

Sepsis and Inflammasome

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Abbreviations: Nucleotide-Binding and Oligomerization Domain (**NOD**); Peptidoglycan (**PGN**); Nucleotide-Binding Domain and Leucine-Rich Repeat-Containing (**NLRP**); Apoptosis-Associated Speck-Like Protein Containing Caspase Activation and Recruiting Domain (**ASC**); Toll-Like Receptor (**TLR**); Leucine-Rich Repeat (**LRR**); double-stranded Ribonucleic Acid (**dsRNA**); double-stranded Deoxyribonucleic Acid (**dsDNA**); High Mobility Group Box-1 (**HMGB-1**); Nuclear Factor Kappa B (**NFκB**); Caspase Activation and Recruiting Domain (**CARD**); Pattern Recognition Receptor (**PRR**); Systemic Inflammatory Response Syndrome (**SIRS**); Pathogen-Associated Molecular Pattern (**PAMPs**); Damage (Danger)-Associated Molecular Patterns (**DAMPs**)

A NEW DEFINITION OF SEPSIS AND CLINICAL OUTLINE

Sepsis, which is caused by bacterial infection, can lead to severe complications of the vital organs.

Our benchmark criteria of sepsis has long been based on very simple vital signs that are defined by the Systemic Inflammatory Response Syndrome (**SIRS**) criteria with high accessibility in practical medicine, as shown in scheme 1. The definition of sepsis had not been revised since 2001 for 15 years. The latest recommended consensus for sepsis was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine in March 2016, which is now available online [1]. They concluded that sepsis should be defined as “life-threatening organ dysfunction caused by a dysregulated host response to infection” and as a result, the prior definition of SIRS was abandoned. Furthermore, the definition of “septic shock” was also amended, thereafter defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities and is associated with a great risk of death than with sepsis alone.

According to an updated sepsis fact sheet made by the Center of Disease Control and the sepsis alliance, sepsis can occur in any individual as the result of any type of infection, and can affect any part of the body. It often causes serious damage to tissue, and organs as a result of an uncontrolled host response including the inflammatory immune system and are often complicated with hypo-immune status [2]. In the community, various types of infection including any part of the body, such as the skin, airways (pneumonia probably as most frequency [2,3]), urogenital tract, and abdomen (enteritis, appendicitis, etc.), could be involved with sepsis [4]. Even after a minor infection, trauma, a burn which includes post chemical exposure, or a tooth extraction, secondary sepsis can be caused via broken skin, mucosal barrier etc. It also occurs with food poisoning [5], addiction of drugs, and contact with environmental “potential” microbiological contamination such as in leisure activities by the river and brackish water regions [6]. Cases including health care associated infection have also been reported where healthy individuals are exposed to an environment contaminated with particular virulent microorganism. Such cases might bear more characteristics of iatrogenic or healthcare acquired infection at medical settings although making the decision of such situation is often not easy. Etiologically, any weaknesses of the host immune system as in an immaturely-immune infant, the elderly, individuals bearing malignancy, hypothermia, AIDS or under corticosteroids medications potentially make the individual's condition more vulnerable, otherwise more immune-competent host, to induction of sepsis (Figure 1) [7].

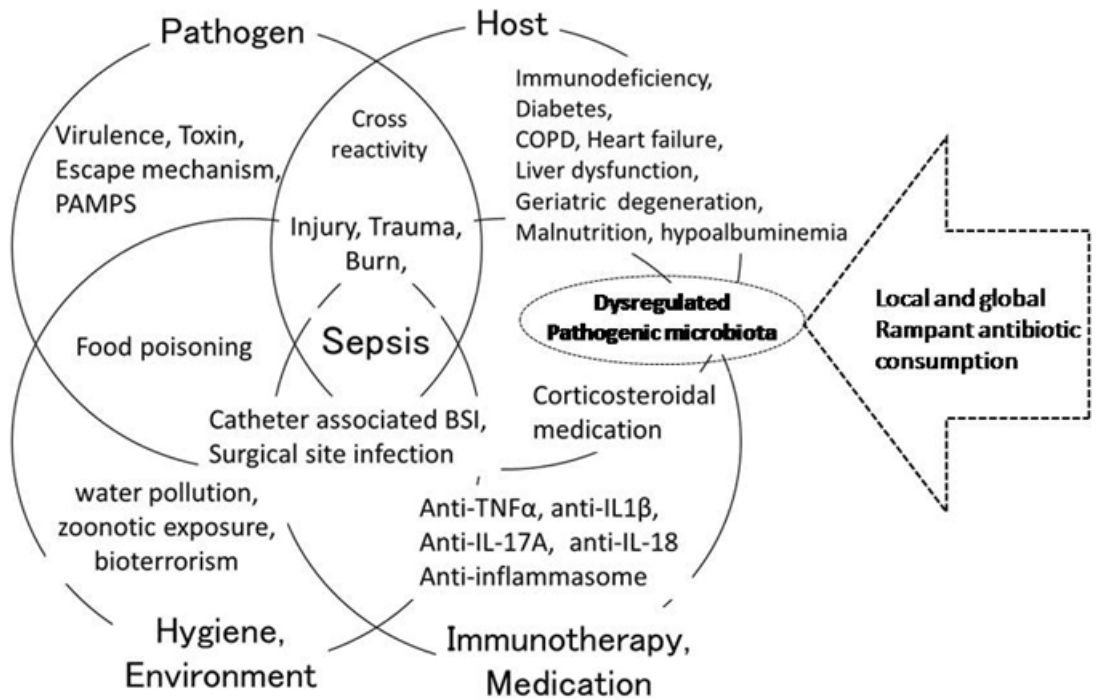


Figure 1: Factors associate to sepsis.

BASIC UNDERSTANDING OF SEPSIS IS STILL UNDER INVESTIGATION

As mentioned earlier, the medical definition of sepsis was reconsidered with a revised clinical rationale by global specialists [1]. However, the revised clinical rationale still appears to have undetermined etiological entities. There also appears to be substantial gaps between the practical criteria and pathobiology despite the considerable advances made in recent years regarding sepsis with molecular information of cell biology and immunology. So why does infection or tissue damage cause systemic inflammatory dysregulation and cellular/metabolic disorders? [2,8].

The following factors are involved in septic disease progression (Figure 1): 1) the particular molecular pattern of microbes, such as the presence of peptidoglycans, lipoteichoic acid, type III secretion system (see terminology section of this chapter), LPS, flagellin, etc., which initiates either signalosome or inflammasome; 2) host conditional susceptibility, like trauma, or hypothermia; 3) the type of immunomodulatory medical treatments used; 4) the environmental factors associated with hygiene in the community and medical institutes; 5) the pathogen-transmitting pathways in particular cases, e.g. with suspected outbreaks; 6) the global overconsumption of antibiotics, which could increase the risk of sepsis since it has been reported that they create “pathobionts” in otherwise harmonious human commensal microbial niche (Scheme 1) [9].

SIRS definition

Fever of more than 38°C or less than 36°C

Heart rate of more than 90 beats per minute

Respiratory rate of more than 20 breaths per minute

Abnormal white blood cell count >12,000 or <4,000

New definition of sepsis (quick SOFA)

An alteration in mental status

A decrease in systolic blood pressure of less than 100 mm Hg

Respiratory rate greater than 22 breaths per minute

New definition of septic shock

Persisting hypotension requiring vasopressors to maintain MAP 65 mmHg

Blood lactate >2 mmol/L despite adequate volume resuscitation

Scheme 1: Newly defined SEPSIS.

Important causative microbiological pathogenicity of sepsis and several antibiotic treatments in practical medicine are described in detail in other chapters and in other publications. This chapter focuses on explaining the mechanisms of inflammasome, since recent canonical progresses of molecular and chemical knowledge have shed light on innate-like infectious immunity that profoundly relates to septic host responses [10,11]. Such molecular information enables us to see what entities induce septic conditions. Sepsis may initially be triggered by molecular interaction between specific components of microorganisms and host cells [8]. Numerous elemental but highly-specific molecules could be etiological factors. In addition, several inflammatory cascades that involve local effect or cell aggregation to the site of infection or insulted tissues and systemic inflammatory immune responses are involved in septic disease progression.

Thus, this chapter describes the fundamental innate pathogen-sensing system and inflammatory cascades caused by molecular components of pathogens as well as host-derived molecules of tissue damage by biological stress, which initiates septic inflammatory condition. Upcoming therapies for sepsis by modulating-inflammasome are also highlighted here.

HOST-PATHOGEN RELATIONSHIPS AND MOLECULAR TRIGGERS OF SEPTIC INFLAMMATION

The surface of the intestinal mucosa, the upper and lower airways, skin barriers, or the urogenital mucosa are the first regions to encounter external microorganisms, and maintain the balance between host epithelial cells and commensal microorganisms. Such parts of the body are surveyed with an innate sensing system called pattern-recognition receptors (PRRs) that recently permeated in medical field and various molecular stimulators for them were also discovered (Table 1) [12]. PRRs recognize or sense exclusive molecular patterns of microorganisms; Pathogen Associated Molecular Patterns (**PAMPs**) that do not usually exist in host physical components. Among numerous of them, the best known PRRs are Toll-Like Receptors (**TLRs**), which are distributed on the cell membrane of epithelia, phagocytes, and intracellular endosomes (Figure 2, Table 1). TLRs are characterized as particular molecular components of host cells that are designed to sense and oriented for external microorganisms. Such TLR-dependent sensing signals are transduced by a common set of protein modules including Myeloid Differentiation factor (**MyD**) 88 and Nuclear Factor (**NF**) κ B, which is a transcription factor that promotes several proinflammatory cytokines and chemokines. The amount of PRRs on cells is self-regulated. When infectious pathogens invade, the TLRs may upregulate themselves [8,11]. Inflammatory responses that are initiated by such pathogen-TLR mediated pathway cascades are conventionally termed “signalosomes” since most TLR signals are mediated via MyD88- and NF κ B-dependent transcription, which promotes local production of essential proinflammatory cytokines including IL-1 β , TNF α , and other chemokines [11].

Table 1: Human TLRs and NOD-like receptors.

Categories	Molecules	Localization	Stimulants	Characters
NOD-like receptors (NLRs)	NOD1 NOD2 NALP3	cytosol cytosol endosome	PGN (GNR) PGN (GPC) ref table 2	bacterial bacterial bacterial, host factors, chemicals
TLR	TLR1 TLR2 TLR3 TLR4 TLR5 TLR6 TLR7, and 8 TLR9	cell membrane cell membrane endosome cell membrane cell membrane cell membrane endosome endosome	dsRNA LPS flagerin lipoproteins ssRNA (viral) unmethylated CpG DNA	heterodimeric with TLR2 heterodimeric with TLR1,6 recognizing LPS responding at lung epithel heterodimeric with TLR2 recognizing LPS autoimmune by sensing cromatin

NOD: Nucleotide-Binding And Oligomerization Domain; PGN: Peptidglycan; NLRP: Nucleotide-Binding Domain And Leucine-Rich Repeat-Containing; TLR: Toll-Like Receptor; dsRNA: double-stranded Ribonucleic Acid; ssRNA: single-stranded Ribonucleic Acid.

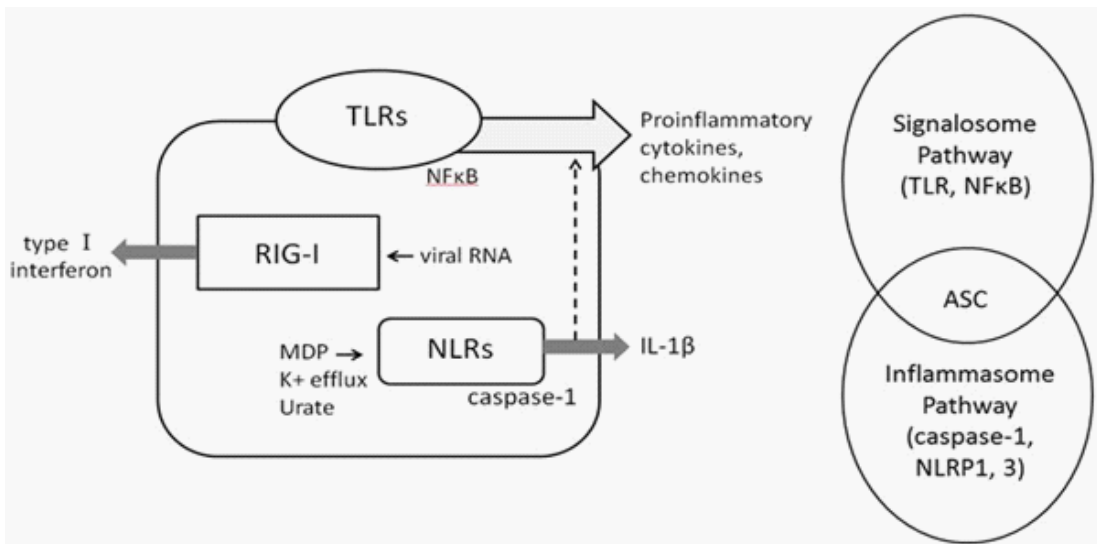


Figure 2: Pattern Recognition Receptors.

INFLAMMASOMES

Small protein molecules, termed type 1 and type 2 Nucleotide-Binding and Oligomerization Domain (**NOD**)-like receptors exist in mammalian cell cytosols. NOD1 and NOD2 are stimulated by a microbial specific structure like Peptidoglycan (**PGN**) that is possessed by bacterial cell wall, but is not present on human cell components. Both promote secretion of inflammatory cytokines via a mitogen-activated protein kinase and NFκB. NLRs are activated when microbes are phagocytosed, when a pore is formed on the host cell membrane along with potassium efflux or Adenosine Triphosphate (**ATP**) influx, or when NLRs contact other host-derived special molecules like Damage-Associated Molecular Patterns (**DAMPs**). Stimuli on NLR by particular small molecule structures initiate a cluster of NLRs conformation change, which triggers a cascade reaction for NLR complex formation. In order to respond to escaping microbes from TLR surveillance, perhaps it may be the first-lined mucosal barriers, this NLR system may be important to recognize them as an alternative probe. Special molecules, such as ATP released from host cells when tissue is damaged by anoxia, mitochondrial dysfunction, or chemicals including uric acid crystals, may trigger an analogous cascade of the NLR system. PAMPs or DAMPs molecules may result in IL-1β and IL-18 extracellular secretion via caspase-1 dependent cleavage cycles and via Caspase Activation and Recruiting Domain (**CARD**) oligomerization.

Inflammasomes consist of a recognizing protein, an adaptor protein, and a catalytic domain called caspase 1 (Figure 3). Different types of NLRs are known to recognize unique molecular patterns. Particularly, Nucleotide-Binding Domain and Leucine-Rich Repeat-Containing (**NLRP**) 3 is the best investigated NLR family and is capable of recognize various molecules. NLRP3 consists

of a leucine-rich repeat domain of N-terminal of NOD and PYD that is further attached to ASC in use of PYD each other. ASC is assembled with procaspase-1, which further unites to form multiple structures. Thus, after NLR proteins detect such specific small molecules, adjacent NLR proteins begin polymerization themselves, all of which constitutes inflammasome (Figure 3).

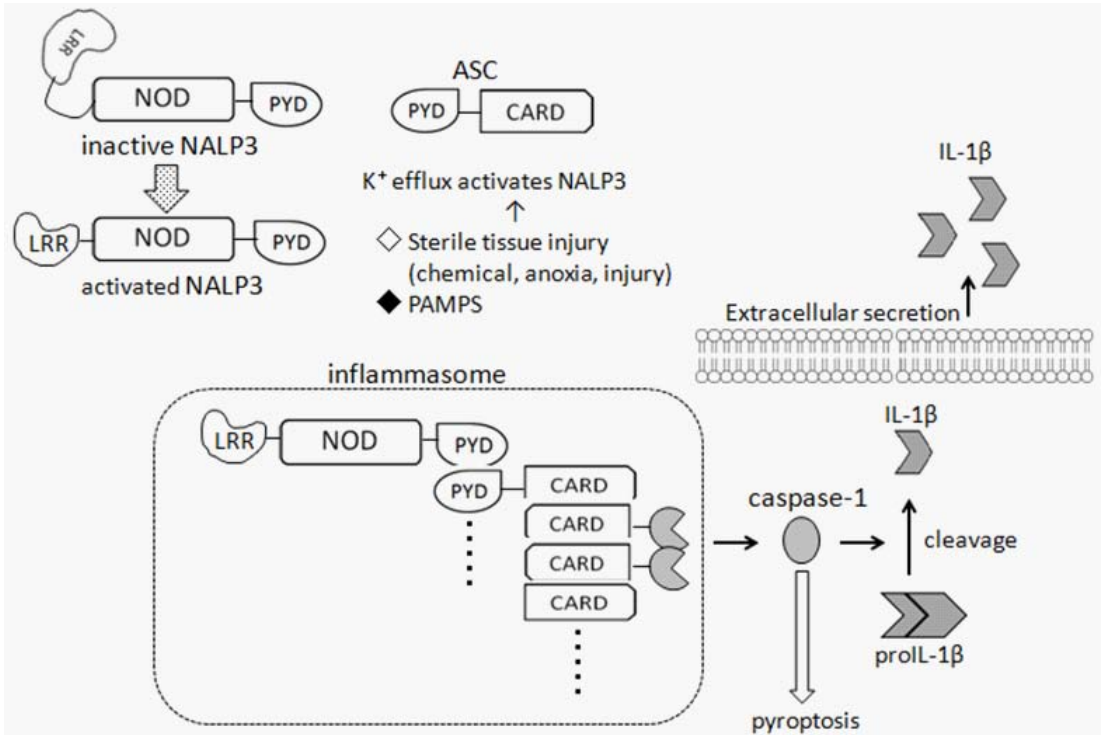


Figure 3: Molecular components of NLRP3.

NLRP3 is activated by stimulants such as Muramyl Dipeptide (**MDP**), ATP derived from dead cells, uric acid crystals, cathepsin B, K efflux due to pore-formation toxin (bacterial type III secretory system), and thioredoxin protein that is activated by mitochondrial superoxide (Table 2).

Table 2: Molecular stimulants of NOD-like receptors, AIM2, and RIG-I.

NLRP1B	NLRP3 (=NALP3, cryopyrin)	NLRC4	Naip5	NLRP7	RIG-I	AIM2
MDP anthrax toxin	K ⁺ efflux MDP microbial DNA ATP uric acid cathepsin B neigericin Al OH silica as best	flagerin Salmonella typhimurium Listeria monocytogenes type III, IV secretion (T3SS, T4SS) rod protein	legionella flagerin	mycobacterium lipopeptide	viral dsRNA	dsDNA Francisella tularensis

Moreover, NLRP3 has been reported to respond specifically to phagocytosed gram-positive pathogens, e.g. Staphylococci and *Listeria* spp., or to the influenza virus. While NOD1 and NOD2 receptors are likely to respond to particular small molecules on bacteria, NLRP3 is stimulated not only by pathogen-specific molecules, but also by host-derived molecules and environmental chemicals. NLRP3 then quickly polymerizes and secretes IL-1 β and IL-18.

Chemicals including silica crystals, asbestos, aluminum salts [13], and β amyloid [14] may be phagocytosed by macrophages, which cause lysosome injury that promotes cathepsin B release. Such stimuli also induce NLRP3 activation, thereby stimulating cells to secrete IL-1 β and IL-18 (Figure 3). This process can lead to lung fibrosis owing to silica or asbestos, and Alzheimer's disease due to β -amyloid deposition.

STERILE TISSUE DAMAGE ALSO INITIATES INNATE INFLAMMATION SIMILAR TO INFECTION

Tissue damage caused by post-traumatic injury, burn, anoxia, and chemical exposure etc., release several particular molecules from damaged host tissues. Such molecules include various proteases, Heat Shock Proteins (**HSP**), fibrinogen, hyaluronic acid, and High Mobility Group Box (**HMGB**)-1 (see terminologies' section). HMGB-1 is reported to be a useful biomarker that may indicate the degree of organ damage and hence host prognosis during sepsis [15,16].

Although the etiology is not the same between virulent infectious pathogens and sterile tissue damage, both initiate host inflammatory responses through innate immune systems (Figure 3). Although bacterial pneumonia and urinary tract infection are major clinical etiologies that cause septicemia, aseptic lung tissue injury also induces SIRS, which may promote life-threatening disease condition [17-19]. Inflammasome has recently been investigated for its potential as a target for the treatment of inflammatory diseases, especially to treat septicemia and other chronic inflammatory disorders [19]. Inflammasome is localized intracellularly, sensing particular PAMPs and DAMPs, then promoting caspase-1 cleavage and IL-1 β extracellular secretion. Thus, this system is also postulated as an alert system when the host encounters biological risk factors, thereby reported as it is basically inevitable function for protection from microorganisms [20] or with recovering from tissue injury such as trauma or burn [21,22].

TLR activation induces NLR polymerization, as observed with aseptic tissue damage, which then enhances TLR expression. Thus, PRR systems are noted as efficient alarm networks that may respond rapidly and synergistically to augment signals in order to protect the host from various risks such as tissue injury, infection, and other chemical contamination.

TERMINOLOGY RELATED TO THIS CHAPTER

PAMPs

Various microorganisms such as viruses, bacteria, and fungi possess a restricted pattern of unique molecules that do not exist in vertebrate cells. Most of these molecules have recently been

termed as Pathogen-Associated Molecular Patterns (**PAMPs**). In regards with that such molecular patterns are also exists in our commensal bacteria, PAMPs should not strictly be defined within only “pathogenic” microorganisms [11]. PAMPs are recognized with PRR domain that exists in particular molecules such as TLR and NLR (Table 1 and Figure 2,3).

DAMPS

Damaged cell (danger) Associated Molecular Patterns (**DAMPs**) released from cells cause necrosis. Stress proteins, mitochondrial DNA, HMGB-1, mono sodium urate, ATP, ROS, histone, and potassium efflux are considered as DAMPs.

HMGB-1

High mobility group box-1 is a protein that is normally retained within the nucleus of cell to stabilize chromatin and help transcriptional factors bind to DNA. It is released in the late inflammatory phase by various cell stresses including infection, anoxia, and trauma. When released from the cells, it may become bound to Receptors For Advanced Glycation End products (**RAGE**), CD24, and TLR2,4 thereafter activating immune cells via NF κ B for TNF- α and IL-6 promotion. It enhances expression of vascular endothelial ICAM-1, VCAM-1, and RAGE, and induces extra-vascular release of neutrophils and lymphocytes.

Signalosomes

To aid the understanding molecular biological complexity, signalosome was conventionally termed for such pathogen-dependent innate inflammatory responses initiated by PAMPs via TLRs-dominant and NF κ B-dependent pathways that are contrasting to inflammasomes [11]. However, this terminology is somewhat confusing because most septic inflammatory cascades include inflammasome run while using numerous signals [11]. It may be useful to realize this terminology as an early pathogen-dependent inflammatory cascade directed for the pathogen elimination. Clinically, the host response to this pathway may lead to a febrile transient symptomatic period, and then confer remission with acquisition of immunity.

Inflammasomes

As mentioned above, NLR family-mediated host responses are considered to be an alarm system against infection and other risks such as sterile injury compared with TLR-dominated signalosomes. In practice, both signalosomes and inflammasomes may work together in certain balances. As with other pro-and anti-inflammatory mediators, inflammasome itself may be strictly regulated to maintain, for instance, mucosal commensal flora of the intestine; however, in certain pathological situations, it promotes intractable chronic inflammatory diseases such as Crohn’s disease CINCA, or rheumatoid arthritis. According to medical case reports, NLR family or IL-1 β -dependent chronic febrile symptoms could be treatable by using a blocking strategy for inflammasome or IL-1 β [23,24] (Table 3).

Table 3: Chemical agents and drugs modifying inflammation.

Category of target	Target	Role on target	Drugs or Chemicals	Human study	On animal trial	Reference	Report
	LPS TLR4	LPS neutralization	E5556 TAK242 GR-270773				
	CD14 NF κ B						
	TNF α MIF		AZD9773 a felimomab CytoFab	Improve survival decreased TNF and IL-6		Panacek et al Rice et al	2004 2006
	HMGB1 RAGE IL-1 β IL-18	mimicking IL-1Ra mAb anti-IL-1 β IL-1 trap	Anakinra Canakinumab Rilonacept				
Inflammasome	NLRP3 P2X7R	agonist antagonists	AcALY18 AZD9056 CE224, 535 EVT-401 GSK1482160			Thacker et al	2012
Oxidant	ROS	antioxidant	N-aceryl cistein	Reducing IL-8, Improving liver blood flow		Peterson et al	2003

ASC

Apoptosis-associated speck-like protein containing a caspase Activation and Recruiting Domain (**ASC**) facilitates inflammasome assembly which may trigger caspase-1 activation and IL-1 β processing. ASC may also regulate the NF κ B pathway. Thus, it may link the pathogen-driven signalosomes and inflammasomes (Scheme 3).

AIM2

Absent in melanoma 2 is a protein that consists of an N-terminal pyrin domain and a C-terminal oligonucleotide binding domain. The C-terminal domain senses the double stranded (**ds**) DNA of either bacterial or host origin that leads to the oligomerization of the inflammasome complex. AIM2 interacts with ASC to activate caspase-1. This molecule is reported to detect the dsDNA of *F. tularensis*, the vaccinia virus, and the cytomegalo virus.

CARD

Caspase activating and recruiting domain is an interaction motif protein involved in inflammatory and apoptotic processes. It mediates multiple larger protein complex formation through mutual interaction between CARDS; hence its function is also crucial in inflammasome formation.

CAPS

Cryopyrin-associated periodic syndrome comprises a category of autoinflammatory syndromes, including Familial Cold Autoinflammatory Syndrome (**FCAS**), Muckle-Wells syndrome, and Neonatal-Onset Multisystem Inflammatory Disease (**NOMID**, or Chronic Infantile Neurological, Cutaneous and Articular Syndrome: **CINCA**). These syndromes are related to the genetic abnormality of the cryopyrin (**NLRP3**) gene and its manifested disorder of IL-1 β production.

Type III Secretion System (T3SS)

Gram-negative bacterium, such as *Shigella*, *Salmonella*, and *E. coli*, harbor a needle-like protein termed T3SS, which is structurally similar to flagella. Although the needle complex was originally identified in *Salmonella typhimurium*, it has been subsequently detected in several other bacteria and it is therefore believed to be a core component of all T3SSs. It is composed of a multi-ring base, which anchors the structure to the bacterial envelope, and a needle-like projection that protrudes several nanometers from the bacterial surface. T3SS is important for the pathogenicity of GNRs, hence a loss of T3SS renders a bacteria a virulent.

RIG-I

Retinoic acid inducible gene, melanoma-differentiation-associated gene, and LGP2 are homologous molecules that consist of two CARD regions, an RNA helicase region, and regulatory domains. RIG-I senses viral dsRNA, and then activates itself by a conformation change involving the CARD domain when this molecule encounters viral dsDNAs.

ROS

Reactive oxygen species is important in cell physiology as messengers for growth factors and endocrine peptides. ROS is also crucial for intracellular killing against viruses and other invading microbes.

SEPSIS AND COAGULATION SYSTEM

Inflammatory reaction to tissue injury accompanied with sepsis manifests as microvascular flow impairment, mitochondrial dysfunction in relation with excessive ROS production, and glutathione depletion [18]. Such conditions exacerbate tissue injury and thereby activate the clotting system, which promotes further detrimental inflammation. Activated Protein C (**APC**), an endogenous anticoagulant, also has anti-inflammatory functions. In turn, sepsis consumes endogenous APC. Septicemia often causes actual hemodynamic and coagulation disorders and anoxic tissue damage, which engages multi-organ dysfunction hence require intensive care when it becomes severe disease course [25]. Disseminated Intravascular Coagulation (**DIC**) is a secondary manifestation of hemostatic activation in various disease conditions [25]. Most of the septic DIC cases are derived from the accessory effect of locally or systemically augmented inflammatory responses; hence sepsis may require anti-coagulant therapy in certain conditions with critical consideration of the timing, dosage, and duration of the treatment [26].

SEPSIS AND ANTIBIOTICS CONSUMPTION

In an animal study, antibiotic-treated mice succumbed rapidly to a sepsis-like death. Such morbidity was critically associated with the systemic presence of multi-drug resistant *E. coli* that possesses a type III secretion system and this type III secretion system is one of distinct molecules that stimulate inflammasome [9]. This animal study also found that septic pathogenesis required

activation of the Naip5-Nlrc4 inflammasome and concluded that disrupted intestinal homeostasis by intensive combined antibiotic exposure could result in aberrant pathobiont-induced innate immune signaling, resulting in rapid sepsis-like death.

ANTI-INFLAMMATORY TREATMENTS

Immunomodulatory agents have also been tested to improve mortality, otherwise potentially fatal septic disease conditions, among several investigations that treating sepsis in both sides of human and animals [4]. Until the early 2000s, several clinical trials were conducted appeared to block IL-1 β or TNF α , because they are key inflammatory agents that dictate sepsis prognosis [2]. Alternative studies were also performed using on-going anticoagulant, steroid, and elastase inhibitor in practice and C5a, with much interest for research scope.

As several inflammatory mediators are described with molecular biology above, some of them are further candidates for anti-inflammatory therapeutic target. This is because such critical inflammatory mediators drive septic disease progression with their own multiple positive feedback, then results in overlapping signal cascades derived of systemic damage, regardless of infectious or sterile stress triggers. It should be noted that although sepsis may occur similarly due to several microorganisms, individual inflammatory characteristics or differentiation may not be the same. One treatment of anti-inflammatory therapy can cause adverse effect that make host vulnerable to certain infectious organisms. For example, anti-TNF α therapy is considered to have a high risk of lung infection with *S. pneumoniae* and *M. tuberculosis*. Instead, same treatment, of TNF-inhibitors improved disease severity although despite of several clinical trials, this agent did not reach to any improvement for survival outcomes [2].

SUMMARY AND PERSPECTIVES

The mediators of sepsis described in this review are now considered as significant determinants in septic host disease progression. Indeed, in clinical microbiology, particular microbiological products, including LPS, toxins, and the type III secretion system, may be critical to the understanding of associated infectious disease onset and severity. In septic conditions, PAMPs and DAMPs initiate PRR-dependent signals and mediator cascade, which may dictate disease progression.

Anti-inflammasome therapy has been studied, but the efficacy of current trials is limited to a few disease categories (eg rheumatoid arthritis), and cryopyrin-associated periodic syndrome, a pathological autoimmune syndrome [27]. Although human trials to treat sepsis have been conducted for long periods targeting several key mediators, the reseems to have been little significant improvement with regard to survival in septic conditions. Rather practically, the use of antimicrobial agents against infective pathogens, corticosteroids when necessary and anti-coagulant drugs are the only available requirement with much priority during severe septic conditions. However, in certain host conditions under septicemia or SIRS, it might become of

promising strategy if using such anti-inflammatory agents in a “proper timing”, “adjusted choice and tailored” for “host condition” that remain investigated.

Sepsis progresses in a highly time-sensitive way and host inflammatory responses are variable in each individual. It is believed that critical target mediators such as TNF α should be blocked with accurate and appropriate timing [21]. Tailoring such as targeting a key mediator, focusing an organ, and adjusting doses and timing are common conundrums in medical research of sepsis. The source and virulence of causative microbial pathogens varies even in the same species. Even a healthy individual can have varying susceptibility. Such multiple factors make a clinical trial of these anti-inflammatory therapeutic treatments for sepsis quite difficult. Several clinical and animal model studies have made great advances in our current understanding of septic abnormality and pathobiology in the host following infection and injury. The current animal sepsis model in use of cecal ligation, the most reliable approach for studying sepsis, provided abundant molecular knowledge about septic inflammatory cascades. However it does not directly reflect human sepsis as the model has several different aspects, for one example, majority of clinical sepsis arises from pneumonia [2].

In practice, for example, anti-IL-1 β treatment was proven as a therapeutic strategy in CINCA and rheumatoid arthritis [27]. It has also been shown that gout and metabolic disorder can be treated with logically analogous blocking of inflammasome cascades. One of potent chemicals to block inflammasome, such as flavonoids, reduced overwhelming ROS production, which could exaggerate hyper inflammasome activation, and its cytotoxicity in anti-cancer drug-induced hyper inflammatory response. It appears that such particular molecular agents are host-protective against hyper inflammatory conditions, but they have limited effects on improving the survival of patients with sepsis.

To investigate further mechanisms of human sepsis, inflammatory differentiation involving several molecular agents should be organized according to their cascades on a time axis, realize each mediator could work differently in its amount, in interaction with other mediators, in different timing and different organ. Modulating inflammatory agents is nevertheless an attractive therapeutic possibility for sepsis. Anti-inflammasome treatments are already available and have been proven to be effective in human chronic inflammatory diseases other than sepsis. Each agent could be a functional therapeutic target if its role was recognized more precisely according to individual conditions in tailored approaches.

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