Recognition of Bacteria and Bacterial Products by Host Immune Cells in Sepsis

J. Pugin

Introduction

Bacterial sepsis is the leading cause of death in non-coronary intensive care units, and accounts for over 200,000 deaths per year in the United States of America [1]. In critically ill patients with a suspected or a proven source of infection, sepsis is characterized by physiological disturbances such as fever or hypothermia, tachycardia, tachypnea, leukocytosis or leukopenia [2, 3]. Severe sepsis is defined by the same condition with evidence of organ dysfunction. Patients in septic shock meet the criteria of severe sepsis with in addition presence of hypotension refractory to volume loading [2]. The condition of physiological disturbances such as in sepsis, but in the absence of infection, is known as “systemic inflammatory response syndrome” (SIRS) [4]. These new definitions of sepsis and related infectious syndromes in critically ill patients underline the trend towards a pathogenic definition of these conditions. Indeed, those definitions reflect the will of clinicians to recenter the disease on host responses, rather than on the triggering infectious microorganism. This is supported by clinical and basic researchers who also recently realized that the pathogenesis of bacterial sepsis depended on host responses rather than on the infectious process [5]. It has recently become clear that bacterial infections initiate host responses through activation of biochemical and cellular cascades, leading to the production of effector immune cells and of endogenous mediators [1, 6, 7]. This response is often adequate and necessary for a rapid immune response directed against the invading microorganism. However, in some cases, this response is inadequate and deleterious for the host himself, and causes the syndrome known as severe sepsis. It is not completely understood what makes this response inappropriate. In the case of bacterial sepsis, it is believed that it is essentially the high levels of mediators reached during sepsis that might be responsible for the syndrome and for the damage to host organs. It is also likely that in some conditions like SIRS, microorganisms trigger overwhelming responses to bacteria, just as if the host were “prepared” to respond in that exaggerated manner. Some experimental data tend to support this point: pretreatment of animals with interferon-γ (IFNγ) renders them hypersensitive to bacterial endotoxin. This concept of overwhelming host responses triggered by bacterial products was actually already well delineated by Lewis Thomas in “The Life of a Cell” (1974):
When we sense (bacterial) lipopolysaccharide, we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all tissue in the area. ... All this seems unnecessary, panic driven. There is nothing intrinsically poisonous about endotoxin, but it must look awful, or feel awful, when sensed by cells." [8]

The whole process begins with recognition of bacteria and bacterial products by cells of the immune system. The model of endotoxin stimulation of cells is by far the best studied model in the field of molecular and cellular pathogenesis of bacterial sepsis. The initial steps of recognition of bacterial products by immune cells are not only important for understanding the pathogenesis of the disease, but also to identify molecules that might be therapeutically targeted in order to decrease or abrogate damage induced to the host. This approach has led to the discovery of critical molecules of the host which mediate cell activation and the release of various substances by host cells important for the pathogenesis of sepsis. These substances include "pro-inflammatory cytokines" such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and IL-6, chemokines (IL-8, MCP-1), growth factors (CSFs), lipid mediators (platelet activating factor (PAF), prostaglandins, leukotrienes), reactive oxygen and nitrogen species, enzymes, etc. ... all of which have been implicated in some aspects of the pathogenesis of sepsis [1, 6, 7].

The mechanisms by which specialized host molecules recognize and mediate cellular activation in response to bacterial products will be described later in this chapter. The role of lipopolysaccharide (LPS)-binding protein (LBP), the membrane receptor CD14 protein and intracellular kinases in mediating the initial steps of cellular activation by bacterial products will be discussed herein in details. Some aspects of the differential responses to LPS and to other bacterial molecules by different cell types such as monocytes/macrophages and endothelial cells will also be discussed. Finally, the new concept of the existence of "sentinel" or "pattern recognition" receptors of immune cells recognizing molecules from various bacterial families and initiating immune responses characteristic to the innate immunity will be introduced.

Lipopolysaccharide-Binding Protein (LBP) and other Serum Proteins

Lipopolysaccharide (LPS, endotoxin), a component of the outer gram-negative bacterial membrane, is the prototypic example of a conserved bacterial molecule capable of initiating septic shock [6]. In pioneer work, Ulevitch et al. [9, 10] showed 15 years ago that the biochemical properties of LPS were affected by the presence of serum. Moreover, the presence of serum seemed required for efficient myeloid cell activation by LPS [11]. It is with the discovery of a unique serum protein, lipopolysaccharide-binding protein (LBP) by Tobias et al. in 1986 [12] that we started to understand the fate of LPS in serum and in biological systems. LBP is a 60 kDa glycoprotein mainly but not exclusively produced by the liver [13–15]. It is found in human plasma or serum at basal levels of 5 to 10 μg/mL, but concentrations may raise 20–50 times during an acute phase response [16]. Hepatic LBP production is regul-