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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,

hyperglycaemia observed during an inflammatory insult is most likely not a failure of homeostatic control of serum glucose levels but represents an adaptive strategy to augment immune function by ensuring that activated immune cells remain well supplied of this critical metabolite. Supporting this line of reasoning, the correlation between hyperglycaemia and increased glucose demand by activated immune cells is also reflected by metabolic reprogramming occurring during immune cell activation.

4. Glucose: fuelling the immune system

The reliance of immune cells on glucose raises another question: why do immune cells use glucose while fatty acid oxidation would provide more energy? One possibility is that, while the ATP *yield* of glycolysis is lower than oxidative phosphorylation, the *rate* at which glycolysis produces ATP may mean that glycolysis may produce more ATP in a given time interval [31]. Thus, during an infection, the urgent need to mobilise the immune system may licence immune cells to make use of a fast but inefficient process for energy production. Another key reason relates to the fact that proliferating cells do not only require ATP, but must also synthesise various other molecules in order to expand biomass prior to cell division. In this regard glucose is a remarkably versatile molecule, being able to provide carbon units for biosynthetic activities as well as sustaining energy production (Fig. 1).

Pyruvate kinase (PK) catalyses the final step in glycolysis (the conversion of phosphoenolpyruvate to pyruvate) and consequently a decrease in PK activity would result in the build-up of glycolytic intermediates. These glycolytic intermediates can be fluxed into biosynthetic pathways such as the PPP, which provides NADPH and also contributes to nucleotide synthesis [32]. Another important anabolic pathway into which glycolytic intermediates are fluxed is one carbon (1C) metabolism [33]. As an example, the glycolytic metabolite 3-phosphoglycerate is used to synthesise the amino acid serine, which in turn is utilised in 1C metabolism during the synthesis of nucleotides and NADPH [34]. In fact, serine, considered a non-essential amino acid that can be synthesised, is critical for the clonal expansion of activated T cells [35], as well as proliferating cancer cells [36]. In T cells, serine deficiency has been found to stunt cell growth by curtailing nucleotide synthesis [35]. Importantly, these nucleotides produced in one carbon metabolism and PPP do not only imply genomic duplication during cell division: inhibiting RNA synthesis also attenuates T cell expansion [37]. Similarly, NADPH produced in either PPP or 1C metabolism has a number of functions. Indeed, NADPH, as an universal electron donor, plays a pivotal role in a variety of biosynthetic functions [38]. Also, NADPH is consumed by glutathione reductase during the cycling of glutathione disulphide back to the glutathione: indeed, purgation of PPP is a major response to oxidative stress [39]. However, in activated immune cells, NADPH more likely plays an opposite role in producing biocidal radicals via NADPH oxidase system [40]. Thus, glucose ultimately supports biosynthetic activities by supplying glycolytic intermediates for PPP and 1C metabolism where nucleotides are synthesised and NADP is converted to NADPH.

Central to controlling the metabolic fate of glucose is the M2 isoform of the glycolytic enzyme pyruvate kinase: PKM2 is typically expressed by cells that are rapidly dividing and exhibit heightened levels of metabolic activity such as proliferating cancer cells [41], foetal tissue [42] and immune cells [43]. Whereas the M1 isoform forms a constitutively activated tetramer, the tetramerization (*i.e.* activation) of the M2 isoform is regulated by a number of factors, imposing more levels of control on the fate of glucose. As an example, the glycolytic intermediate fructose 1,6-bisphosphate promotes tetramerization (*i.e.* activation) of PKM2 [44]. Thus, in the presence of ample glycolytic intermediates, PKM2 activity would be augmented with a resulting increase in ATP production. Similarly, serine activates PKM2 [34]: here low serine levels (as a result of high demand for serine in one carbon metabolism [45]) would impede the tetramerization of PKM2, with the

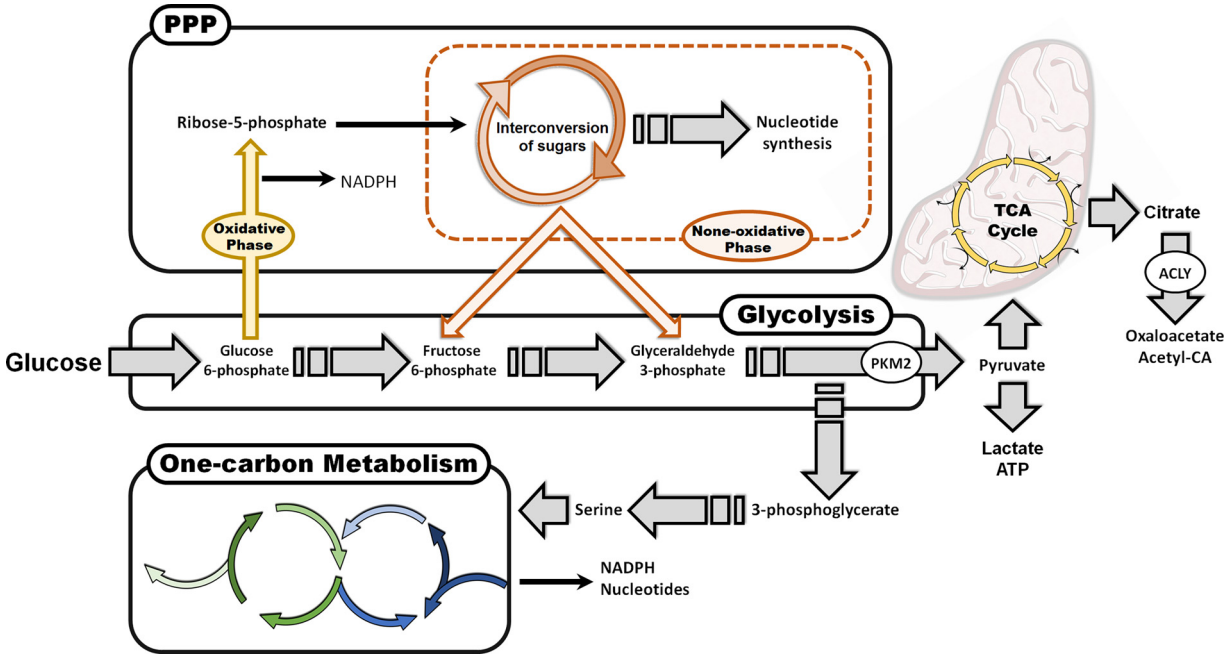

Fig. 1. The reliance of activated immune cells on glucose relates to the metabolic versatility of glucose in promoting both anabolic and ATP-producing activities. Glycolytic intermediates flux into the pentose phosphate pathway (PPP), where NADP+ is converted to NADPH (oxidative phase). Interconversion of sugars (non-oxidative phase) may be shunted back into glycolysis or be consumed during nucleotide synthesis. Glycolytic intermediates are also used in the synthesis of serine, an amino acid which plays a key role in one-carbon metabolism where nucleotides are synthesised and NADPH is produced. Pyruvate, the final product of glycolysis, may either be fermented to produce ATP or enter the tricarboxylic acid (TCA) cycle. In activated immune cells, the citrate produced in the TCA cycle is exported from the mitochondria into the cytosol, where it is metabolised by ATP citrate lyase (ACLY) into acetyl-CoA (critical for cholesterol and lipid synthesis) and oxaloacetate. Note the position of pyruvate kinase M2 isoform (PKM2) at the final step of glycolysis: here allosteric inhibition of the PKM2 expands the pool of glycolytic intermediated, fuelling PPP and one carbon metabolism. Conversely, increased activity increases ATP production via fermentation.

result that more glycolytic intermediates would build up, allowing for the replenishment of serine levels through the *de novo* synthesis from glycolytic intermediates. The expression of PKM2, a key enzyme in glycolysis, not only reflect the central role of glucose in activated immune cells, but also demonstrates the need to control the flux of glucose-derived carbon into anabolic and catabolic processes.

Additionally, glucose fluxed into the TCA cycle also plays an important role in sustaining immune function. Succinate, a metabolic intermediate of the TCA cycle, stabilises HIF-1α following an LPS challenge [46]. In addition to regulating HIF-1α, TCA intermediates also support anabolic processes. As an example, citrate exported from the mitochondria is converted to Acetyl CoA by ATP citrate lyase (ACLY). Interestingly, ACLY is rapidly elevated following activation of macrophages, and the inhibition of this enzyme is associated with a blunted inflammatory response [47], highlighting the critical role of fatty acid (FA) synthesis in activated immune cells. Importantly, the critical role of fatty acid synthesis in activated immune cells is also relevant to how study results are interpreted. Administration of C75, an inhibitor of fatty acid synthase (FAS), was also found to reduce serum-free fatty acid accumulation in the liver and it also reduced serum TNF and IL-6, ultimately promoting survival [48]. In this regard, other authors have similarly pointed out the indispensable role of FA synthesis in the activation of macrophages following immunogenic challenge [49]: mechanistically, FA and phospholipid synthesis are necessary to enlarge membrane components such as protruding filopodia, the expansion of ER and the synthesis of membrane-bound organelles. Additionally, inhibition of fatty acid synthesis was also seen to impede the development of inflammatory Th17 cells, but not regulatory T cells, which, unlike Th17 cells, are able to take up exogenous supply of FAs [50]. Collectively, these observations establish the pivotal role of FA synthesis in sustaining immune cell function and also implicate a crucial role for glucose as a major source of carbon for sustaining FA synthesis.

In conclusion, classic studies have shown that the sensitivity of ATP-demanding processes to energy supply follows a hierarchical organisation, with protein and nucleotide synthesis not only being the most energy-intensive processes, but also being the most sensitive to a drop in ATP levels [51]. Because glucose can easily be fluxed towards either anabolic pathways (one-carbon metabolism or the PPP) or directed towards energy production, it is an ideal metabolite for rapidly proliferating cells that must finely balance anabolic and catabolic processes. The induction of hyperglycaemia by inflammatory mediators is thus likely an evolutionary conserved adaptation to ensure that immune cells are able to proliferate rapidly in order to launch an effective immune response.

5. Inflammatory mediators: bad to the bone?

The preceding discussion has outlined the mechanistic basis for the reliance of the immune cell on glucose and suggests that hyperglycaemia during an inflammatory insult is directly aimed at sustaining rapid cell proliferation of effector immune cells. Remarkably, another observation also supports this hypothesis: bone resorption. It is well established that inflammatory mediators promote the breakdown of bone [5], yet the purpose of this phenomenon is poorly understood.

We have recently argued that the evolutionary conserved induction of bone reabsorption by inflammatory mediators promotes the release of ions critical for the immune system [52]. As an example, phosphate is an indispensable electrolyte, being quickly consumed by glycolysis (by the phosphorylation of glycolytic intermediates), forming a key element in nucleotide and phospholipids. Similarly, bone contains more than half of all the body's magnesium [53]: in this regard, magnesium is a critical cofactor for various enzymes that catalyse reactions involving phosphate. As an example, magnesium plays a central role in regulating the activity of glycolytic enzymes such as various kinases (*e.g.* phosphofructokinase, phosphoglycerate kinase, pyruvate kinase and hexokinase) [54,55] as well as polymerases [56]. This suggests that bone resorption may in fact sustain cell proliferation by providing phosphate as well as magnesium, a critical co-factor in glycolysis and genome duplication.

It is also likely that other electrolytes may perform important functions during an infection. As an example, since many adhesion molecules require calcium, it is possible that calcium released by bone resorption may augment immune cell migration. Similarly, the ability of citrate to induce the expression of inflammatory mediators has been reported to be dependent on calcium [57]. Calcium has also been implicated in the activation of the transcription factor EB, a central regulator of lysosomal biogenesis, thus performing a critical function in regulating autophagy [58]. In turn, autophagy has a diverse set of roles during an infection, including the degradation of pathogens [59].These observations also highlight the possibility that electrolyte disturbances seen in critical care patients may result from physiological activities aimed at augmenting the immune response. This line of reasoning suggests the potential of exploring the immunological impact of supplementing critical electrolytes. However, the stoichiometric relationship between elements in bone is likely not optimised for immune function: that is, calcium, phosphate and magnesium may not be released in the exact quantities required by immune cells, suggesting that it is likely that bone resorption may unavoidably also alter electrolyte concentrations. Though much interest is currently sparked in elucidating the significance of macronutrient metabolism, there are clear indications that electrolytes may also influence immune cell function.

6. Sepsis-induced immune-suppression

The preceding discussion has highlighted the contribution of a catabolic state in peripheral tissue during an infection (Fig. 2). A decrease in appetite, a common manifestation of sickness behaviour, would necessitate the mobilisation of endogenous stores of metabolic substrates in order to support the elevated anabolic rate of immune cells. This line of reasoning implies that the induction of a catabolic state which might starve activated immune cells of nutrients may also attenuate immune function.

It has long been appreciated that insulin exerts an anti-inflammatory effect in critical care patients [60]. Mechanistically, it was recently demonstrated that insulin can antagonise inflammation by attenuating the TLR4-MyD88-NF-κB signalling pathway [61]. However, given the critical role of glucose in immune cells, another potential mechanism by which intensive insulin therapy exert s an anti-inflammatory effect is through glycaemic control: since GLUT-1 transporters facilitate glucose transport, the rate of glucose influx into a cell would depend on the serum concentrations. Thus, many patients may benefit from glycaemic control as a strategy to avoid an unnecessary or excessive inflammatory response. However, emerging evidence suggests that suppressing immune function may not be beneficial in context of an infection such as sepsis.

Sepsis and the accompanying organ failure have been predominantly ascribed to an over-excessive inflammatory response or a 'cytokine storm'. However, a number of observations suggest that the development of sepsis may also be associated with an immune-suppressive state. In a mouse model of sepsis, a susceptibility towards secondary infection by bacteria has been observed [62], suggesting that sepsis may be associated with a compromised immune system. In humans, peripheral blood mononuclear cells exhibit an endotoxin-tolerant transcriptome early during sepsis [63]. Compared to healthy controls as well as non-septic patients, sepsis seem to predispose towards a reactivation of various latent virus infections [64], consistent with the hypothesis that sepsis is associated with an attenuation of immune function. Evidence of an immune-suppressive phenotype also comes from the epidemiological observation that sepsis is more prevalent among the extreme age brackets. As an example, sepsis is much more prevalent in the aged population, who also exhibit impaired immune function [65]. Similarly, sepsis is also a major burden among paediatric

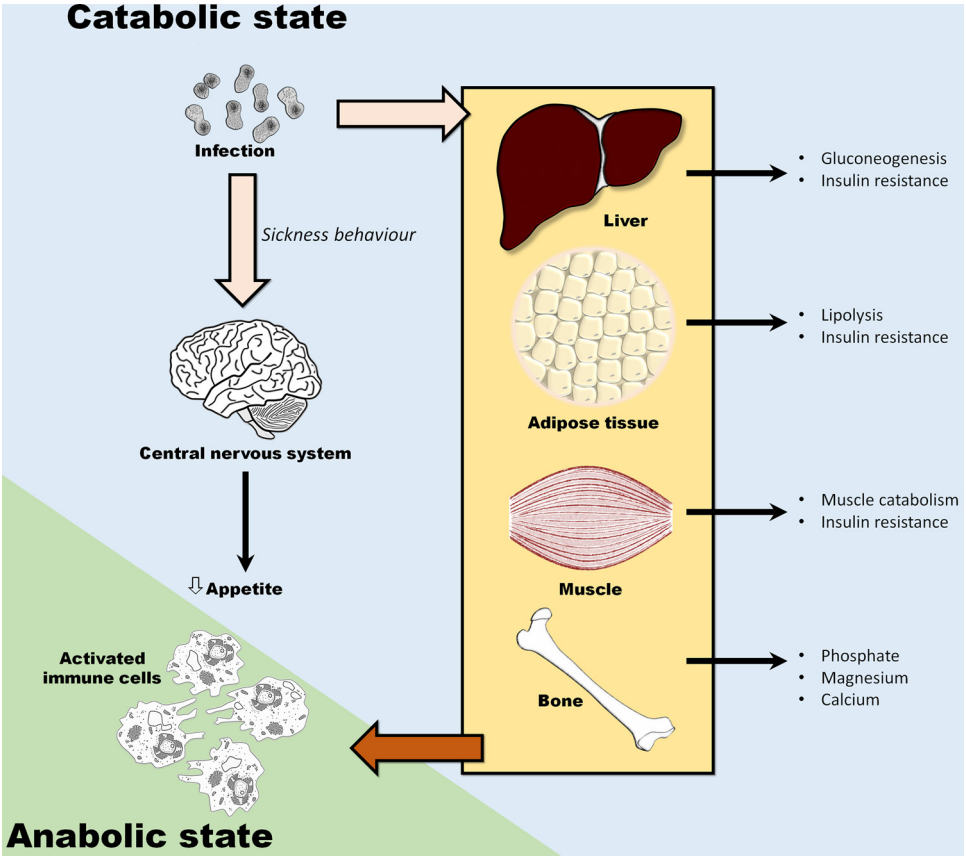

Fig. 2. Inflammatory mediators promote a decrease in appetite, which necessitate the release of nutrients by peripheral tissue to promote the expansion of activated immune cells.

patients (median age of three years) [66], a cohort associated with an underdeveloped immune system [67]. The fact that sepsis manifests in very young and very old, both age brackets, where the immune system is typically not seen as optimally functional, supports the notion that sepsis is more likely in patients with a defective immune system. Finally, there is also a growing appreciation that therapies with pro-inflammatory mediators such as Il-7 [68] and Granulocyte-macrophage colony-stimulating factor [69] may benefit patients with sepsis. Indeed, there is a growing appreciation that sepsis does not manifest as an out-of-control inflammatory response but also includes the development of an immunosuppressive state [70,71].

There is thus clear evidence that sepsis often manifests either as a cause or a result of attenuated immune function. Since glucose has a pro-inflammatory role and is critical in mobilising the immune system, tolerating elevated glucose levels may be important to preserve immune function during an infection. Conversely, given the anti-inflammatory effects of insulin, the immune system may be adversely affected in certain patients, exacerbating the immune cell dysfunction. This line of reasoning also supports the latest recommendations from the Surviving Sepsis Campaign advocating tolerating higher (< 180 mg/dL) glucose levels (compared to the previous tight control targeting levels below 110 mg/dL) [72]. However, it is also evident that attenuating inflammation may benefit certain patients, specifically sterile inflammation associated with surgical patients, or in a context where a severe life-threatening inflammatory response is developing.

7. Conclusion

During an infection, sickness-associated anorexia necessitates the mobilisation of nutrients from peripheral tissue such as bone, muscle and fat in order to sustain the rapid expansion of immune cell populations. It is thus likely that the various metabolic alterations induced by inflammatory mediators may be adaptive and directed towards sustaining the immune system during a period when food intake is compromised. However, such an adaptive response may be inappropriately activated in other contexts such as the chronic low grade inflammation observed in obesity. Here, the same processes engaged by inflammatory mediators contribute to the manifestation of metabolic syndrome. Also, the metabolic reprogramming of immune cells as well as the resulting reliance on key metabolites suggest the prospect of implementing anti-inflammatory therapies that target immune cell metabolism. Finally, there is also a need to elucidate the functional significance of these metabolic alterations to better understand the potential consequence of therapeutic interventions and to tailor supportive strategies.

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Conflict of interest

The authors declare no conflict of interest.

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