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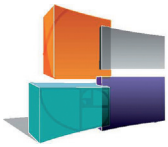

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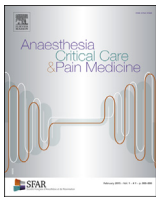

Review

Innate danger signals in acute injury: From bench to bedside

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ABSTRACT

The description of the systemic inflammatory response syndrome (SIRS) as a reaction to numerous insults marked a turning point in the understanding of acute critical states, which are intensive care basic cases. This concept highlighted the final inflammatory response features whichever the injury mechanism is: infectious, or non-infectious such as extensive burns, traumas, major surgery or acute pancreatitis. In these cases of severe non-infectious insult, many endogenous mediators are released. Like infectious agents components, they can activate the immune system (via common signaling pathways) and initiate an inflammatory response. They are danger signals or alarmins. These molecules generally play an intracellular physiological role and acquire new functions when released in extracellular space. Many progresses brought new information on these molecules and on their function in infectious and non-infectious inflammation. These danger signals can be used as biomarkers and provide new pathophysiological and therapeutic approaches, particularly for immune dysfunctions occurring after an acute injury. We present herein the danger model, the main danger signals and the clinical consequences.

1. Introduction

It has long been considered, particularly in organ transplants, that the immune system role was solely to distinguish self from non-self through the recognition of exogenous antigen by lymphocytes [1]. In 1989, Janeway proposed a new model in which foreign mediator activates the immune system when pathogen-associated molecular patterns (PAMPs) activate antigen presenting cells via dedicated receptors [1,2].

In 1994, Matzinger developped this model and suggested that the immune system might be activated by endogenous mediators expressed in response to an acute insult of any origin: bacterial, viral, thermal or traumatic [3]. These messengers are called alarmins, danger signals or damage-associated molecular patterns and are the endogenous equivalent of PAMPs [4,5].

Danger signals generally have several features: they exist in the physiological state and their function is often related to cell repair; they are rapidly and massively released after a non-programmed cell death or cell distress; they can be produced by immune cells and trigger an innate immune response; and they contribute to the restoration of homeostasis by stimulating the reconstruction of tissues damaged by a direct injury (trauma) or by inflammation side effects [5,6].

As such, they interest anti-infective immunity specialists as well as trauma or major surgery specialists in anesthesia and intensive care.

Immune system can thus be activated by exogenous mediators (e.g., bacteria) or endogenous mediators, via common mechanisms that can generate similar clinical symptoms. The resulting SIRS is classically defined by at least two of the four following conditions: hyper- or hypothermia, tachycardia, tachypnea, and a white blood cell counting modification [7]. SIRS may result from a wide range of infectious, traumatic, surgical, thermal (extensive burns) or inflammatory (acute pancreatitis) typical intensive care injuries. Sterile inflammation is the term used in these pathologies when no bacteria are involved [8].

Inflammatory response is crucial for the organism's reaction to infectious or non-infectious insult. Inflammation is necessary to fight infections and to initiate damaged tissue repair. An immune system modulation carried out after this type of injury could

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improve patients' prognosis but remains a yet an unproven therapeutic proposal.

The review aims to present the latest immune activation pathophysiological models, a recent synthesis of data on danger signals in acute injury, while underlying their dual function (physiological and danger signaling function) and the expected new clinical applications.

2. Data acquisition and bibliographic research modalities

Computerized bibliographic research was carried out with articles published on Medline database from January 2009 to August 2014, using the following keywords: "alarmins", "damage-associated molecular pattern", "endogenous danger molecules", "calgranulin" and "leukocyte L1 antigen complex". The last 2 keywords were added as part of a PhD thesis focused on these proteins. The term research was limited to English- and French-written articles. Articles selection was based on their title and abstract to eliminate those not directly dealing with this topic. The results of this research were supplemented by the reference lists of the selected articles and references from the authors' personal bibliography (Fig. 1).

3. Data synthesis

3.1. History: from sepsis traditional model to danger model

Sepsis is a complex syndrome resulting from the host innate immune response to an infection. It was first described in septic shock as an uncontrolled inflammatory response associated with compensatory mechanisms intending to limit excessive inflammation. In this model, the immune system activation by pathogenic agents triggers a "biphasic" immune response. Therefore, various innate immune system cells (macrophages, dendritic cells, polymorphonuclear neutrophils) are involved. This activation passes through receptors such as Toll-like receptors (TLR), discovered in 1996 [9].

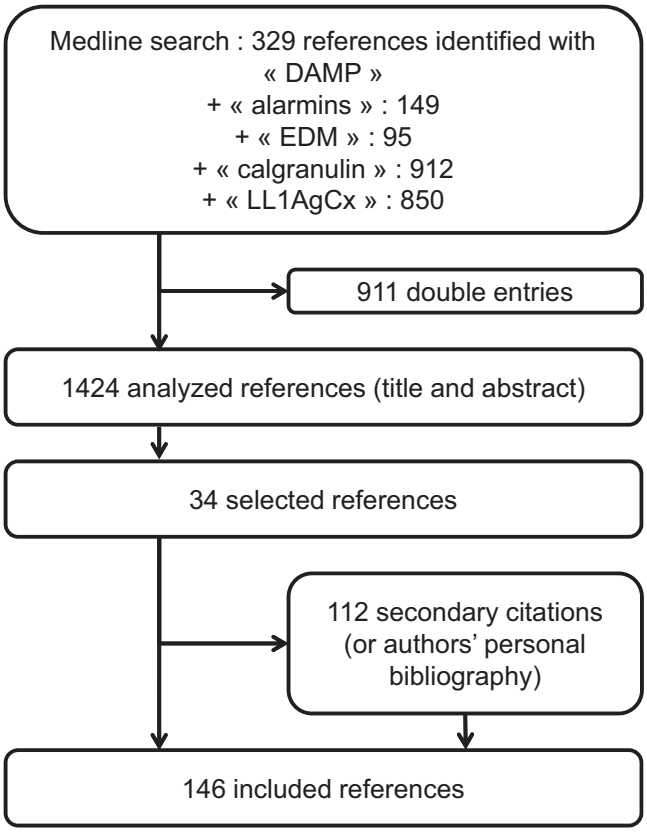

Fig. 1. Bibliographical research scheme. DAMP: damage-associated molecular pattern. EDM: endogenous danger molecules. LL1AgCx: leukocyte L1 antigen complex.

TLRs recognize microbial components also called pathogen-associated molecular patterns (PAMPs). These PAMPs include lipopolysaccharide (Gram-negative bacilli endotoxin), lipoproteins, peptidoglycan or Gram-positive bacilli lipoteichoic acid. TLR4 recognizes Gram-negative bacteria endotoxin, TLR2 recognizes Gram-positive bacteria and bacterial lipoproteins, and TLR9 detects unmethylated CpG sequences derived from bacterial DNA [10].

TLR activation by a ligand triggers an intracellular signaling cascade that leads to the activation of NF-kB and mitogen-activated protein (MAP) kinases. The coordinated action of these intracellular proteins causes a massive transcription of pro-inflammatory cytokines (such as interleukin-1 and TNF) and anti-inflammatory cytokines (such as interleukin-10) [11].

This massive and early inflammatory response is necessary to eradicate the causative agent but it can however engender local collateral damage in the infected site, systemic damage and organ failure. The concomitant combination of this inflammatory response with an anti-inflammatory response may generate a complex immune dysfunction favoring the occurrence of secondary hospital-acquired infections. Systemic anti-inflammatory response is characterized by the synthesis of anti-inflammatory mediators, such as IL-10, that inhibits the production of pro-inflammatory cytokines and transforms the lymphocytic spectrum inducing T-cells regulatory subsets [12].

In 1994, Matzinger presented the danger model, a revolutionary vision in immunology going beyond the "simple" transplantation immunity. In addition to the recognition of non-self, the role of the immune system is to detect and protect the body from infectious or non-infectious dangers [1,3]. In this model, the immune system can be also activated by danger or alarm signals originating from damaged cells exposed to pathogens or toxins (Fig. 2). A physical, thermal or chemical trauma can activate the immune system and thus lead to SIRS.

PAMPs and endogenous danger signals constitute the group of damage-associated molecular patterns (DAMPs) whose role is to activate the immune system [5,13]. From that perspective, endogenous DAMPS are also called "alarmins" as they can activate the immune system [4]. Some authors assimilate endogenous danger signals to DAMPs [10] or identify PAMPs and DAMP's alarmins as danger-associated molecular patterns [14].

When the immune system reacts to bacterial insult, there can be two coexisting signals: a danger and a bacterial signal (Fig. 2).

3.2. Danger signals data (description, localization and functions)

Danger signals have been described as numerous and of different origins, without any consensus regarding classification. So, they are herein presented according to their intracellular localization (intranuclear, intracytoplasmic or mitochondrial) (Fig. 3).

Most danger signals are molecules contributing to intracellular functioning and acquiring new functions when released extracellularly in response to an insult (Table 1).

3.2.1. Intranuclear danger signals

3.2.1.1. High mobility group box-1 protein (HMGB1). HMGB1 is a small intranuclear protein of 30 kD [15] involved in DNA transcription, replication, repair and compaction [16,17].