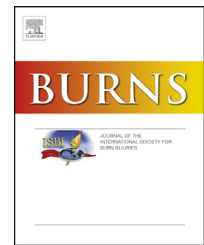


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Review

The role of complement in the acute phase response after burns

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ABSTRACT

Severe burns induce a complex systemic inflammatory response characterized by a typical prolonged acute phase response (APR) that starts approximately 4-8h after-burn and persists for months up to a year after the initial burn trauma. During this APR, acute phase proteins (APPs), including C-reactive protein (CRP) and complement (e.g. C3, C4 and C5) are released in the blood, resulting amongst others, in the recruitment and migration of inflammatory cells. Although the APR is necessary for proper wound healing, a prolonged APR can induce local tissue damage, hamper the healing process and cause negative systemic effects in several organs, including the heart, lungs, kidney and the central nervous system. In this review, we will discuss the role of the APR in burns with a specific focus on complement.

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1. Introduction

Severe burns induce a massive inflammatory response, both systemic and locally in the burn wound. This inflammatory response not only affects the healing process of the burn wound, but also has effects systemically. In addition, increased burn size leads to increased morbidity and mortality of burn patients due to especially increased inflammatory response [1]. As part of the acute phase response (APR), the complement system has been shown to negatively affect the local pathophysiology of the burn wound, but also to have negative systemic effects in burned patients [2-4]. It is therefore of utmost importance to get better insights in the role of the APR and the complement system after burns.

The skin is composed of an outer epidermal layer, that functions as a barrier to bacterial and environmental toxins and an inner dermal layer, which provides e.g. temperature regulation, blood supply and strength and suppleness of the skin [5]. Prolonged exposure to temperatures higher than 40°C, as occurring in burn wounds, causes denaturation of proteins and loss of plasma membrane integrity [6]. This process is very rapid and may only take a second when exposed to temperatures higher than 60°C. Post-burn, necrosis occurs at the center of the injury and becomes progressively less severe at the periphery [6]. Tissue loss is rapidly followed by activation of inflammatory mediators, via the APR (\pm 4-8h post-burn) [7-10]. The complement system is a central part of the APR [11]. It is composed of several proteins that interact in three different enzymatic cascades: the classical, lectin and alternative pathways (Fig. 1).

Activation of the classical pathway is mediated by the formation of the C1 complex, consisting of C1q, C1s and C1r at the targets surface. The lectin pathway is mediated by the mannose-binding lectin-associated serine proteases (MASPs), MASP-1/MASP-2 together with a collectin (usually mannose-binding lectin, MBL) or ficolin at the mannose residues of pathogens. Subsequently proteases C1s and MASP-2 bound in these complexes cleave the circulating complement components C2 and C4, releasing C4b and C2a, which form a C3-convertase.

In relation with burns, it has been shown that MBL plays an important role in the first-line host defence against infectious agents after burn. MBL initiates the lectin pathway and acts as an opsonin [12,13].

In the alternative pathway, C3b, derived from spontaneous hydrolysis of C3, together with factor B from the blood forms an alternative C3-convertase (C3bBb) on the target surface [14]. All three pathways converge at the point of C3, which is cleaved by C3-convertase and forms C3a and C3b. The C3 cleavage-product C3b formed in either the classical or lectin pathway, may initiate the alternative pathway as well. Thereby, the alternative pathway functions as an amplification loop for the other two activation pathways. Binding of C3b to the C3-convertase, forms a C5-convertase

on the target surface, which in turn cleaves phase C5 in C5a and C5b. The complement cascades end when C5b forms the membrane attack complex (MAC), together with C6, C7, C8 and C9. MAC forms a pore in the membrane, which triggers the lysis of the targeted host cells or pathogens. When C3 and C5 are cleaved, the respective anaphylatoxins C3a and C5a are released [15,16]. These have a wide variety of pro-inflammatory properties, including the recruitment and activation of inflammatory cells.

Burn wounds induce a prolonged inflammatory response with excessive complement activation, which not only negatively affects the healing process of the burn wound, but additionally exerts systemic effects in different organs. An important factor herein is the APR, in which complement is playing a central role. It is known that acute phase proteins (APPs) are elevated up to months after burn, both locally and in the blood [17-19]. The exact reason for prolonged persistence of the APR after burn is still unclear, however increased complement levels were shown to be related to the severity of burn trauma and to the clinical outcome. The initial aim of the APR is to restore homeostasis. However, a sustained or exaggerated APR has been shown to be life threatening [9,10,20-27].

In this review we discuss this post-burn APR, including its local and systemic pathophysiological effects, in more detail.

2. Post-burn alteration of APPs in blood

After burn trauma, the APR results in the alteration of acute phase protein (APP) levels in the blood (Fig. 2). The APR starts when interleukin-6 (IL-6) is produced by Kupffer cells in the liver and then induces the secretion of APPs including C-reactive protein (CRP) and complement [17,26,28-33].

Several studies in both burned humans as well as in animal burn models have shown a post-burn increase of the pro-inflammatory CRP and complement (C3, C3a and C5a) levels in the blood, up to months after the initial trauma (Fig. 2) [33-38]. It also was found that both CRP and C3 blood levels did correlate with the severity of the burn trauma, i.e. to the area (% Total Body Surface Area (TBSA)) and depth of the burn [38-42]. In addition, it has been shown that the age of patients also influenced the APR and clinical outcome post-burn. In elderly patients, significantly higher C3a blood levels were found, coinciding with significantly more thrombotic blood vessels in deep dermal tissue and delayed wound healing [43]. Indeed it is known that activated platelets can initiate activation of the complement system and formation of the C5b-9 complex, but also the other way around [44]. The APP CRP can activate the complement system via the classical pathway [11], which in turn can cause inflammatory cell attraction via the release of anaphylatoxins C3a and C5a, and also via an increase in vascular permeability by these anaphylatoxins (Table 1) [36,45-48]. Remarkably, prior to the long-term increase, complement C3 and C3a levels were found

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