Biochimica et Biophysica Acta 1863 (2017) 2633–2644

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

The biochemical alterations underlying post-burn hypermetabolism☆

Christopher Auger, Osai Samadi, Marc G. Jeschke *

Ross Tilley Burn Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, M4N 3M5, Canada

ARTICLE INFO

Article history:
Received 16 December 2016
Received in revised form 22 January 2017
Accepted 15 February 2017
Available online 20 February 2017

Keywords:
Burns
Hypermetabolism
Insulin resistance
Catabolism
Trauma
Mitochondria

ABSTRACT

A severe burn can trigger a hypermetabolic state which lasts for years following the injury, to the detriment of the patient. The drastic increase in metabolic demands during this phase renders it difficult to meet the body's nutritional requirements, thus increasing muscle, bone and adipose catabolism and predisposing the patient to a host of disorders such as multi-organ dysfunction and sepsis, or even death. Despite advances in burn care over the last 50 years, due to the multifactorial nature of the hypermetabolic phenomenon it is difficult if not impossible to precisely identify and pharmacologically modulate the biological mediators contributing to this substantial metabolic derangement. Here, we discuss biomarkers and molecules which play a role in the induction and mediation of the hypercatabolic condition post-thermal injury. Furthermore, this thorough review covers the development of the factors released after burns, how they induce cellular and metabolic dysfunction, and how these factors can be targeted for therapeutic interventions to restore a more physiological metabolic phenotype after severe thermal injuries. This article is part of a Special Issue entitled: Immune and Metabolic Alterations in Trauma and Sepsis edited by Dr. Raghavan Raju.

1. Introduction

Burns affect nearly 300 million patients annually worldwide, with an associated substantial mortality. In the USA half a million Americans per year get burned, with approximately 40,000 requiring hospitalization [1]. Thermal injuries induce systemic biomolecular changes with profound physiological alterations, such as increased muscle and bone catabolism, hepatic steatosis, higher susceptibility to infections, multiple organ dysfunction, insulin resistance and sepsis. The hypermetabolic response, a profound increase in metabolic demand reflected by an elevated resting energy expenditure (REE), is the primary contributor to aforementioned complications, and can persist for up to 3 years after a severe burn [2]. While great strides have been made in the treatment of thermal injuries, such as improved wound care, fluid and infection management and rigorous nutritional guidelines, our understanding of the hypermetabolic phenomenon which contributes drastically to patient morbidity and mortality is lagging behind. A thorough exploration of the affected tissues and the mediators of this response is required to inform the development of improved treatment options for burned patients.

The metabolic changes following burns are not dissimilar to other traumas but very different in terms of their extent and persistence; characterized primarily by an 'ebb' phase within 48 h where metabolism, cardiac output and oxygen consumption are all decreased. This is typically followed by a 'flow' phase at around 120 h post-burn, where these variables gradually increase and plateau [3]. There are numerous reasons to believe this adaptive response is to the patient's benefit. For instance, the acute response allows vital organs to conserve energy, and mild to moderate hyperglycemia provides fuel for the brain and immune system after trauma. Burn injuries, however, stand out in their intensity and duration. The chronic persistence of the hypermetabolic response, which appears to be driven by catecholamines, stress hormones, and pro-inflammatory cytokines, far surpasses the ability of the patient to respond, and physiological exhaustion ensues. Augmented rates of glycolysis, lipolysis and proteolysis induce a loss of lean and total body mass which subsequently causes immune dysfunction, decreased wound healing and severe infections [4]. Left untreated, the amalgamation of these systemic injuries leads to organ dysfunction, sepsis and death.

Here, we present a comprehensive review of the downstream biomolecular changes that occur after a severe burn injury and examine recent findings to elaborate on how these may contribute to the hypermetabolic phenomenon, patient morbidity and mortality. Burn severity is normally determined via the total body surface area (TBSA) covered by the injury, with anything above 20% being considered a severe burn likely to result in the occurrence of the hypermetabolic condition. However, we recently presented new evidence that even a 10% TBSA burn can cause substantial and pathological alterations similar to a

☆ This article is part of a Special Issue entitled: Immune and Metabolic Alterations in Trauma and Sepsis edited by Dr. Raghavan Raju.

* Corresponding author at: University of Toronto, Department of Surgery, Division of Plastic Surgery, Department of Immunology, Director Ross Tilley Burn Centre - Sunnybrook Health Sciences Centre, Rm D704, 2075 Bayview Ave., Toronto, ON M4N 3M5, Canada.
E-mail address: marc.jeschke@sunnybrook.ca (M.G. Jeschke).

http://dx.doi.org/10.1016/j.bbadis.2017.02.019
0925-4439/

burn over 30% TBSA [5]. Current best clinical practices and areas of improvement will be discussed, with an eye towards the advancement of patient care following severe thermal injuries.

2. Cytokines and stress hormones

The immediate post-burn response encompasses a cascade of biological mediators which contribute to patient hypermetabolism. These include pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) [2,4] and [6]. A marked increase in plasma catecholamines like dopamine, epinephrine and norepinephrine can persist for years after the initial insult, contributing to muscle catabolism, insulin resistance and immunosuppression [2]. Moreover, sustained increases in the hormones cortisol and glucagon further compound the problem via enhanced breakdown of protein in muscle and the liver in addition to increasing circulating glucose and consequently, hyperglycemia (Fig. 1) [2,7]. The complexity and redundancy of the systemic response to burns renders it difficult to identify which factors contribute most to long-term hypermetabolism and can be singled out for therapeutic interventions. Here we discuss the mediators released following thermal injury and how they may play a role in the hypermetabolic phenotype.

2.1. TNF-α

As a pro-inflammatory cytokine of the acute phase reaction, levels of TNF- α are predictably higher in burned patients when compared to healthy controls. The role of TNF-α in inflammation, which includes amplifying the cellular and mediator response, as well as inducing apoptosis of injured cells and repairing inflammatory damage, renders it essential following trauma [8]. However, this cytokine is also known to increase the formation of reactive oxygen species (ROS) and accelerate the rate of lipolysis, thus increasing adipose catabolism and the release of free fatty acids (FFAs) in patients affected by thermal injuries [9]. In differentiated human adipocytes, TNF-α activates mitogen-activated protein kinase kinase (MEK), extracellular signal-related kinase (ERK) and increases intracellular cyclic adenosine monophosphate (cAMP), subsequently initiating lipolytic pathways [10]. As circulating FFAs have been known to induce insulin resistance, a hallmark feature of the hypermetabolic response, their presence after burns is detrimental to the patient. Furthermore, these moieties accumulate in the liver and muscle, leading to cellular dysfunction [11–14].

The adverse effects of TNF-α have been demonstrated in a mouse model of non-severe burn injury (<10% TBSA) covered by scald burn [15]. Despite the lack of a hypercatabolic response in these mice, there is a clear decrease in bone volume following the injury. As TNF-α has been shown to affect bone synthesis and degradation, antibodies against this inflammatory cytokine appear to restore bone thickness and volume following burn [15]. In a 30% TBSA burn model, TNF-α induces apoptosis in gut epithelial cells at a rate three times higher than that of sham animals [16]. This cytokine has also been associated with loss of skeletal muscle and impaired wound healing post-burn [17,18]. Anti-TNF-α antibodies diminish the mucosal atrophy after burn by inhibiting apoptosis without affecting proliferation [16]. However, attempts to modulate inflammatory mediators in humans have been met with mixed results [6]. Fortunately, high TNF-α levels are not sustained in burn patients, rendering it likely that this mediator's contributions to hypermetabolism are restricted to the acute phase post-burn.

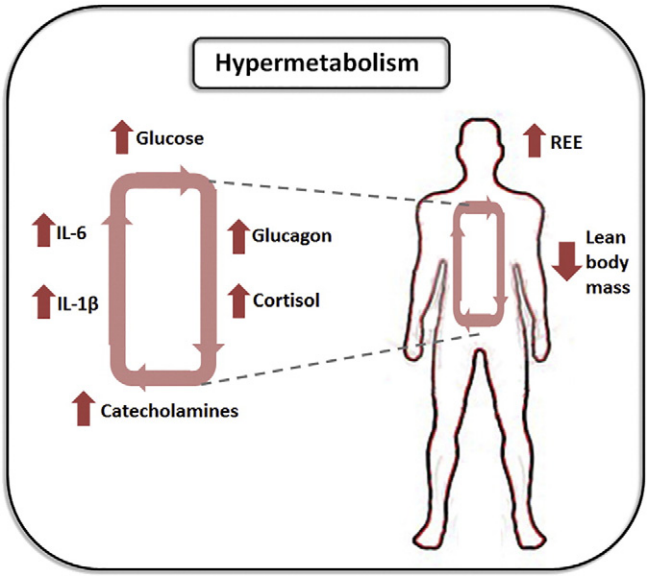

Fig. 1. The hypermetabolic response post-burn is characterized by an increase in resting energy expenditure (REE) and loss of lean body mass driven by stress hormones and pro-inflammatory cytokines.

2.2. IL-1β

In addition to TNF-α, circulating IL-1β has been associated with increases in REE and cachexia in critical illnesses such as cancer and AIDS. The maturation and secretion of IL-1β occurs following activation of inflammasomes, large multimeric protein complexes which recognize pathogen-associated molecular patterns [19]. One such biomolecule, the NLRP3 inflammasome, named for its Nod-like receptor domain, has been shown to detect obesity-associated endogenous damage-associated molecular patterns (DAMPs) [20]. The suggested mechanisms for the activation of NLRP3 include such factors as an increase in saturated fatty acids, mitochondrial dysfunction and augmented formation of ROS, all prominent components in the aftermath of a severe burn [19]. As mature IL-1β has been shown to interfere with insulin sensitivity via down-regulation of insulin receptor substrate-1 expression, it's postulated that this cytokine contributes to the stress-induced diabetes and hyperglycemia which precede long-term metabolic dysfunction and hypermetabolism following thermal injury [21]. Indeed, following a severe burn, there is a 3-fold increase in leukocyte levels in the adipose tissue, indicative of inflammation [22]. The subsequent activation of NLRP3 stimulates the maturation of IL-1β which would indeed contribute to the post-burn hypermetabolic response.

2.3. IL-6

As serum IL-6 has been associated with higher REE, the sustained increase of this mediator post-burn renders it an interesting therapeutic target. However, its multifactorial role, acting as both a pro- and anti-inflammatory cytokine with hormone-like characteristics, renders it difficult to determine when and if it would be of benefit to the patient to modulate this biomolecule. Infusion of recombinant human IL-6 in healthy volunteers mimics the hypercatabolic state seen in burn patients, such as increased energy expenditure and plasma concentrations of glucose and FFAs [23]. One possible mechanism by which IL-6 can contribute to hypermetabolism is by stimulating the liver to induce an acute phase response. IL-6 signalling proceeds via binding of its membrane bound receptor which signals the JAK/STAT pathway, leading to the translocation of activated STAT proteins into the nucleus [24]. More recently, the relationship between the STAT-regulated proteins and mitochondrial bioenergetics has been outlined, and IL-6 has been implicated in the browning of white adipose tissue (WAT) [25,26]. Brown adipose tissue (BAT) displays higher rates of lipolysis which increases the circulation of FFAs after a thermal injury and these contribute to the hypermetabolic condition [26].