The Role of Adhesion Molecules in Acute Lung Injury

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Introduction

Sepsis and the complications which arise following onset of the phenomenon in humans remain one of the most common and devastating problems encountered in critically ill patients. The incidence of sepsis in the United States has more than doubled over the last ten years affecting more than 400,000 patients annually. Highly effective antimicrobial agents and vastly improved supportive management in modern intensive care units have failed to significantly reduce the estimated 40 to 50% mortality rate observed in patients with septic shock and the resulting multiple organ failure. The appearance of multiple organ failure clearly impacts the mortality rates in the setting of sepsis with higher rates exhibiting a direct relationship to the numbers of organs failed.

An important feature in the evolution of organ injury is the activation and subsequent sequestration of neutrophils from the circulation into organ microvasculature. A complex interplay between circulating soluble proinflammatory mediators which appear following onset of sepsis and cellular adhesion molecules play a critical role in the dynamic interactions which occur between neutrophils and vascular endothelium. Through interactions between critical families of adhesion receptors neutrophils in an activated state are brought to a halt out of the stream of axial blood flow onto endothelial surfaces where they roll and then adhere firmly. The intercellular clef which forms between tightly adherent, activated neutrophils and endothelium subsequently forms a microenvironment protected from circulating antiproteases and endogenous antioxidants into which neutrophils secrete proteolytic enzymes (i.e. neutrophil elastase) and reactive oxygen intermediates (i.e. hydrogen peroxide). This “environment for injury” results in the devastating vascular injury observed following onset of sepsis.

Induction of Sepsis

The systemic inflammatory response syndrome (SIRS) and its infectious counterpart “sepsis” may occur following infection with fungi, bacteria, viruses or certain protozoa, or following severe trauma or burns. Sepsis and septic shock following infection with enteric gram-negative organisms currently stands a “model” of understanding concerning our knowledge of sepsis pathogenesis.
Entry of lipopolysaccharide (LPS) into the circulation promotes the appearance of critical proinflammatory cytokines (i.e. tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6) following its binding to the CD14 receptor on the surface of blood monocytes and macrophages (Fig. 1). Following a brief period, cytokines, which are not preformed mediators, surge to significantly high levels in circulation. Early response cytokines such as TNFα and IL-1 initiate a “cascade” of cytokines which subsequently appear in circulation in temporal fashion following onset of sepsis. TNFα and IL-1 are the most well characterized mediators of the septic process because of their early appearance. Alone or in combination, TNF and IL-1 and their isotypes promote significant effects on circulating blood neutrophils.

**Importance of Blood Neutrophils**

The local accumulation of neutrophils in areas of inflammation is essential for effective host defense and repair. Dutrochet in 1824 first reported that leukocytes left the circulation and adhered to vessel walls prior to diapedesing through the endothelium. Leukocyte emigration is responsible for successful host response to tissue damage and infection but if excessive and uncontrolled is potentially harmful. Neutrophil (leukocyte) emigration from the circulation occurs under normal circumstances with 10% of the total blood neutrophil population migrating per hour with few re-entering the circulation. Under normal conditions, a significant number of PMN do not actively circulate but are sequestered in the microcirculation of various organs particularly the lung. In man, up to 50% of the intravascular granulocyte pool consists of non-circulating cells [1]. Factors controlling adherence of PMN to endothelium have long been investigated but only over the past decade has the discovery of adhesion molecules and the generation of monoclonal antibodies to these surface adhesion antigens, advanced understanding of the mechanisms involved. Metchinikoff postulated that neutrophils alone were primarily responsible for adhesion and migration. The endothelium was considered a passive barrier to be breached.