Neutrophil-mediated tissue injury and its modulation

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Abstract Neutrophils play a key role in the development of the systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). Since the lungs are the main target in these syndromes, with adult respiratory distress syndrome (ARDS) as the outcome, extensive research has been undertaken to prevent or mitigate ARDS. As evidence of the involvement of neutrophils in ARDS has accumulated, modulation of their function has become a major goal in terms of a therapeutic approach. In this short review, we sought to update our knowledge about neutrophils. Firstly, we summarized the various stimuli which activate neutrophils. Secondly, we described the different mediators, including cytokines, which are released by neutrophils. Lastly, we discussed the possible modulation of their function. Although we cannot assess the clinical usefulness of biochemical substances merely on the basis of their in vitro effects, understanding these mechanisms is fundamental to the success of the new therapeutic approach which is currently under way.

Key words Neutrophil · Mediator · SIRS · ARDS · Treatment · IL-8 · Cytokine

Introduction

In critically ill patients, a variety of clinical insults, such as sepsis, trauma, burns and pancreatitis, induce fairly similar systemic inflammatory manifestations, referred to as the “systemic inflammatory response syndrome (SIRS),” which includes the “multiple organ dysfunction syndrome (MODS)” [1]. Although some evidence exists that tissue injury can occur under certain neutropenic conditions [2–4], as progress has been made in understanding the pathophysiology of SIRS and MODS, neutrophils have been identified as key cells in causing the tissue injury which leads to organ dysfunction. A variety of biochemical mediators are known to be involved in the pathophysiological mechanisms of the tissue injury caused by neutrophils, and it has recently been demonstrated that neutrophils can produce cytokines, in addition to their classical mediators. Hence, neutrophils are not merely terminal effector cells, but immunoregulatory cells capable of communicating with other inflammatory cells. In this short review, we describe both the mediators which stimulate neutrophils and the mediators which are produced by neutrophils. We then discuss the prospects for potential therapeutic approaches via modulation of these mediators.

Neutrophils play a key role in ARDS

ARDS, defined as non-cardiogenic pulmonary edema, is a major component of the MODS seen in critically ill or injured patients [5]. Although extensive research has been undertaken in the last two decades, the pathophysiology of ARDS has not been fully elucidated. The evidence accumulated thus far, however, points to the involvement of neutrophils in the pathogenesis of this fatal syndrome.
ARDS is known to be accompanied by local neutrophil accumulation. At least a part of the acute lung injury is inducible by injecting animals with live bacteria [6], lipopolysaccharide (LPS) [7], interleukin-1 (IL-1) [8] or tumor necrosis factor alpha (TNF-α) [9]. Pathological studies of these animals have shown that neutrophils accumulate both in the lungs and in other injured organs. Moreover, prior neutrophil depletion with an immunosuppressant attenuates certain types of acute lung injury [7, 10].

Recently a potent neutrophil chemotactic and activating protein has been identified and termed “interleukin-8” (IL-8) [11]. Homologous proteins have been cloned and are referred to as “chemokines.” IL-8 has been demonstrated to play an important role in ARDS and other organ dysfunction. Donnely et al. have suggested that patients with detectable IL-8 in their bronchoalveolar lavage (BAL) fluid are at higher risk of developing ARDS than those without detectable BAL IL-8 [12]. In inhalation injury, we found that the concentration of IL-8 in the BAL fluid of burn patients predicted the development of respiratory insufficiency (Fig. 1) [13].

In vitro and ex vivo, various stimuli, such as TNF-α, have been found to injure endothelial or other stromal cells via neutrophil-mediated mechanisms [14]. These stimuli not only directly activate neutrophils to release various mediators, but induce the production of a variety of mediators by many types of cells, and these stimulate neutrophils indirectly as well. These findings also suggest the involvement of activated neutrophils in the pathophysiology of tissue injury, ARDS and MODS.

### Stimuli which activate neutrophils

Numerous stimuli can activate neutrophils via specific receptor for each stimulus. Figure 2 shows the functional receptors and adhesion molecules which have been identified on neutrophils to date. IL-1 and TNF-α are potent activators of neutrophils which induce the production of oxygen metabolites and the release of granular enzymes [15]. LPS is another potent neutrophil activator [16]. Although the mechanism of LPS-induced activation has not been fully determined, CD14 has been identified as a specific receptor for LPS-LPS binding protein (LBP) complex [17]. Although neutrophils possess only a few surface CD14 molecules, they display a potent response to LPS. Thus, a portion of the neutrophil activation may be mediated via other as yet unidentified LPS receptors on the cells. Complement fragments (C5a) [18], bacterial fMLP [19] and IL-8 [11, 20] are potent chemotactic stimuli which also induce degranulation and respiratory bursts. GM-CSF [21], G-CSF [22] and interferon gamma (IFN-γ) [23] induce weak activation, or prime neutrophils for secondary stimuli. Among the various bioactive lipids, leukotriene B₄ (LTB₄) [24], lipoxin A [25] and platelet-activating factor (PAF) [26] are known for their neutrophil-oriented activity. In addition to direct activation by surface receptor binding, there are indirect pathways, e.g., phagocytosis of exogenous substances is a potent neutrophil stimulus, whether or not these substances are opsonized or bound to C3b and FCyI, II, III receptors [27]. Neutrophils express several adhesion molecules, including Mac-1, LFA-1 and sialyl Lewis x [28] and immobilization of these molecules via the binding of Mac-1.