The role of cytokines in enhanced recovery after surgery
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Abstract
Immune response and metabolic regulation are highly integrated and the proper function of each is dependent on the other. Cytokines are helpful towards the host response but potentially hazardous if uncontrollable or in excess. This is seen metabolically in the ‘diabetes of injury’ and the immunosuppression that follows major surgery or trauma. The brief review evaluates the role of cytokines in the metabolic response to surgery and the association with the new insight of enhanced recovery after surgery.

Keywords: Cytokines, Surgical stress, Metabolism, Insulin resistance, Enhanced recovery

A precise understanding of the cytokine response to surgical trauma may bring in interventions that would optimize the perioperative care of the patient, decrease morbidity and enhance recovery. The objectives of the article were firstly to evaluate the role of cytokines in the metabolic response to surgery and the association with the new insight of enhancing recovery after surgery and secondly to elucidate the relationship between the defects in neutrophil chemotaxis, phagocytosis and lysosomal enzyme contents identified during major surgery and the hyperglycaemia (diabetes) of injury.

Discussion
Immune response and metabolic regulation have been evolutionary conserved throughout species. They are highly integrated and the proper function of each is dependent on the other[1]. Cytokines are soluble molecular substances which include pro-inflammatory [interleukins (IL)-1, 2, 6, 8, TNFα, interferon (IFN)γ] and anti-inflammatory [IL-4, IL-10, prostaglandin E2 (PGE2), transforming growth factor beta (TGFβ)] produced by inflammatory cells following tissue injury (Fig. 1). They initiate a myriad of systemic effects (acute phase response) which includes the stimulation of the hypothalamic-pituitary axis that produces the stress hormones (adrenaline, glucagon, cortisol, growth hormone) and the acute phase proteins [complement (C3), c-reactive protein, fibrinogen, proteases] from the liver required for host defense (Fig. 2). Glucocorticoids and cytokines have a mutual relationship by potentiating the pro-inflammatory cytokines’ (IL-1, IL-6) in stimulating acute phase proteins synthesis in the liver, but inhibiting this role and their formation during excessive cytokine production (Fig. 3)[2,3]. Thus, cytokines are helpful toward the host response but potentially hazardous if uncontrollable or in excess as manifested in the systemic inflammatory response syndrome, septic shock and multiple organ failure[4]. There are selective immunosuppressive effects of the cytokines during surgical stress. Minor operations may stimulate the immune response but the predominant effect of major surgery is immune depression. The anti-inflammatory PGE2 inhibit the T helper1 cells that produce pro-inflammatory IL-2 and IFNγ and along with TGFβ stimulate the T helper 2 cells that produce the anti-inflammatory IL-4 and IL-10 cytokines[5]. The latter would also inhibit the T helper 1 subset that produces the pro-inflammatory cytokines. In addition, major resectional surgery down regulates major histocompatibility complex (MHC) class II

Figure 1. The neuro-endocrine axis: its activation and response[2] (with permission).
antigen on the monocytes and lymphocytes mediated by the anti-inflammatory interleukins (IL-4, IL-10) released by the T helper 2 cells[6,7]. The sequelae is the increased susceptibility to infection with intracellular pathogens (listeria, mycobacteria) due to defects in neutrophil chemotaxis, phagocytosis and lysosomal enzyme contents[8,9]. The key anti-inflammatory cytokines, PGE2 and TGFβ also control T helper 17 differentiation and thus interleukin-17 secretion that produces antimicrobial immunity at epithelial mucosa barrier against candida and staphylococcus[10]. The anti-inflammatory cytokine (IL-10) secretion is increased by monocytes after major surgery[1,8]. Although this may be a homeostatic response it would be interesting to know how much of these may be the effect of the hyperglycaemia (diabetes) of injury. This is corroborated by the observation that cytokine secretion by monocytes decrease following preoperative carbohydrate loading but increase in fasting[11,12]. This may explain why the preoperative anabolic setting of the patient through preoperative carbohydrate loading reduce metabolic stress and avoid these complications[13,14]. Attempting to adjust the MHC class II antigen level clinically by administering IFNγ may benefit those whose posttraumatic MHC II recovery was delayed or did not recover[7,14]. The first reported trial of treatment of trauma patients with recombinant human interferon provided supportive but not statistically significant data[15]. The multiplicity of factors that that influence the outcome of major surgery especially with regard to their initial level of receptor expression and the variability of the individual’s response will obviate the effect[15,16]. Despite the major impact of prophylactic antibiotics, the overall incidence of sepsis after elective surgery remains static (5%–10%)[2,21]. Though technical factors may play a part this residual sepsis may be reflection of perturbation of the immune system due to surgical stress[12,6,14]. However, many operations are accompanied by haemorrhage and the postoperative immune depression may also be caused in part by blood loss and cellular hypoxia rather than surgery[12,6,14]. Perioperative blood transfusion may also contribute to immunosuppression but the underlying mechanism is largely unknown[17].

The afferent stimuli from tissue injury produces neurohumoral responses in the form of cytokines and the stress hormones that rapidly stimulate a cardiovascular and metabolic response (Fig. 1). The metabolic response has a short ebb phase lasting 12–24 hours is the period of traumatic shock with general depression of enzymatic activity and oxygen consumption. As the blood volume is restored, more accelerated responses occur (the flow phase) in which the patient exhibits an increase in total energy requirement. This is followed by an anabolic (recovery) phase which is now influenced by the anabolic hormone, insulin. The flow phase has an initial catabolic phase from sympathetic nervous stimulation which is of most concern in the management of the operated or injured patient and lasts for 3–8 days. Muscle and fat stores are plundered by sympathetic nervous stimulation in order to maintain the adequate energy for the whole organism. There is increase in glucose production from glycogenolysis and gluconeogenesis with simultaneous increase in insulin secretion (Fig. 4). However, due to the antagonistic effects of the stress hormones there is decrease tissue sensitivity to insulin. The endoplasmic reticulum is the site for the metabolic signals that increase serine phosphorylation of the insulin receptor substrate-1 in an inositol requiring c-Jun N-terminal kinase dependent manner that blocks insulin action[18]. The insulin resistance developing after surgery gives rise to hyperglycaemia (diabetes of injury) similar to type 2 diabetes mellitus, rises with the magnitude of surgery and is potentiated by sepsis or postoperative complications[3,13]. In major colorectal operations, up to 90% of

| Pro-inflammatory | Anti-inflammatory | Acute reactants | phase |
|------------------|------------------|----------------|------|
| Tumour necrosis factor (TNFα) | Interleukin-10 (IL-10) | achromotropin | | |
| Interleukin-1 (IL-1) | Prostaglandin E2 (PGE2) | Complement C3 | | |
| Interleukin-2 (IL-2) | Transforming growth factor (TGFβ) | Caesalpin | | |
| Interleukin-8 (IL-8) | Interleukin-1 (IL-1) | Fibrinogen | | |
| Interleukin-12 (IL-12) | | | | |
| Interferon (IFNγ) | C-reactive (CRP) | protein | | |

**Figure 2.** Cytokines.

**Figure 3.** Mutual relationship of glucocorticoids and cytokines[2].

**Figure 4.** Metabolic response to surgery [ebb phase (<24 h)—metabolic response to acute stress; flow phase (weeks)—metabolic response after operation; anabolic phase—recovery after operation].
the preoperative insulin sensitivity can be lost after the operation\cite{12,13}. Hyperglycemia increases complications and mortality as it overloads the mitochondria blocking glycolysis and the Kreb cycle. Thus, enhancing further inflammatory response and cytokine production leading to the vicious cycle of insulin resistance and hyperglycemia (Fig. 5). The organs mainly affected are the kidney, endothelia of blood vessels and heart, blood cells and neural tissue as they have an uncontrolled inflow of glucose, with no storage capacity\cite{13}. By minimizing cytokine production through minimally invasive (laparoscopic) surgery, minimizing the pain effect of cytokines via the use of thoracic epidural anaesthesia, preoperative anabolic setting of the patient and avoiding fasting would thus avoid the stress hormones and stress-induced hyperglycemia and its sequelae (Fig. 5)\cite{13,19}. The complex network of cytokines balances proinflammatory and anti-inflammatory effects but an imbalance or the uncontrolled production can result in inflammatory disease. The independent factors predicting length of hospital stay are the type of surgery, perioperative blood loss and postoperative insulin resistance\cite{19,20}. Therefore, a better understanding of the cytokine response to surgical trauma may offer therapeutic opportunities against insulin resistance, and enhance perioperative care and recovery.

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The author declares that there is no financial conflict of interest with regard to the content of this report.

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