catabolism) syndrome. Thus both the initial inflammatory response to tissue injury and the secondary modulating r esponses can be seen to di ff ering degrees in di ff erent individuals or at di ff erent stages of the critical illness. Either circumstance can cause harm, and rapid restoration of homeostasis and preventing secondary inflammation or sepsis are key therapeutic principles that influence late outcomes as well as immediate ones.

BODY ME TA BOLISM ACTH GH ADIPOCYTE LIPO LY SIS HEPATIC ADRENALINE GLUCONEOGENESIS CO RT ISOL SKELE TA L MUSCLE PROTEIN DEGRAD AT ION HEPATIC ACUTE PHASE GLUCAGON PROTEIN SYNTHESIS IL-1 TNF PYREXIA IL-6 IL-8 Innate immune INSULIN HYPERMETABOLISM system IGF-1 TESTOSTERONE T3 , tumour necrosis factor alpha.

The metabolic response to surgery and injury: key characteristics /uni25CF α /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

Rapid onset driven by proin /f_l ammatory cytokines (e.g. IL-1, IL-6 and TNF) Broadly related to injury severity; most severe in sepsis, burns and major trauma Varies in severity between individuals (genetic) Causes catabolism, muscle breakdown, immunosuppression and organ dysfunction/failure Counterbalanced by antagonist response but the balance may be imperfect Prolonged by sepsis and other secondary insults Can become chronic Associated with most late deaths from injury or surgery in developed health systems

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