MEDIATORS OF THE METABOLIC RESPONSE TO INJURY Tiss

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Tissue injury is sensed in several ways. Tissue damage causes the release of cellular and other molecular fragments known as damage-associated molecular patterns (DAMPs) or alarmins. These DAMPs are sensed by pattern recognition receptors (PRRs), such as Toll-like receptors and NOD-like receptors (or nucleotide-binding leucine-rich repeat receptors) on cells of the innate immune system, which includes macrophages, neutrophils and dendritic cells. These cells are attracted and activated, triggering the formation of complex intracellular proteins known as inflammasomes. This results in the activation of caspases; these are enzymes that, in turn, activate key inflammatory cytokines including interleukin-1 (IL-1), IL-6 and many others. PRR activation also leads to release of tumour necrosis factor alpha (TNF), interferons, chemokines and other mediators. Thus begins a sterile systemic inflammatory cascade tha t leads to local inflammation and, when su ffi ciently severe, to a clinically detectable SIRS. Once activated by DAMPs, inflammasomes also contribute to cell death, tissue damage and immune suppression. DAMPs can activate inflammasome formation in endothelial cells and platelets, resulting in leaky capillaries and coagulopathy; these are changes that can result in the production of more DAMPs owing to local ischaemia from microcirculatory e ff ects. Local inflammation begins the process of tissue repair but SIRS, when uncontrolled or prolonged, becomes a risk factor for acute kidney injury , acute lung injury and coagulopathy , and hence for MODS and organ /uni00A0 failure. Within the injured brain, secondary brain injury can occur. DAMPs thought to be important in tissue trauma include heat shock proteins, high mobility group protein B1 (HMGB1), S100 proteins and fragments of nucleic acids . Commonly , DAMPs can activate several di ff erent receptors and pathways. This crossover, or redundancy as it is termed, is a characteristic of inflammation and has been one of the barriers to developing

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more, DAMPs can be self-perpetuated during the complicated course of a surgical critical illness, amplifying and prolonging the inflammatory process and related organ dysfunction. Trig ger s to further release of DAMPs include sepsis, haemorrhage, massive transfusion, acidosis, surgery , crush syndrome and ischaemia–reperfusion. Thus the secondary insults of delayed or ine ff ective trea tment of complications such as ongoing bleeding, ischaemia or sepsis will tend to maintain and amplify the inflammatory process and its resulting immune dysfunc tion. This can become a prolonged or self-perpetuating process (Table 1.1). /uni25CF /uni25CF /uni25CF /uni25CF /uni25CF

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TABLE 1.1 Some secondary triggers of the metabolic response to injury. Secondary triggers of in /f_l ammatory pathways in trauma and surgery Sepsis Haemorrhage Massive transfusion Acidosis Surgery Crush syndrome Ischaemia–reperfusion These events can amplify or prolong the catabolic phase, leading to organ failure or immune dysfunction.

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