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Inflammation-induced metabolic derangements or adaptation: An immunometabolic perspective

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ABSTRACT

Inflammatory mediators have a well-established role in mediating metabolic disturbances. Chronic low-grade inflammation is implicated in the pathogenesis of obesity and the development of metabolic syndrome. This phenomenon is even more pronounced in severe inflammatory states such as in critically ill patients where hyperglycaemia invariably manifests. Similarly, though inflammatory mediators have a well-established role in promoting bone resorption, the adaptive function of this process remains unknown. Here we review emerging evidence from the field of immunometabolism suggesting that these two processes serve a common goal, namely, to sustain the rapid proliferation of immune cells during an infection. Activated immune cells exhibit an increased demand for glucose which not only provides energy, but also glycolytic intermediates which are fluxed into biosynthetic processes. Similarly, phosphate liberated from bone is consumed during the phosphorylation of glycolytic intermediates, which plays a critical role in the synthesis of nucleotides and phospholipids. Taken together, these considerations suggest that metabolic alterations induced by inflammatory mediators do not manifest as an inability to maintain homeostatic levels of metabolites but represent an adaptive shift in the homeostatic set point during an infection.

1. Introduction

The application of invasive medical procedures, the increased survival of patients with chronic health conditions, and the aging population are all factors contributing to the increased incidence of sepsis [1]. Yet, although sepsis is a major cause of death in critically ill patients, treatment remains challenging. Part of the manifestation of sepsis-related pathologies includes the severe metabolic derangements that take shape in the context of a severe inflammatory response. Indeed, inflammation is often associated with a range of poorly understood metabolic disturbances, not only in a critical care setting, but also in other conditions associated with low-grade inflammation such as metabolic syndrome [2]. One of the most characteristic metabolic derangements is hyperglycaemia in critically ill patients suffering from either sterile (*e.g.* trauma or surgery) or infectious sources of inflammation. Given the well-established detrimental effects of hyperglycaemia described for diabetic patients, as well as the correlation between hyperglycaemia and mortality [3], intensive insulin therapy is often initiated to control glycaemic levels. Similarly, critically ill patients also often present with electrolyte disturbances, including hypophosphatemia, hypocalcaemia and hypomagnesemia [4]. In this regard, another perplexing observation is that inflammatory mediators induce bone resorption [5], an observation which raises the question as to why activation of the immune system should be accompanied by bone resorption. Although the reasons for bone resorption have thus far been poorly explored, electrolyte disturbances may be explained by therapeutic interventions such as fluid resuscitation and insulin therapy (which cause an influx of phosphate into cells).

Here we review emerging evidence suggesting that induction of insulin resistance and the development of hyperglycaemia in response to inflammatory mediators manifest as an evolutionary conserved immunological response aimed at augmenting immune function. Recent developments in the field of immunometabolism have highlighted the critical role of glucose in activated immune cells, suggesting that hyperglycaemia may play a central role in sustaining rapid cell proliferation and the expansion of effector immune cell populations. We also point out another clinical observation that supports the view of hyperglycaemia, namely, that bone resorption liberates electrolytes critical in sustaining the metabolism of rapidly proliferating cells, including phosphate and magnesium. Although this process may be pathological in the context of metabolic syndrome or participate in the generation of an overly excessive or unnecessary inflammatory response, these metabolic alterations likely evolved as part of the unique physiological adaptations necessary for mounting a competent immune

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response. These observations bear relevance in a critical care context where glycaemic control remains a heated debate, and also highlights the potential impact of electrolyte homeostasis on immune cell function.

2. Hyperglycaemia: an immunological response?

Inflammatory mediators have an established role in promoting hyperglycaemia through a number of synergistic mechanisms. Early studies have reported the release of factors by LPS-challenged macrophages that dramatically abrogate the anabolic effect of insulin on adipocytes [6]. It is now well established that these LPS-induced factors released by macrophages include inflammatory mediators such as Il-6 [7], TNF [8] and interferons [9] – all of which contribute to the development of insulin resistance. Inflammatory mediators also promote an increase in gluconeogenesis. The induction of a catabolic state by inflammatory mediators [10] supplies amino acids and glycerol from which the liver produces glucose. Following an LPS challenge, the liver may increase glucose production by increasing gluconeogenesis through the uptake of amino acids [11] and the breakdown of glycogen stores [12]. It should be noted though that stress hormones also have a well-established role in promoting hyperglycaemia. As an example, it has long been known that epinephrine increases gluconeogenesis following surgery [13]. However, inflammatory mediators may potentiate this effect. As an example, in the presence of adrenergic agents, Il-6 potentiates the release of glucagon [14]. Thus, though inflammatory mediators play a decisive role in mediating hyperglycaemia, the metabolic control exerted by the immune system takes shape in the context of other signalling factors. Taken together, these observations highlight the fact that inflammatory mediators play both a direct and an indirect role in inducing hyperglycaemia.

Hyperglycaemia observed in severe inflammatory states is generally seen in the context of a generic stress response, where mobilised glucose is used to fuel muscle for a flight-or-fight response. This view is supported by the observed elevation of stress hormones during sepsis. However, the fact that inflammatory mediators play a central role suggests that hyperglycaemia during an infection does not simply represent a non-specific stress response, but also a dedicated immunological reaction to infection. This raises the question: why would the immune system induce hyperglycaemia? In fact, serum glucose levels correlate with increased risk of mortality during sepsis [3] and similarly, hyperglycaemia has traditionally been viewed as a pathological state that “impairs the ability of the host to combat infection” [15]. Yet, hyperglycaemia is an evolutionary conserved response observed in model mammalian systems as well as in other domesticated/companion mammals, suggesting that some functional value must select for the maintenance of this trait. Also, the immune response is likely subjected to constant evolutionary pressure (as suggested by the Red Queen hypothesis [16]). Considering the ubiquity of infections and the resulting fact that the immune response is subjected to strong selective pressure, it is difficult to explain why the immune system would enact a maladaptive response.

We have recently proposed that hyperglycaemia observed in critically ill patients may represent an adaptive response aimed at fuelling immune cell metabolism [17]. Briefly, following activation, immune cells must sustain elevated levels of anabolic activity in order to expand cell pollutions to effective levels. Rapidly proliferating cells such as cancer and immune cells both make use of glucose, suggesting that hyperglycaemia may be aimed at supporting an elevated demand for glucose. Various lines of evidence support this view.

3. Immune cell activation and the induction of glycolysis

The reliance of activated immune cells on glucose is reflected by the observed upregulation of transcription factors involved in the metabolic switch towards glycolytic metabolism. Hypoxia-inducible factor 1-alpha (HIF-1α) has a well-established role in upregulating glycolytic enzymes as well as glucose transporters, thus enabling cells to better tolerate hypoxic environment by generating ATP by glucose fermentation [18]. However, HIF-1α activity also drives aerobic glycolysis (referred to as the Warburg effect) observed in rapidly proliferating cancer cells [19] by upregulating glucose transporters as well as key enzymes in glycolysis [20]. Similar to cancer cells, HIF-1α plays an indispensable role in modulating the induction of a glycolytic phenotype in macrophages [21] and, correspondingly, in both humans and mice macrophages LPS stimulates the activity of HIF-1α [22]. These observations do not only indicate that activated immune cells upregulate their ability to utilise glucose but also implicate a potential role for glucose in promoting the expansion of biomass.

However, the induction of HIF-1α in macrophages, though promoting anabolic activity, does not seem to play a role in cell proliferation: while LPS and IFN-γ promote HIF-1α activity in macrophages, they also lead to a decline in Myc activity, accompanied by a suppression of cell proliferation [21]. This suggests that glycolysis in activated macrophages, unlike cancer cells, does not drive cell proliferation, but plays a role in the synthesis of inflammatory mediators and the biosynthesis of cellular components associated with immune cell activation and differentiation into effector cells. Supporting this conclusion, the authors also demonstrated that either knockdown of HIF-1α or inhibition of glycolysis by 2-Deoxy-D-glucose protected mice form lethal LPS challenge [21]. These observations do not only indicate the central role of glycolysis in promoting a pro-inflammatory environment, but also establish HIF-1α as central in role in regulating a glycolytic phenotype.

The central role played by HIF-1α in mounting an immune response has similarly been indicated by the observation that knockdown of HIF-1α with small interfering RNA compromises the ability of mice to control *Pseudomonas aeruginosa* infection [23] and also plays an important role in promoting the polarisation of macrophages towards an inflammatory M1 phenotype [24]. Moreover, the significance of HIF-1α in sustaining glycolysis and promoting immune cell anabolism is also reflected by the fact that HIF-1α acts in concert with other canonical anabolic signalling pathways. Treatment with rapamycin, a well-known inhibitor of anabolic regulator mTOR, results in a declined glycolytic capacity in CD8 + T cells [25]. Using transgenic cell lines, these authors shown that the ability of mTOR to promote a glycolytic phenotype was HIF-1α-dependent, thus implicating HIF-1α as a downstream mediator of mTOR-induced glycolysis. Taken together, these observations connect the glycolytic phenotype of activated immune cells with an anabolic metabolism.

A key role for glycolysis is also observed in other immune cells. As an example, activated dendritic cells exhibit very similar induction of glycolysis via the upregulation of HIF-1α activity [26]. In contrast, a tolerogenic or anti-inflammatory phenotype of both macrophages and dendritic cells is associated with an increased oxidative capacity [26,27]. Neutrophils, with sparse mitochondria, must meet their energy demand via glycolysis and correspondingly exhibit high levels of aerobic glycolysis [28]. Collectively, these observations suggest that the acute hyperglycaemia induced by inflammatory mediators may play an important role in mobilising the innate immune system. However, more recent findings have also indicated an essential role for glucose during antibody production. B cells, upon immunogenic activation, upregulate GLUT-1, but also expand their mitochondrial network [29]. However, chronic exposure to B-cell activating factor (BAFF) resulted in a dramatic shift towards increased glycolysis and sustained antibody production [29]. However, in long-lasting plasma cells, glucose plays an additional role: though glucose is consumed in glycolysis, most glucose is consumed during the glycosylation of antibodies [30]. These observations collectively demonstrate that glucose is an import substrate for a variety of immune cells.

It is thus evident that glucose represents an indispensable metabolite in a variety of immune cells. In light of these observations,