

Negative Regulators of the Host Response in Sepsis

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Abstract: The inflammatory response of the innate immune system to invading pathogen is complex and requires precise regulation in order to eradicate the organism while protecting the surrounding host tissues. Two main signal transduction pathways, the NF- κ B and mitogen activated protein kinase (MAPK) pathways, are activated by the invading pathogens requiring a set of negative regulatory processes once the pathogen is eradicated. In this review we focus on three key negative regulatory processes: intracellular inhibitors, regulatory phosphatases and epigenetic mechanisms.

Keywords: Sepsis, signal transduction, phosphatases, epigenetics, microRNA.

INTRODUCTION

Our understanding of the mechanisms involved in sepsis have come a long way since Lewis Thomas first proposed the theory that the clinical manifestations of sepsis, the systemic inflammatory response which is secondary to either documented or clinically evident infection, were caused by the host response to the invading organism [1]. The development of therapeutic agents targeting this host response quickly followed our increased understanding of the mediators involved in the pathophysiology of sepsis. Unfortunately, the clinical trials aimed at modulating the host response in sepsis have generally failed [2], which has refocused efforts on further understanding the regulation of the cellular mechanisms involved in the host's response in order to identify potential therapeutic targets.

The host response in sepsis involves a dysregulation of the inflammatory signaling cascades which leads to an imbalance between pro-inflammatory and anti-inflammatory mediators resulting in an immunologic dissonance [3-7]. This immunologic dissonance is a result of complex interactions of signal transduction pathways triggered by host exposure to pathogen associated molecular patterns (PAMP). These PAMPs bind toll-like receptors (TLR) on the cell surface and utilize a variety of pathways to transmit their signal to the nucleus. The propagation of signals in these pathways rely on interconnected networks of multifunctional, signaling molecules which ultimately elicit a gene expression response that impacts cellular functions [8].

Two primary pathways for signal transduction following TLR activation are the NF- κ B and Mitogen Activated Protein Kinase (MAPK) pathways. Although these two pathways utilize distinct kinases to propagate their signal, common upstream proteins are necessary for the initiation of the intracellular signal following activation of the TLR. TLR

activation begins with the binding of the PAMP to a specific TLR which may be enhanced by adaptor proteins such as MyD88 or TRIF. After PAMP binding with or without adaptor protein assistance, the serine/threonine kinase IL-1R associated kinase (IRAK) is recruited to the TLR-PAMP complex and is phosphorylated. Once phosphorylated IRAK is activated and in turn phosphorylates and activates TNF receptor-associated factor 6 (TRAF6). The activated TRAF6 then becomes a key branch point by activating both the NF- κ B and MAPK pathways, which lead to transcription and translation of the various proteins involved in the host response [9].

Regulation of the host response occurs at all levels of the signal propagation including: receptor expression and PAMP binding, availability and activity of adaptor proteins, activity of upstream kinases (especially IRAK), activity of the kinases involved in the NF- κ B and MAPK pathways as well as the transcription and translation of the response genes. A detailed description of the regulation of all of these steps is beyond the scope of this review. Instead, we will focus on those negative regulators of the signal transduction pathways that have been implicated in sepsis and directly impact inflammatory gene expression with specific emphasis on those regulators that seem to hold promise for developing novel therapeutic strategies. Our focus will include the inducible intracellular inhibitors, the regulatory phosphatases and recent evidence implicating epigenetic regulatory mechanisms which are involved in controlling the host response as they relate to innate immunity.

INDUCIBLE INTRACELLULAR INHIBITORS

Several intracellular inhibitors are involved in the regulation of TLR signaling [10, 11], however only three intracellular inhibitors, IRAK-M, suppressors of cytokine signaling (SOCS) proteins and A20, have been shown to be induced by TLR activation. These three intracellular inhibitors are of special interest in sepsis because they provide negative feedback regulation of the upstream portion of TLR signaling and their loss of function is associated with a dysregulation in the production of host inflammatory mediators.

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IRAK-M is a member of the IRAK family and is predominantly expressed in monocytes and macrophages [12-14]. IRAK^{-/-} mice demonstrate enhanced production of IL-12, IL-6 and TNF- α in response to LPS stimulation [12]. Unlike other members of the IRAK family, IRAK-M has no kinase activity and the exact mechanism by which IRAK-M regulates TLR signaling has not been fully delineated. IRAK-M does not prevent the association of IRAK1 with the TLR complex but may prevent the disassociation of the TLR/IRAK complex to limit activation of TRAF6 [11]. Recent evidence suggests an additional role for IRAK-M which may be to stabilize other negative regulators, specifically the dual specific phosphatase MKP-1, thereby enhancing the down regulation of TLR signaling [15].

IRAK-M's role in the negative feed back loop for TLR signaling is also noted by its requirement for endotoxin tolerance. Macrophages isolated from IRAK-M^{-/-} mice were not tolerized by low dose LPS and had adequate cytokine production upon restimulation with high dose LPS [12]. IRAK-M levels in isolated human monocytes are also rapidly elevated in an *ex vivo* model of endotoxin tolerance following the restimulation dose of LPS [16]. Monocytes isolated from septic patients or patients receiving an intravenous endotoxin challenge also exhibit high levels of IRAK-M and decreased cytokine production to *ex vivo* LPS stimulation [16, 17]. Thus, IRAK-M appears to be a key member of the endogenous system aimed at regulating PAMP-triggered inflammation.

A second inducible inhibitor of TLR signaling is the family of SOCS proteins. Eight SOCS proteins have been identified each being induced by a variety of cytokines as well as PAMPS (e.g. LPS) [18]. SOCS negatively regulate TLR signaling by functioning as an E3 ubiquitin ligase to promote the degradation of proteins involved in or by directly inhibiting kinases within the signaling pathways [18]. As it relates to TLR signaling SOCS 1 is the best studied proteins in this class.

SOCS 1^{-/-} mice are hyper-responsive to LPS challenge resulting in increased serum levels of TNF- α as well as increased mortality [19, 20]. Macrophages isolated from these mice show impairment of endotoxin tolerance related to an increased activation of both p38 and JNK [19, 20]. The SOCS 1^{-/-} macrophages also show increased TNF- α , IL-12 and NO production following LPS stimulation when compared to WT macrophages [18]. Similar to IRAK-M, these data support the role of SOCS 1 as a negative regulator of TLR signaling pathways.

A20 is a third inducible enzyme that appears to regulate the host response by providing a negative feedback loop for NF- κ B activation [21]. NF- κ B activation leads to the induction of A20 and once expressed, it can negatively regulate ongoing NF- κ B expression [22]. This regulation of NF- κ B by A20 occurs through a unique ubiquitin-editing function in which A20 has both peptidase and ligase activity [23]. A20^{-/-} mice show enhanced inflammatory response and sustained NF- κ B activity in response to TNF- α [24] as well as the requirement of A20 for the termination of TLR signaling [25]. Together, these observations suggest inducible, negative regulators of cytokines could be targeted for subsequent drug development.

PHOSPHATASES AS REGULATORS

In addition to the induction of intracellular proteins following TLR activation, several phosphatases are activated, which also negatively regulate the host response. Phosphatases act by removing a phosphate group from serine, threonine or tyrosine residues reducing the activity of the target enzyme. The kinases involved in the inflammatory pathways, NF- κ B and MAPK, are activated through phosphorylation by upstream kinases and are thus prime targets for phosphatase regulation.

Phosphatases are divided into two major classes based on the amino acid residues they dephosphorylate with several families in each class (Table 1). Two families of phosphatases, the serine/threonine phosphatase and the dual specific phosphatases, appear important in the regulation of the host response.

Protein Serine/Threonine Phosphatases

Nearly 30 catalytic subunits of the protein serine/threonine phosphatases have been identified based on their amino acid sequence of the catalytic subunit [26]. The serine/threonine phosphatase, protein phosphatase 2A (PP2A), is one of the more important regulators of the host inflammatory response.

PP2A has many roles in the regulation of cellular processes but its regulation of the NF- κ B and MAP kinase signaling pathways is important for limiting the host response. The role of PP2A as a regulator of the NF- κ B pathway is well established. Initially, data using purified proteins suggested that PP2A negatively regulated I kappa kinase (IKK), the central kinase in the NF- κ B pathway [27]. However, more recently investigations showed that PP2A forms a stable complex with IKK and that in the settings of PP2A inhibition (with OA or fostriecin), the degradation of I κ B was attenuated thus suggesting PP2A is a positive regulator of the NF- κ B pathway [28].

A broader role for PP2A in regulating the MAPK pathway is also well established. Studies using a human acute monocytic leukemia cell line, THP-1 cells, show that the PP2A co-percipated with JNK. When these cells were treated with the phosphatase inhibitor okadaic acid (OA) JNK kinase activity and AP-1 transcriptional activity increased resulting in increased IL-1 β expression [29]. The regulation of the p38 MAPK pathway by PP2A has also been established [30-33] and this has been shown to involve stabilization of mRNA by altering tristetraprolin (TTP) binding to the 3' untranslated regions of unstable transcripts [33]. Delineating the role of PP2A in regulating the host response *in vivo* is the goal of ongoing studies within our laboratory.

Dual Specific Phosphatases (DUSP)

The dual specific phosphatases (DUSPs) have the unique characteristics of being able to dephosphorylate both phosphothreonine and phosphotyrosine residues. Thirty genes that code for DUSP have been identified in the human genome [34]. A subfamily of the DUSPs, the MAPK Phosphatases (MKPs), are important regulators of the MAPK pathway and are further divided by their subcellular localization (Table 2).

Table 1. Classes of Phosphatases

Serine/Threonine Phosphatases	Tyrosine Phosphatases
<u>PPP Family</u>	<u>Class I cysteine-based PTP</u>
PP1	“Classical” PTPs
PP2A	Receptor-like PTP
PP2B	CD45
PP4	RPTP α Cytosolic PTPs
<u>PPM Family</u>	Nonreceptor PTP
PP2C	SHP-1
	SHP-2
	PTP1B
	Dual-Specificity Phosphatases
	MKP-1
	MKP-2
	MKP-3/Pyst1
	<u>Class II cysteine-based PTP</u>
	Low-Molecular Weight PTP's
	<u>Class III cysteine-based PTP</u>
	CDC25

*Modified from Shanley TP Crit Care Med 2002; 30: S80-S88.

As regulators of the MAP kinase pathways the MKPs add flexibility and specificity to the inflammatory response by 1) having different kinetics of induction of MKPs in response to different stimuli, 2) varying subcellular compartmentalization of the phosphatases and thus the regulatory processes, 3) differentially expressing in various cell types involved in the inflammatory response, and 4) by mediating cross-talk between the different MAPK pathways [35]. To date eleven MKPs have been identified of which three, MKP-1, PAC-1, and MKP-5 have been shown to be key in regulation of the innate immune response.

MKP-1(DUSP-1)

MKP-1 is a 39.5 kDa nuclear phosphatase that predominately dephosphylates p38 and JNK. It has been shown to be a negative regulator of macrophage function in response to LPS, LTA, heat and osmotic shock, ultraviolet radiation and heat-inactivated *S. aureus* [36-41]. Also, recent studies involving MKP-1^{-/-} mice confirmed the negative regulatory role of MKP-1 in animal models of sepsis [41-44]. When compared to WT mice, the MKP-1^{-/-} mice had elevated levels of pro-inflammatory cytokines and increased mortality. MKP-1^{-/-} mice developed septic shock with multi-system organ dysfunction in response to lower doses of LPS when compared to WT mice [41]. In addition, there was an attenuation of IL-10 levels produced in MKP-1^{-/-} mice as well as isolated macrophages [41, 42]. The alteration in

Table 2. Classification of Dual Specific Phosphatases

Subgroup	Phosphatases
Nuclear	MKP-1
	PAC-1
	MKP-2
Cytoplasmic	hVH3
	MKP-3
	MKP-X
	MKP-7
Nuclear and Cytoplasmic	hVH5
	MKP-4
	MKP-5

cytokine response was mediated through the p38 MAPK pathway [36-38, 40-42].

MKP-5 (DUSP-10)

MKP-5 is a 52.6 kDa phosphatase that also primarily dephosphorylates JNK and p38 [45, 46] and has a role in not only regulating the inflammatory host response but may also play a role in connecting the innate and adaptive immune responses [47]. Macrophages from MKP-5^{-/-} mice release more TNF and IL-6 in response to LPS, peptidoglycan and poly I: C [48]. T-cell activation was also increased in MKP-5^{-/-} mice when compared to wild-type animals but the T-cells had reduced proliferation [48]. In addition, MKP-5 regulates INF- γ and IL-4 production by Th1 and Th2 cells [48]. These studies illustrate the importance of MKP-5 in the complex regulation of the interaction between innate and adaptive immunity.

PAC-1 (DUSP-2)

PAC-1 is a 32 kDa phosphatase that is expressed only in hematopoietic cells [49]. Unlike the negative regulatory role of MKP-1 and MKP-5, PAC-1 has a positive regulatory role in the host response [50]. PAC-1^{-/-} macrophages show reduced production of the pro-inflammatory cytokines IL-6, IL-12, IL-1 β and TNF- α [50]. The reduced cytokines are a result of decreased transcription factor activation mediated by JNK/ERK cross-talk [50]. Additional cross-talk between PAC-1 and other DUSPs as a contributing factor for the positive regulation has not been completely addressed [49]. These data indicate a key regulatory role for the DUSPs of the host response following PAMP stimulation.

EPIGENETIC PROCESSES AS REGULATORS

Epigenetics refers to those heritable changes in genomic function that are not passed on through changes in DNA sequences [51]. The role of epigenetic changes in regulating the host response to disease has only recently been investigated. Although the complete regulation processes are not completely understood, several lines of evidence suggest a key role for epigenetic processes. The two epigenetic

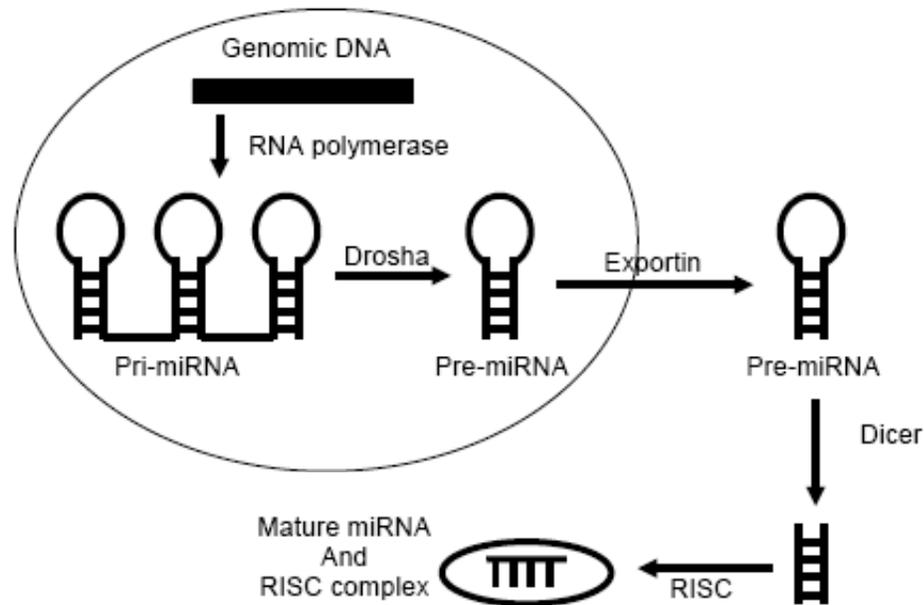


Fig. (1). Processing of miRNA. Primary-microRNA (pri-miRNA) is transcribed from genomic DNA by RNA polymerase. The RNase complex Droscha then cleaves Pri-miRNA to pre-miRNA which is exported from the nucleus by the transport complex Exportin. Once in the cytoplasm pre-miRNA is further processed by the Dicer enzyme complex into mature miRNA and loaded into the RNA-induced silencing complex (RISC) where it combines with target mRNA resulting in degradation or repression of the target mRNA.

mechanisms of regulation that seem important in the host response are histone modifications and microRNA.

Histone Modifications

Epigenetic modifications of chromatin structure play a crucial role in controlling gene expression though the role of these modifications play in regulating the host response in sepsis are just beginning to be investigated. Eukaryotic DNA is wound around an octamer of histone proteins (H2A, H2B, H3, H4), forming a nucleosome and must be unwound to allow transcription to occur. The chromatin remodeling complexes (CRCs) which are recruited to promoter sites by bound transcription factors or modified histones are responsible for unwinding the DNA and exposing promoter sequences [52]. These histone modifications include methylation, phosphorylation and acetylation and have been linked to the regulation of the host inflammatory response [52]. Inhibition of histone deacetylase enzymes results in the reduced production of TNF- α and nitric oxide [53] as well as IL-10 [54] production in response to cellular stimulation. Histone deacetylase inhibitors have also been shown to decrease the activation of macrophages and dendritic cells resulting in an imbalance between Th1 and Th2 cells [55]. Histone methylation is involved in the suppression of cytokine production in endotoxin tolerance [56, 57]. Wen *et al.* showed that histone modifications regulate the dendritic cell production of IL-12 resulting in long-term immunosuppression [58]. Thus several lines of evidence suggest a regulatory role for histone modifications in response to the inflammatory response to pathogens.

microRNA

MicroRNAs are small (approximately 22 nucleotides) strands of RNA that regulate cellular processes at the post-

transcriptional level. They are transcribed from endogenous non-coding regions of the genome into primary-miRNA complexes. Droscha, an RNase, then cleaves the primary-miRNA into shorter stem-loop complexes termed pre-miRNA [59]. Pre-miRNA is transported from the nucleus to the cytoplasm by the transport proteins of the Exportin 5 complex where they are again processed by the Dicer enzyme complex into mature-miRNA [60]. The mature miRNA are loaded into the RNA-induced silencing complex (RISC) [59] where they combine with target mRNA resulting in the degradation or repression of the target mRNA [59] (Fig. 1).

Several microRNAs have recently been shown to not only be induced in response to TLR ligands but also regulate the signal pathways involved in the host inflammatory response. Expression profiling of human monocytes revealed increases in miR-146a/b, miR-132 and miR-155 in response to LPS [61]. Further studies of these three miRNAs indicated that miR-146 negatively regulated the response to LPS through down regulation of IRAK 1 and TRAF 6 [61]. IL-1 β signaling is also negatively regulated by miR-146 regulating the production of both IL-8 and RANTES in lung alveolar epithelial cells [62]. Additionally, miR-155 was also found to be induced by TLR 2, 3, 4 and 9 ligands as well as TNF- α suggesting a broad acting role for miR-155 in the innate inflammatory host response [63]. In a mouse model of sepsis, miR-155 and mir-125b were both induced in response to LPS [64] and studies in transgenic mice lacking functional miR-155 suggest a negative regulatory role for miR-155 in response to LPS [64]. Although the exact mechanisms by which microRNAs regulate the host inflammatory response are not clearly defined, several lines of evidence are establishing their importance as a negative regulatory agent.

SUMMARY

The regulation of the host inflammatory response is complex and occurs at several points along signal transduction pathways. The roles of key endogenous regulators including intracellular inhibitors, the regulatory phosphatases, and epigenetic regulatory mechanisms are just starting to be understood. As our understanding of these regulatory elements increases, new targeted therapies will hopefully improve our ability to manipulate these regulatory processes allowing us to achieve “perfect” balance in the host inflammatory response and ameliorates the organ injury associated with immunologic dissonance

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