To Explore Sepsis, We Need New Thought

Lei Li, Guie Liu and Qing Ouyang

Abstract Sepsis is a life-threatening condition initiated by invasion of pathogenic microorganism. In essence, it refers to the excessive inflammatory response induced by various harmful stimulating factors after infection. Numerous sepsis-related factors, like triggers, involved cells and receptors, signaling pathways and secreted products by immune or inflammatory cells, form a complex network, confusing and frustrating current researchers. For this reason, we need a new way of thinking and the term-*inflammationomics* might be an idea.

Keywords Inflammatory response · Inflammatory cells · Inflammationomics

Sepsis, in essence, refers to the inflammatory damage caused by excessive stimulation of various harmful stimulating factors on the body. Since 1991 when the modern concept of sepsis was proposed, its definition has been constantly revised, with both the connotation and denotation. The treatment strategies and techniques are improved as well. However, it is a pity that up to now sepsis-induced mortality rate has not been reduced significantly [1, 2]. The development law of medical science tells us that the establishment of an ideal treatment depends on the full understanding of the pathogenesis of a disease. It is obvious that for sepsis, there are still many unknowns that need to be explored.

1 Diversity of the Triggers for Sepsis

The main stimuli to sepsis response on body are harmful pathogenic bacteria. In addition, fungi, viruses and parasites also can invoke sepsis, and even some normally harmless bacteria in some cases can induce sepsis as well. In fact, the stimulus for the

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X. Fu and L. Liu (eds.), *Advanced Trauma and Surgery*,
DOI 10.1007/978-981-10-2425-2_17

occurrence and development of sepsis is not limited to pathogenic microorganisms [3]. The broken and necrotic cells, cell metabolites such as high uric acid, and even the disorder of electrolyte balance can induce or aggravate the inflammatory response of the body and eventually lead to severe inflammatory damage [4]. The stimuli to the occurrence and development of sepsis are complex and varied. Therefore, it is hard to improve the therapeutic effects of sepsis by only blocking one or two stimuli [5].

2 Variety of Cells Involved in Sepsis

For a long time, there has been a misunderstanding that the inflammatory response is only an immune consequence induced by sepsis and those participating in the response are immune cells [6]. In fact, cells involved in the sepsis response are diverse, mainly in two aspects. First, the cell types are varied. Not only the traditional immune cells, such as mononuclear macrophages, lymphocytes and granulocytes directly take part in the inflammatory response, but also some somatic cells such as endothelial cells, liver cells, etc., are involved in the synthesis and release of inflammatory mediators. Second, the immune cells in the inflammatory response themselves have subsets or varied polarity. Usually, they participate in the inflammatory response in the form of subsets or with different polarity, either accelerating, or maintaining, or restraining the inflammatory response [7, 8]. The most typical ones are ratio of CD4/CD8 and the shifts of Th1/Th2 subsets [9]. Recently, even the macrophages have been found to have obvious polarity and subsets, which takes major role to balance the inflammatory response stimulated by harmful factors. Therefore, it is not enough to achieve effective treatment for sepsis only by regulating a certain cell, which is no doubt like a drop in the bucket. In recent years, some articles report relatively ideal therapeutic results of severe sepsis from animal experiments by stem cells injection. However, whether the stem cells are effective for human body is still unclear and needs to be tested and verified [10].

3 Intricacy of Receptor Signal Pathways in Sepsis-Related Inflammation

Various harmful factors are likely to be the activating factors of sepsis [11, 12]. The recognition of harmful factors by pattern recognition receptor is the key link in the initiation of sepsis. Besides, the most important event that induces the inflammation shifting toward to sepsis is out of control of the dynamic network balance of the protein signaling pathways of inflammation-related receptors [13]. The intricacy is expressed in at least three aspects: First is the intricacy of receptor locations. That

is, the receptor can be at the cell membrane, in the cytoplasm or in the nucleus, and even outside the cell, there are soluble receptors with negative regulatory role. Second is the diversity of receptor functions: accelerating or inhibiting the inflammatory response. Third is the diversity of reaction ways: direct activation or direct inhibition of inflammatory response; acceleration effect of positive feedback, or speed limit effect of negative feedback. This vast network balance is to maintain the balanced development of the inflammatory response. Otherwise, if it is out of control, the whole body will face a catastrophe [14].

4 Complexity of the Metabolites of Sepsis-Related Inflammation

Once the sepsis has been initiated, the outbreak release of various inflammatory mediators claims major responsibility for the development of sepsis, which eventually induces multiple organ failure and leads to death [15]. Inflammatory mediators, according to their functions, can be divided into pro-inflammatory factors which promote the development of inflammation and anti-inflammatory factors which suppress inflammatory response (immunoparalysis) [16]. They can be also divided into vasoconstriction promotion factors and capillaries dilation inducing factors which cause the outleakage of blood constituent; or blood coagulation promotion factors which accelerate thrombotic formation and overactive fibrinolysis inducing factors. According to their own physicochemical properties, inflammatory factors can be divided into proteins, lipids, polysaccharides, and even electrolytes which may involve in the development of sepsis [17]. Various mediators combine as a huge network and interact with each other as both cause and effect. Through this way, they together regulate the occurrence, development and final results of sepsis. Therefore, it is meaningless to control septic inflammatory by blocking the release of inflammatory mediators [18, 19]. As mentioned above, the pathophysiologic process of sepsis is very complex, so single and linear thinking mode is no longer suitable for sepsis study. The implementation of human genome project is prominent not only because it is a landmark for the human to fully understand themselves, but also because it provides a new mode of thinking. Especially with the development of chip technology and the arrival of the big data era, the concept of "-omics" provides us with a new thinking way in the face of complex pathophysiologic status of diseases. We used DNA chip technology to carry out a large scale of detection, analysis and comparison of gene expression, which brought the birth of genomics. In the same thinking way we proposed proteomics, which means we analyze and compare the expressions, functions and interactions among a family of proteins for one type of cells or tissues.

Correspondingly the concepts of enzymeomics and metabonomics are put forwarded. Therefore, it is necessary to set up a thinking mode of "-omics" in inflammation study, namely inflammationomics, which carries out systematic research on the occurrence, development and regulation of inflammatory diseases. As for sepsis response, when the body is exposed to a variety of harmful stimuli, inflammatory reaction cell receptors on the membrane and plasma are rapidly activated, and all the related inflammatory signal protein networks are aroused sequentially, which leads to a cascade amplification and activation of a series of inflammation mediators. Centralized release of abundant inflammation mediators is completed in a very short time, just like waterfall. Corresponding negative regulation pathways and proteins are also rapidly activated. A large amount of anti-inflammatory mediators, especially those inhibiting body's immune defense functions, are synthesized and released to achieve a new dynamic balance. When the dynamic response is in control and reduces normally, the patient's condition is improved. On the contrary, if the dynamic balance gets out of the control and goes to the extreme, the disease tends to deteriorate and eventually leads to death.

5 Puzzle in the Treatment of Sepsis

There are so many reports declaring that they could effectively prevent the occurrence and development of sepsis, even significantly reduce the mortality rate of severe sepsis recently. However, the common sense suggested that the more the treatment methods, the less the therapeutic effects. As the four aspects mentioned above, our limited understanding of the mechanism of sepsis seriously restrict us to produce accurately assessment about the pathophysiological state of sepsis patients. In addition, the current deficient detection techniques also limit the accurate estimation of immune status on sepsis patients.

Though the mechanism of the occurrence and development of sepsis remains unclear, it may be an ideal strategy for sepsis treatment that we speculate sepsis patient's immune function condition based on some existing immunological or inflammatory indicators and then carry out targeted therapy. Unfortunately, there are at least three shortcomings we have to face right now, real time, specificity and dynamics.

For real time, it means that these techniques can immediately reflect the patient's condition. Regrettably, some significant data reach physician' hand after 12 or even 24 h, even more due to the obligatory process of collecting samples, sending for clinical laboratory, machine testing and analyzing, etc. It is well known that the condition of sepsis patient changes rapidly within 3–5 days after trauma, and therefore, the delayed parameters can hardly reflect the real state of the patient.

For specificity, actually every detected indicator has its own limitation. TNF-alpha, whose original biological significance is in the killing effect of tumor cells and promotion of cell apoptosis, has a raised expression early and reach to its peak at around 2 h after severe trauma. Normally speaking, the more severe the trauma is, the higher level TNF-alpha will reach. But for some very severe trauma, TNF-alpha may do not show any increase respond and go to profoundly decrease directly. Theoretically, the Gram-negative bacteria may stimulate the expression of TLR4. In fact, there are a variety of negative feedback signal pathways which could inhibit the elevated expression of TLR4, therefore, TLR4 often are present in an abnormal low level. Actually, the number of cytokines involved in trauma or sepsis is large. That is how the term "cytokines storm" derived. To determine the patient's status simply through the level of several cytokines is far from enough and may have the adverse effect of overgeneralization, which is no doubt like the Chinese proverbial the blind men and the elephant. Apparently, the more specific parameters related to the pathophysiological status of sepsis patient are emergent needed, in spite of there are long way to go.

For dynamics, immunological parameters change with human biological circadian in one day even under normal physiological state. Definitely, this change becomes even intense after trauma, especially at the early stage. Hence, the routine daily monitoring can not reflect the true condition of the patient. Therefore, instantaneous, dynamic and sequential monitoring, especially at the early period of trauma sepsis, should be paid particular attention.

In fact, pathogenic microorganisms are the key stimuli triggering sepsis inflammatory reaction. Broken tissues and necrotic cells, electrolyte balance disorder, and some noninfectious harmful stimuli promote the development of sepsis. Receptors recognizing various noxious stimuli exist not only on the cell membrane, but also in the cytoplasmor even outside the cell. Inflammation factors are usually proteins, but some nonproteins like lipid, reactive oxygen species (ROS) also directly participate in the development of inflammation. Therefore, it is necessary to study thewhole process of inflammatory systematically and comprehensively. The authors think that the so-called inflammatoryomics means that inflammation study, based on functional proteomics, should focus on inflammation-related genome and proteome, meanwhile combine the nonproteins involved in the inflammatory reaction to reveal the dynamic changes and interactions among the abovementioned substances and systematically explain the pathophysiologic process of the occurrence and development of inflammation. Inflammatoryomics provides a foundation for human intervention and reasonable regulation of various inflammatory diseases. All in all, we would like to summarize Inflammatoryomics as the following diagram (Fig. 1).

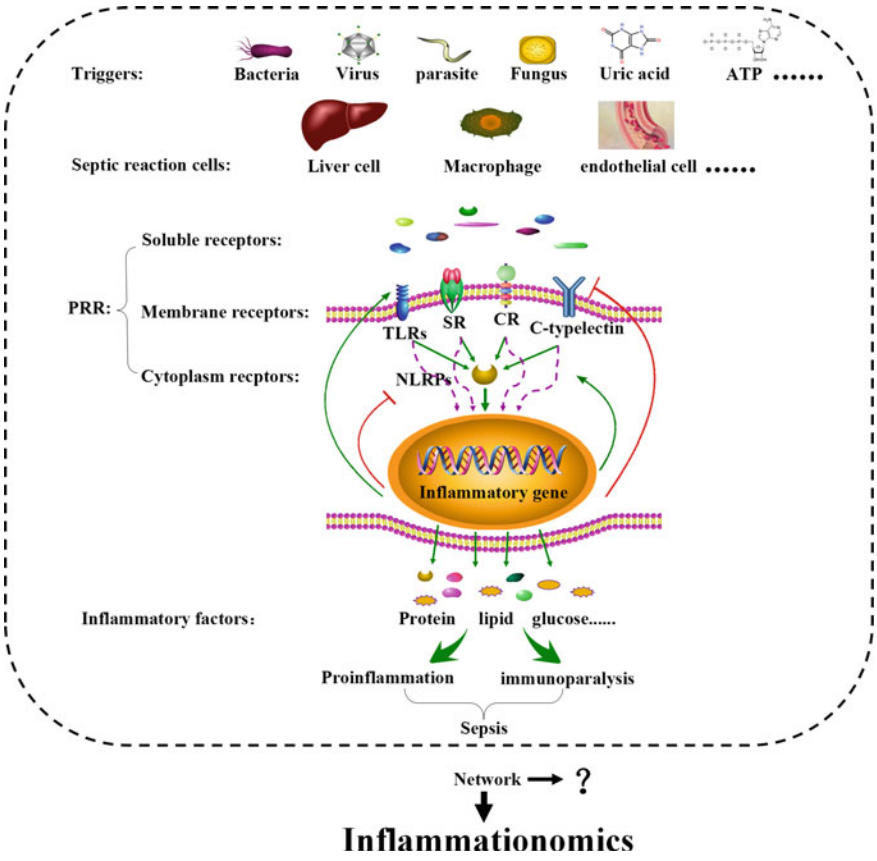

Fig. 1 Normally, sepsis is triggered by infection, however besides the microorganism, many harmful factors, such as necrotic cells, adenosine triphosphate, etc. also take part in the process of the excessive inflammatory response after infection and tissue injury. Not only the immune cells, such as macrophages, DC cells, but some other cells like liver cells, endothelial cells, etc., play important roles during sepsis as well. The pattern recognition receptors involved in sepsis cover extracellular proteins, transmembrane proteins, cytoplasma proteins, even nuclear proteins. These proteins constitute a complex signaling pathway network to regulate or balance the septic response. After being stimulated, the septic cells deliver overwhelmed inflammatory cytokines or factors that cause organ dysfunction and other severe inflammatory damage. Faced with such a crisis, a simple ordinary way of thinking may need to be replaced by "**omics**" idea

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