Eukaryotic Translation Initiation Factor 5A Small Interference RNA–Liposome Complexes Reduce Inflammation and Increase Survival in Murine Models of Severe Sepsis and Acute Lung Injury

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Background. Many novel therapeutics have failed to reduce all-cause mortality associated with severe sepsis. Eukaryotic translation initiation factor 5A (eIF5A) is a regulator of apoptosis as well as inflammatory cell activation, making it a potential target for sepsis therapy.

Methods. In a murine model of severe sepsis, mice were intraperitoneally challenged with lipopolysaccharide (LPS). Mice were treated both before and after LPS challenge with liposome complexes containing either an eIF5A-specific or control small interference RNA (siRNA), and both survival and serum concentrations of inflammatory cytokines were monitored. The ability of eIF5A siRNA to reduce inflammatory cytokines was also tested in a model of acute lung injury established by intranasal administration of LPS to mice.

Results. There was a statistically significant increase in the rate of survival for mice intraperitoneally challenged with LPS that received eIF5A siRNA, compared with that noted for mice that received control siRNA (71% vs. 5%; \(P < .001\)), as well as a reduction in cytokine expression in serum. Concentrations of proinflammatory cytokines were also reduced in the lung homogenates and serum of mice that were intranasally challenged with LPS and received eIF5A siRNA (\(P \leq .05\)).

Conclusions. eIF5A siRNA-liposome complexes reduced inflammation and contributed to increased survival in a model of severe sepsis, decreased inflammation in a model of acute lung injury, and should be considered for clinical use.

Approximately 900,000 cases of sepsis occur annually in the United States, causing roughly 210,000 deaths and resulting in costs of almost 17 billion dollars [1]. Sepsis is characterized by an initial hyperinflammatory state, which is followed by a hypoinflammatory, immunosuppressive state during which apoptosis occurs [2]. Because of the dearth of therapeutics for sepsis, new strategies and tools are needed for sepsis management.

Polyamines are important mediators of inflammation [3], and studies have indicated that polyamine biosynthesis is increased during sepsis [4, 5]. Although the functions of the up-regulated polyamines during sepsis and inflammation are not clear, we hypothesize that polyamine levels may increase during inflammation to help fuel hypusine biosynthesis, which is a polyamine-dependent reaction. Eukaryotic translation initiation factor 5A (eIF5A) is an abundant, constitutively expressed protein, and it is the only known protein to contain the unique amino acid hypusine.

The hypusine residue is formed posttranslationally in a 2-step process that results in the mature, active form of eIF5A. The first step, catalyzed by deoxyhypusine syn-
phase (DHS), involves the transfer of a butylamine group from the polyamine spermidine to a conserved lysine on eIF5A [6]. The second hydroxylation step, which is mediated by deoxyhypusine hydroxylase (DOHH), results in the formation of the mature hypusine-modified eIF5A [7]. Inhibitors of DHS and DOHH that block the hypusination reaction have been found to have anti-inflammatory properties [8, 9]. eIF5A is widely believed to have a function in regulated mRNA transport [10–12], protein translation [13, 14], and cell proliferation [15–21]. It also appears to be involved in the activation and/or proliferation of T lymphocytes [22] and seems to be required for the maturation and function of dendritic cells [23], thereby suggesting that eIF5A may be an important target in inflammatory diseases.

eIF5A also has an important role in apoptosis [24–26], and small interference RNA (siRNA) targeting eIF5A can protect cells from apoptosis caused by tumor necrosis factor (TNF)–α [24] and genotoxic stress [26], thus making it a potential target for sepsis therapy. Many studies have identified apoptosis, particularly apoptosis of lymphocytes, as a risk factor for death due to sepsis [2, 27, 28]. Recent therapeutic strategies have used siRNA to knock down the genes that are involved in apoptosis and up-regulated during sepsis. For example, Fas ligand and caspases have been targeted in mice with sepsis, resulting in increased survival [29]. To determine whether a reduction in eIF5A expression may have anti-inflammatory effects, an siRNA targeting eIF5A was tested in murine models of severe sepsis and acute lung injury, and the effects on proinflammatory cytokine production and animal survival were monitored.

MATERIALS AND METHODS

Mice
Female C57BL/6 and BALB/c mice (body weight, ≈20 g; Jackson Laboratories) were housed at 68°F–72°F with a 12-h light/dark cycle, fed standard laboratory food and water ad libitum, and kept under specific pathogen-free conditions. The protocols used in the present study were approved by the animal care and use committees of the University of Virginia and the University of Colorado.

Reagents and Drugs
Lipopolysaccharide (Escherichia coli O111:B4) was purchased from Sigma. 1,2-dioleoyl-3-trimethylammonium propane (DOTAP) was obtained from Roche Diagnostics. Ketamine and xylazine were purchased from Vedco. In all cases, the vehicle used was PBS.

siRNA
The siRNAs used in the present study were synthesized by Dharmacon. An siRNA directed against mouse eIF5A (GenBank accession no. NM 181582) suppresses eIF5A expression in the mouse cell line L929 (R. Fayad, G. Fantuzzi, L. L. Reznikov, C. A. Taylor, J. E. Thompson, and C. A. Dinarello, unpublished data). The target sequence for the eIF5A siRNA was 5'-AACGGAATGACTTCCAGCTGA-3'. A search of BLAST (the Basic Local Alignment Search Tool) revealed no mouse transcripts with significant homology to the eIF5A siRNA. A control siRNA with the reverse sequence of the eIF5A-specific siRNA, which does not target eIF5A or any other known mouse gene product, was also synthesized by Dharmacon. The target sequence for the control siRNA was 5'-AAAGTCGACCTTCAAGGCG-3'.

The Severe Sepsis Model: Intraperitoneal Challenge with LPS

Rationale. DOTAP:siRNA complexes delivered by intraperitoneal injection are able to efficiently transfect murine peritoneal macrophages [30, 31], and anti-TNF siRNAs delivered using this method are able to protect mice from LPS-induced septic shock [30]. Interleukin (IL)–1 siRNA delivered in a complex with DOTAP also transfected cultured murine alveolar macrophages and reduced liver-mediated pulmonary inflammation after intraperitoneal delivery [32]. In the present study, the effect of eIF5A siRNA:DOTAP complexes on inflammation was determined in a murine model of sepsis.

Survival. Inoculation of C57BL/6 and BALB/c mice with intraperitoneally administered E. coli O111:B4 LPS (25 mg/kg and 5 mg/kg, respectively) caused death among 95% of controls. Animals received either eIF5A siRNA–(n = 78) or control siRNA-liposome complexes (n = 20). A 50-µg dose of eIF5A siRNA was given intraperitoneally in conjunction with 100 µg of transfection micelle comprising sterile DOTAP at a volume of 1 mL per mouse. The timing of siRNA-liposome complex dosing varied for the subsets of animals tested. To assess differential survival between treatment groups, animals were followed until death, but they were not euthanized unless clearly moribund, and then euthanasia was performed for ethical reasons.

Cytokine quantification after intraperitoneal challenge with LPS. In cytokine quantification experiments, the eIF5A and control siRNA were dosed at t = −48 h and t = −24 h before administration of LPS. Mice were euthanized at 90 min or 8 h after LPS administration, and blood samples were obtained via intracardiac puncture. The timing of sample collection allowed evaluation of early- and late-appearing cytokines. A protein bead–based multiplex immunoassay system (Bio-Rad Laboratories) used flow cytometry technology to quantify serum cytokines. We measured IL-1α and IL-1β, TNF-α, interferon (IFN)–γ, IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, IL-12 p40 and p70, IL-17, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)–1α, and RANTES (regulated on activation, normally T cell expressed and secreted). The selection of these analytes allowed for the evaluation of early- and late-appearing, as well as proinflammatory and anti-inflammatory, cytokines.
Comparison of eIF5A siRNA with dexamethasone. Mice were treated with dexamethasone (10 mg/kg) administered intraperitoneally; 1 h later, they received a nonlethal intraperitoneally administered dose of LPS (3.75 mg/kg). Blood samples were then obtained 90 min later. For comparison, mice were treated intraperitoneally with 50 μg of control or eIF5A siRNA, and, after 24 h, LPS was injected intraperitoneally. Ninety minutes after LPS administration, all mice were euthanized, and blood samples were obtained for measurement of the TNF-α concentration.

The Acute Lung Injury Model: Intranasal Challenge with LPS

Rationale. Intranasal administration of uncomplexed siRNA has been shown to have good uptake in the lung tissue of mice [33, 34], and it has been used as an antiviral agent against respiratory viruses [34]. In the present study, intranasally administered eIF5A siRNA was evaluated for its ability to suppress inflammatory markers in mice challenged with intranasal LPS.

Measurement of inflammation after intranasal challenge with LPS. Once the animals were anesthetized with isoflurane, 50 μL of a solution containing 50 μg of eIF5A or control siRNA was applied to the external nares of C57BL/6 mice until the solution was inhaled. Forty-eight h later, the mice were again anesthetized, and 75 μg of LPS (3.75 mg/kg) was similarly instilled by use of the external nares route. For one experiment, to assess the effect of systemically administered eIF5A on pulmonary inflammation, eIF5A or control siRNA was delivered intraperitoneally before intranasal challenge with LPS. Twenty-four h after LPS challenge, mice were euthanized by inhalation of isoflurane, followed by cervical dislocation, and the lungs and/or blood was removed.

Both lungs were minced and placed in a homogenizer (Tissue-Tearor; BioSpec Products) with 1 mL of ice-cold extraction buffer containing 20 mmol/L HEPES (pH 7.4), 20 mmol/L glyceroephosphate, 20 mmol/L sodium pyrophosphate, 0.2 mmol/L Na3VO4, 2 mmol/L EDTA, 20 mmol/L sodium fluoride, 10 mmol/L benzamidine, 1 mmol/L dithiothreitol, 20 ng/mL leupeptin, 0.4 mmol/L Pefabloc SC, and 0.02% Tween. Lung homogenates were divided into 2 sets of aliquots. One aliquot was incubated at room temperature for 1 h; a second aliquot was incubated with 0.5% (vol/vol) Triton X-100, and all samples were frozen at −70°C.

Myeloperoxidase was measured as described elsewhere [35]. For cytokine assays, the homogenates were thawed at room temperature and then were centrifuged at 14,000 g at 4°C for 15 min. The supernatant was collected, and the protein concentration was determined using the bicinchoninic acid assay (Pierce). Data were expressed as the number of cytokines per milliliter of homogenate or per milligram of protein. Both methods revealed the same differences.

We compared lung concentrations of TNF-α after administration of LPS with or without Triton X-100 extraction, which lyses membranes releasing protein components. The TNF-α concentration was significantly higher when the Triton extrac-
Table 1. Effect of eukaryotic translation initiation factor 5A (eIF5A) on serum cytokine concentrations 90 min after intraperitoneal challenge with lipopolysaccharide (LPS).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>After receipt of eIF5A siRNA</th>
<th>After receipt of control siRNA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1α</td>
<td>457.6 ± 80.7</td>
<td>1024.7 ± 351.8</td>
<td>.1</td>
</tr>
<tr>
<td>IL-1β</td>
<td>970.2 ± 210.5</td>
<td>1001.9 ± 166.2</td>
<td>.2</td>
</tr>
<tr>
<td>IL-2</td>
<td>68.3 ± 10.9</td>
<td>99.3 ± 12.9</td>
<td>.006</td>
</tr>
<tr>
<td>IL-3</td>
<td>37.9 ± 6.3</td>
<td>57.3 ± 2.8</td>
<td>.001</td>
</tr>
<tr>
<td>IL-4</td>
<td>7.8 ± 1.0</td>
<td>12.7 ± 0.7</td>
<td>.001</td>
</tr>
<tr>
<td>IL-5</td>
<td>43.6 ± 6.1</td>
<td>65.4 ± 4.0</td>
<td>.009</td>
</tr>
<tr>
<td>IL-6</td>
<td>306,613.4 ± 180,002.4</td>
<td>2,041,862 ± 809,364.4</td>
<td>.05</td>
</tr>
<tr>
<td>IL-10</td>
<td>708.1 ± 156.8</td>
<td>1001.9 ± 166.6</td>
<td>.2</td>
</tr>
<tr>
<td>IL-12 (p40)</td>
<td>26,429.6 ± 5416.0</td>
<td>96,886.1 ± 19,577.9</td>
<td>.003</td>
</tr>
<tr>
<td>IL-12 (p70)</td>
<td>2410.9 ± 514.4</td>
<td>3906.9 ± 485.5</td>
<td>.05</td>
</tr>
<tr>
<td>IL-17</td>
<td>1029.4 ± 103</td>
<td>1086.4 ± 128.8</td>
<td>.7</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>273.2 ± 59.2</td>
<td>361.4 ± 27.0</td>
<td>.3</td>
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<tr>
<td>GM-CSF</td>
<td>38.9 ± 42.8</td>
<td>541.7 ± 17.6</td>
<td>.004</td>
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<tr>
<td>MIP-1α</td>
<td>5061.5 ± 1416.7</td>
<td>13,577.7 ± 2922.7</td>
<td>.02</td>
</tr>
<tr>
<td>RANTES</td>
<td>1276.7 ± 256.3</td>
<td>4121.9 ± 788.4</td>
<td>.003</td>
</tr>
<tr>
<td>TNF-α</td>
<td>28,111.5 ± 8383.5</td>
<td>23,424.7 ± 351.8</td>
<td>.1</td>
</tr>
</tbody>
</table>

**NOTE.** BALB/c mice were treated with eIF5A small interference (siRNA) 48 and 24 h before challenge with 5 mg/kg LPS. The mice were euthanized 90 min after challenge with LPS for evaluation of serum cytokine concentrations. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normally T cell expressed and secreted; siRNA, small interference RNA; TNF, tumor necrosis factor.

* There were 10 mice per experimental group.

Table 2. Effect of eukaryotic translation initiation factor 5A (eIF5A) on serum cytokine concentrations 8 h after intraperitoneal challenge with lipopolysaccharide (LPS).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>After receipt of eIF5A siRNA</th>
<th>After receipt of control siRNA</th>
<th>P</th>
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<tr>
<td>IL-1α</td>
<td>580.468 ± 67.804</td>
<td>859.7 ± 139.3</td>
<td>.09</td>
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<tr>
<td>IL-1β</td>
<td>1003.4 ± 171.9</td>
<td>1994.3 ± 326.7</td>
<td>.01</td>
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<tr>
<td>IL-2</td>
<td>78.925 ± 11.5</td>
<td>115.429 ± 14.6</td>
<td>.06</td>
</tr>
<tr>
<td>IL-3</td>
<td>48.2 ± 7.8</td>
<td>66.7 ± 8.4</td>
<td>.1</td>
</tr>
<tr>
<td>IL-4</td>
<td>10.6 ± 1.5</td>
<td>12.8 ± 1.3</td>
<td>.3</td>
</tr>
<tr>
<td>IL-5</td>
<td>82.972 ± 18.6</td>
<td>87.8 ± 14.0</td>
<td>.8</td>
</tr>
<tr>
<td>IL-6</td>
<td>246,353.5 ± 119,250.6</td>
<td>674,670.4 ± 20,9941.0</td>
<td>.08</td>
</tr>
<tr>
<td>IL-10</td>
<td>241.0 ± 14.3</td>
<td>471.0 ± 84.6</td>
<td>.03</td>
</tr>
<tr>
<td>IL-12 (p40)</td>
<td>57,345.7 ± 13,116.8</td>
<td>112,535.7 ± 20,938.3</td>
<td>.04</td>
</tr>
<tr>
<td>IL-12 (p70)</td>
<td>1992.6 ± 342.7</td>
<td>3292.1 ± 687.4</td>
<td>.1</td>
</tr>
<tr>
<td>IL-17</td>
<td>1193.8 ± 168.6</td>
<td>18277.2 ± 403.1</td>
<td>.2</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>644.5 ± 225.9</td>
<td>940.3 ± 172.1</td>
<td>.3</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>447.3 ± 48.6</td>
<td>519.0 ± 56.4</td>
<td>.3</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>783.4 ± 118.7</td>
<td>1175.7 ± 162.9</td>
<td>.07</td>
</tr>
<tr>
<td>RANTES</td>
<td>23,853.3 ± 7903.5</td>
<td>43,711.0 ± 12,594.7</td>
<td>.2</td>
</tr>
<tr>
<td>TNF-α</td>
<td>1007.7 ± 135.9</td>
<td>1424.9 ± 191.7</td>
<td>.09</td>
</tr>
</tbody>
</table>

**NOTE.** Mice were treated with eIF5A siRNA 48 and 24 h before challenge with 5 mg/kg LPS. The mice were euthanized 8 h after challenge with LPS for evaluation of serum concentrations of cytokines. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normally T cell expressed and secreted; TNF, tumor necrosis factor.

* There were 10 mice per experimental group.

RESULTS

The Severe Sepsis Model

eIF5A siRNA and survival after intraperitoneal challenge with LPS. Greater survival of all treated animals, regardless of the dosing regimen, was statistically significant, compared with survival of controls (71% vs. 5%; P < .001) (figure 1). Survival was greatest among BALB/c animals when the eIF5A siRNA-liposome complex was administered 48 and 24 h before and at the time of LPS administration (100% vs. 7%; P = .013) (figure 1A). Importantly, the survival benefit remained significant when the eIF5A siRNA-liposome complex was administered after injection of LPS (P < .001) (figure 1B and 1D). A significant survival benefit was also noted for C57BL/6 mice under similar conditions. The best C57BL/6 response was noted in animals treated at 0, 8, 16, and 24 h after LPS inoculation (survival rate, 67% vs. 0%; P = .0079) (figure 1D).

eIF5A siRNA and serum cytokine concentrations after intraperitoneal challenge with LPS. There was a statistically significant decrease in the serum concentrations of IL-2, IL-4, IL-5, GM-CSF, IL-3, IL-6, IL-12 p40, IL-12 p70, MIP-1α, and RANTES at 90 min after LPS administration in mice treated with the eIF5A siRNA-liposome complex at 48 and 24 h before LPS inoculation (table 1). At 8 h after LPS administration, there was also a statistically significant decrease in IL-1β, IL-12, and IL-10 in siRNA-liposome treated animals, compared with control mice (table 2). There was no significant difference in the concentration of other cytokines tested at either 90 min or 8 h after LPS administration (tables 1 and 2). Finally, a comparison of eIF5A...
siRNA and dexamethasone revealed similarly decreased concentrations of TNF-α in blood at 90 min after intraperitoneal challenge with LPS (figure 2).

The Acute Lung Injury Model

**eIF5A siRNA and inflammation after intranasal challenge with LPS.** As shown in figure 3A, myeloperoxidase (MPO) activity was markedly (>80%) reduced in mice treated with 50 μg of eIF5A siRNA 48 h before intranasal administration of LPS, compared with MPO activity noted in controls. In a second experiment, siRNA was administered 24 h before the LPS challenge. The reduction in total lung MPO activity was also reduced (by 42%) in mice receiving eIF5A siRNA, compared with controls (data not shown). Because eIF5A siRNA reduced the neutrophilic response in the lungs, we next examined the change in lung cytokine concentrations. Mice were again pretreated with either eIF5A or control siRNA 48 h before intranasal LPS challenge. Twenty-four h after the LPS challenge, mice were euthanized and their lungs homogenized. There was a near total absence of total lung TNF-α in mice treated with eIF5A siRNA (figure 3B).

Similar to the near total reduction in lung concentrations of TNF-α, total lung concentrations of IL-1α were also nearly absent (figure 4A). We next measured the concentrations of the chemokine MIP-1α in the same samples. There was a 71% reduction in the lung tissue concentration of this chemokine (figure 4B). We also administered eIF5A and control siRNA intraperitoneally, and, after 24 h, we challenged the mice with intranasally administered LPS. There was a statistically significant reduction in the serum concentrations of TNF-α (figure 5A) and IL-6 (figure 5B) at 4 h.

**DISCUSSION**

The findings of these studies are important because we have shown that it is possible to improve the survival of mice with sepsis by administration of an siRNA complex that targets eIF5A. Furthermore, of clinical importance is the finding that survival occurs even when the siRNA complex is administered after inoculation with LPS. In addition, we confirmed the anti-inflammatory effect of eIF5A siRNA by use of a model of pulmonary inflammation in which LPS is administered via an intranasal route. Finally, in both the lung injury model and the sepsis model, proinflammatory markers in lung homogenate
and serum are significantly attenuated by eIF5A siRNA treatment.

Expression of eIF5A is constitutive in a wide variety of tissues and cell lines, but it appears to be more tightly regulated in human blood cells. Specifically, human peripheral blood mononuclear cells (PBMCs) [22] and immature dendritic cells [23] express low levels of eIF5A. However, increased levels of hypusine, which are required for eIF5A expression, have been associated with activation of lymphocyte growth [37], and expression of eIF5A has been found to be strongly up-regulated in PBMCs in response to stimulators of T cell activation and/or proliferation [22]. Dendritic cells also increase eIF5A expression during maturation [23]. Hypusine-modified eIF5A is thought to be required for the nuclear export CD83 mRNA, because an inhibitor of DHS was found to block CD83 surface expression and inhibit the ability of dendritic cells to activate T lymphocytes [23]. Collectively, these data suggest that eIF5A may be an important factor in the activation of leukocytes and, therefore, an essential component of a normal inflammatory response.

Inhibitors of DHS, such as CNI-1493 [38], and those of DOHH, such as mimosine, have anti-inflammatory properties. Mimosine reduced the inflammatory index and expression of the chemokines monocyte chemoattractant protein (MCP)–1 and MIP-2, in mice infected with the parasite Trichinella spiralis [8], and it suppressed production of the cytokines TNF-α and IL-6 in a model of chronic inflammation [9]. Although these inhibitors may affect pathways other than hypusine biosynthesis, the reduction in hypusinated eIF5A may contribute to the anti-inflammatory properties of these compounds.

Polyamines are known to be endogenous regulators of inflammation, and the polyamine spermidine is important as a substrate for the formation of the hypusine residue on eIF5A [39]. In fact, a critical function of spermidine in the support of yeast cell and serum are significantly attenuated by eIF5A siRNA treatment.

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growth is to act as a substrate for hypusine modification of eIF5A [40]. Sepsis and endotoxemia have been found to stimulate polyamine biosynthesis, resulting in the accumulation of putrescine and spermidine in the liver [4] and jejunal mucosa [5]. In further support of this finding, Soulet et al. [41] found that polyamines, including spermidine, accumulated in the brain after LPS challenge in mice and that inhibition of polyamine synthesis reduced the ability of LPS to trigger TNF and Toll-like receptor 2 transcriptional activation, as well as increased the survival of mice challenged with LPS. Although the role of polyamines in the regulation of inflammation is yet unclear, one possible reason for increased spermidine levels may be to fuel hypusine biosynthesis and the formation of mature eIF5A.

Several studies have also found a role for eIF5A in the regulation of apoptosis. Overexpression of eIF5A has been found to induce apoptosis in lung [25] and colon [26] cancer cell lines. Silencing of eIF5A by use of siRNAs was also found to protect human lamina cribrosa cells from TNF-α–induced apoptosis [24], suggesting that eIF5A may be involved in the TNF-α apoptotic pathway. Cytokines, such as IFN-α [21], IFN-γ [26], and TNF-α [24] stimulate eIF5A expression, and TNF-α triggers a rapid nuclear accumulation of eIF5A in colon cells before apoptotic cell death [26]. These data collectively suggest that eIF5A may be involved in apoptosis triggered by cytokine exposure and that suppression of eIF5A could lead to enhanced cellular survival during acute inflammation.

Taken together, these findings suggest that eIF5A is involved in regulation of the inflammatory response to sepsis via both the initial proinflammatory response and the subsequent hypoinflammatory apoptotic response. Given the lack of efficacy of therapies targeting only the inflammatory phase of sepsis, targeting eIF5A provides a novel, multifactorial approach to modifying the deleterious inflammatory response to sepsis via exploiting siRNA technology to block cell death and through inhalational administration [42]. Further studies are needed to extrapolate these findings to other animal models of sepsis, including cecal ligation and puncture, and to further characterize the role of apoptosis inhibition in the survival benefit associated with eIF5A siRNA complexes.

References


