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Review

Dangers, and benefits of the cytokine mediated response to injury and infection

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SUMMARY

The inflammatory response is essential for survival in an environment where continuous exposure to noxious events threaten the integrity of the organism. However, the beneficial effects of the response are influenced by factors, which disadvantage individuals within a population. These factors include malnutrition, infection, genotype, gender, pre-existing inflammation, and chronic intoxication. Although the inflammatory response is generally successful in dealing with noxious events, life-long exposure to these events takes its toll on the integrity of the body and becomes apparent as chronic disease, atherosclerosis, organ failure, and frailty.

Progress in ameliorating the consequences of lifetime exposure to inflammatory events can only occur if a fuller understanding can be obtained of the factors, which influence the persistence and outcome of the inflammatory response at an individual level. A multitude of studies has shown that specific nutrients, diets, and dietary restriction are able to modulate the inflammatory response in the population as a whole. To advance in this area, precise knowledge is needed of how the disadvantageous factors, mentioned above, affect the individual's response to anti-inflammatory nutrients.

1. Introduction

The acute phase response (APR) is a universal reaction following trauma, burns and infection.[1–3] The universality of the response was first noted in studies by Sir John Hunter, Fellow of the Royal College of Surgeons, and Physician to King George III, who observed in 1794 in a "Treatise on Blood, Inflammation and Gunshot Wounds", that "many types of injury produce a similar inflammation". Since that time the precise mechanisms of this similarity in response have become clearer. Both the clinical and the metabolic responses after trauma are an integral part of the natural adaptation following injury that serves to facilitate recovery. However, this observation only holds true when considering the human population as a whole. The response is a 'two edged sword' and can damage as well as protect individuals. While each of the metabolic changes and cellular events, which take place during the response, are intended to contribute to the defeat of invading organisms, facilitation of nourishment of the immune system and restoration of tissue structure and function, a successful achievement of these aims is dependent upon the intensity and timing of each component of the response. At the level of the individual, however, the orchestration of these components may be less than ideal and may contribute to raised levels of morbidity and mortality. For example prolonged and excessive loss of body protein, chronic elevation of plasma lipids and chronic impairment of insulin sensitivity may all contribute to disease in individuals. However, each of these metabolic changes, as will be discussed later, is an essential part of the overall response in the population. The response is thus designed to ensure the survival of the species rather than the survival of the individual.

Although the common mechanisms underlying the 'similar inflammation,' noted by Sir John Hunter, have been known for more than 20 years, the reasons why the response differs with the type of injury and varies greatly between individuals, have only recently become clearer. Another conundrum, concerning the nature and outcome of the response is that, although the response is a normal part of the defenses of the body to recover from injury and repel infection, it may also increase morbidity and be fatal. In one patient a postoperative infection may cause a slight delay in wound healing, in another patient the same infection may result in a prolonged stay in the intensive care unit, or worse, death.

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Primarily the response involves the innate immune system through secretion of the pro-inflammatory cytokines, interleukin-1 (IL-1), IL-6 and tumor necrosis factor-α (TNF-α), and the release of catabolic hormones such as catecholamines and glucocorticoids. Clinically the response is characterized by inflammation, anorexia, immobility, increased vascular permeability leading to tissue edema, vasodilatation leading to a lowered blood pressure, tachycardia, and increased cardiac output. From a metabolic point of view a hyperdynamic situation arises, which includes an increased turnover of protein, lipids and glucose at the whole body level. Neuro-endocrine changes occur which facilitate this situation. A degree of insulin insensitivity also occurs. There is a major re-ordering of protein kinetics within the body. This response leads, despite nutritional support, to muscle wasting,[4] compromised synthesis of hair, skin, nails, enterocytes, red blood cells, bone and other structures not primarily essential for survival. These phenomena have generally been viewed as unwanted side effects of the response to trauma that aggravate the patient's disease. This is, however, a misunderstanding of the prime function of the response which is to provide nutrients for the healing response, thereby ensuring survival of the species, if not the individual. A further misunderstanding occurs from the biochemical and physiological changes, which occur during the response (see Table 1).

Many of these changes may be misinterpreted as indicating a deficiency in specific nutrients. For example, a patient may show depressed plasma albumin, zinc, iron, and vitamin A and D concentrations. This may be interpreted as malnutrition in relation to protein, zinc, iron and vitamins A and D intake, respectively. However, decreases in all of these nutrients in blood are a common feature of the response (see further).

In the sections below, we discuss the genomic and phenomic factors which make it more likely that any one individual will suffer adverse rather than beneficial outcomes from the inflammatory response. A greater understanding of how these factors interact with the response to injury and infection should guide treatment strategies and indicate whether the clinician should try to support the natural processes of the cytokine mediated response rather than trying to suppress them. We will describe the "perfect world" in which these processes are optimally orchestrated and lead to complete recovery. We then will describe when and how these processes go wrong and lead to disease or irreversible damage to the integrity of the body. Finally, we will discuss the logic of interventions aiming at influencing the inflammatory response to advantage in patients who are acutely or chronically ill or traumatized and develop a view on future strategies to refine nutrition, for the individual, according to genotype, age and phenotype.

Table 1
Plasma electrolyte, vitamin, micronutrient and protein changes due to acute disease and trauma and due to chronic disease. The changes shown, exemplify influences that may occur apart from true dietary deficiency.

Electrolytes, vitamins, micronutrients, proteins	Acute disease/trauma	Chronic disease/malnutrition
$Na^{+}\downarrow$, $K^{+}\uparrow$	Membrane potential ↓	Membrane potential ↓
K^{+}, Mg^{++}, PO^{3-} ↓	Refeeding Membrane potential ↑	Malabsorption
Ca total ↓	Binding protein (alb) ↓	Binding protein (alb) ↓
Ca^{++} ↓	Distribution volume ↑	Malabsorption Binding protein (alb) ↓
Fe^{++} ↓	Transferrin ↓ Redistribution Fe	Transferrin ↓ Inflammatory activity
Fe^{++} ↓	Transferrin ↑	Iron deficiency (malabsorption)
Cu^{++} ↑	–	Binding protein ↑ Cholestasis
Cu^{++} ↓	Distribution volume ↑	Malabsorption
Zn	Redistribution Distribution volume ↑	Distribution volume ↑ Binding protein ↓ Malabsorption
Se	Distribution volume ↑ Binding protein ↓	Distribution volume ↑ Binding protein ↓ Malabsorption
Hb ↓	Dilution due to vasodilatation	Suppression erythropoiesis Iron deficiency
Albumin ↓	Distribution volume ↑ Transcapillary escape ↑ FSR not ↓	Distribution volume ↑ Transcapillary escape ↑ FSR not ↓
Vit A, D ↓	Binding proteins ↓ Distribution volume ↑	Binding proteins ↓ Malabsorption
Vit C	Binding protein ↓ Distribution volume ↑ Redistribution	Binding protein ↓

2. The clinical healing process

2.1. Local response to injury (Table 2)

Immediately after tissue injury blood elements extravasate from damaged blood vessels into the wounded area. Bleeding stops due to vasoconstriction, and coagulation occurs, due to aggregation of platelets with fibrin. Vasoactive amines increase vascular permeability to allow polymorphonuclear neutrophils (PMNs), platelets, fluid and proteins to extravasate into the wound causing wound edema. After an initial phase of vasoconstriction NO induced vasodilatation occurs increasing delivery of substrate and oxygen to the tissues. Several growth factors are released by platelets into the wound, like platelet derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which further attract PMNs and start an inflammatory process, also induced by pro-inflammatory cytokines, and which are after 2 days are replaced by macrophages. Together these cells remove debris and bacteria from the wound, release growth factors, induce the formation of a capillary network and reorganization of the extracellular matrix. Important in this process is TNF-like weak activator of apoptosis (TWEAK), which modulates wound healing.[5,6] After three days, a proliferation phase begins as fibroblasts invade the wound and start to synthesize collagen. This deposition slows down after 3 weeks but full tissue remodeling takes months to achieve. If TWEAK activity extends beyond this, the full benefit of the remodeling phase cannot be achieved and chronic inflammation may occur.[5] As described in the beginning of this paragraph the wound healing process requires an increase in permeability, which is a necessary step to allow cells, fluid and proteins to invade the interstitium to effectively execute healing (see Table 2)

2.2. Systemic response to injury (see Table 2)

In severe injury, the processes taking place in the wound occur to a lesser degree in other areas of the body. After major trauma, and even more so after severe infection, capillary permeability increases, and PMNs, fluid and proteins invade the interstitium leading to interstitial edema and intravascular dehydration. The question is whether the inflammatory processes occurring in tissues that are not primarily damaged, or infected, serve a useful purpose. Are they a harmful byproduct of the inflammatory response elicited in the primarily damaged site, or do they serve as a signal to other organs to generate metabolic responses necessary for the immune system and the wound to mount an adequate healing response? (seeSection 2.3). These processes include extravasation of PMNs and macrophages, increased transcapillary escape of plasma proteins like CRP, albumin, ceruloplasmin into the interstitium.[7–9]

Due to their scavenging properties, these proteins are beneficial in repairing the damage inflicted by the generation of oxygen radicals and lipid peroxidation products (see further).[10–15] In acute