

COMMENTARY

# Fixing the leak: targeting the vascular endothelium in sepsis

Aaron Spicer<sup>1</sup> and Carolyn S Calfee<sup>2\*</sup>

See related research by Alfieri *et al.*, <http://ccforum.com/content/16/5/R182>

## Abstract

Angiotensin-1 is a Tie-2 receptor agonist that stabilizes vascular endothelium, promoting endothelial maturation and preventing capillary leak. Angiotensin-2 is largely a competitive partial antagonist that is markedly elevated in humans and animal models of sepsis and other inflammatory states, directly disrupts the endothelial barrier, and has been correlated with end-organ dysfunction and death in sepsis. In the previous issue of *Critical Care*, Alfieri and colleagues used intravital microscopy to study the microvasculature in a murine model of sepsis. Treatment with a modified angiotensin-1 molecule led to reversal of albumin vascular leak and improved blood flow to skeletal muscle, as well as a decrease in the levels of several inflammatory cytokines. Importantly, the angiotensin-1 variant was administered 20 hours after initial lipopolysaccharide challenge. This study adds to the evidence that the angiotensin/Tie-2 axis represents a modifiable pathway through which targeted therapy may be able to directly reverse part of the pathology of sepsis.

Despite decades of research and untold investments of time, energy, and money, treatments for sepsis other than antibiotics and supportive care have remained elusive. Over this time, our expanding understanding of the biology of sepsis has led to the development of targeted treatments, including immunomodulatory and anti-coagulant approaches, yet so far all of these approaches have been ultimately unsuccessful.

With this historical backdrop, much recent translational research in sepsis has focused on the importance of vascular endothelial permeability, a pathophysiologic

hallmark of the syndrome and the focus of the work of Alfieri and colleagues in the previous issue of *Critical Care* [1]. The angiotensin (Ang)-1/2 axis is a key regulator of endothelial permeability, operating via the Tie-2 receptor on vascular endothelial cells. Ang-1, the primary Tie-2 agonist, decreases capillary leak and inhibits leukocyte-endothelial interaction, among other effects [2-4]. In contrast, Ang-2, produced primarily in endothelial cells, functions as a context-dependent Tie-2 antagonist [5,6]. Elegant experimental and translational studies have clearly demonstrated that Ang-2 plays a critical role in the organ injury of sepsis by mediating increased endothelial permeability [7,8]. Likewise, clinical studies have identified a strong association between lower Ang-1 and/or higher Ang-2 levels and poor clinical outcomes in sepsis, including acute lung injury, pulmonary leak index, multi-organ dysfunction, and mortality [6,9-11]. Thus, manipulation of the Ang-1/2 axis has become an appealing therapeutic target.

One challenge of therapeutic intervention on the Ang-1/2 axis is that recombinant human Ang-1 has poor solubility and a short half-life [12]. Thus, alternative approaches to effective delivery of Ang-1 have been investigated in experimental models. Cartilage oligomeric matrix protein-angiotensin-1 (COMP.Ang-1) is a soluble and stabilized variant that binds more avidly to Tie-2 than native Ang-1 [12]. COMP.Ang-1, adenovirus-delivered Ang-1, recombinant human Ang-1, cell-based therapies, and a synthetic Tie-2 agonist all reduce vascular leak and end-organ dysfunction in murine sepsis models [13-19]. Each of these approaches has some appeal; Alfieri and colleagues chose to investigate the effects of a modified Ang-1 molecule, MAT.Ang-1, formed by fusing the coiled-coil domain of human matrilin-1 to the fibrinogen-like domain of human Ang-1. MAT.Ang-1 has better solubility than recombinant Ang-1 and yet more similar biologic activity to native Ang-1 than COMP.Ang-1 [12].

To study the effects of this modified Ang-1 in experimental models of sepsis, Alfieri and colleagues implanted window chambers into the dorsal skinfolds of mice, so as to visualize skeletal muscle blood flow with laser Doppler

\*Correspondence: Carolyn.Calfee@ucsf.edu

<sup>2</sup>Departments of Anesthesia and Medicine, University of California, San Francisco, San Francisco, CA 94143, USA

Full list of author information is available at the end of the article

imaging. Lipopolysaccharide (LPS) was injected intraperitoneally at 0 and 19 hours, followed by intravenous MAT.Ang-1 at 20 hours. MAT.Ang-1 returned LPS-induced leak of albumin to control levels at 23 and 24 hours, without affecting vascular permeability in mice untreated with LPS. Microvascular perfusion at 24 hours partially improved in LPS-challenged mice treated with MAT.Ang-1, but did not return to normal. In addition to its effects on vascular permeability and perfusion, MAT.Ang-1 reduced tumor necrosis factor alpha, interferon gamma, triggering receptor expressed on myeloid cells-1, granulocyte colony-stimulating factor, and IL-10 in LPS-unchallenged mice, a novel finding given that other studies have not treated well mice with Tie-2 agonists. LPS-induced elevation in IL-1 $\beta$ , IL-10, and IL-1 receptor antagonist was decreased by MAT.Ang-1, consistent with two other Tie-2 agonists' effects on inflammatory cytokines [14,20].

What can we learn from this new study, and how has it advanced the field? First, MAT.Ang-1 was given after the administration of LPS, rather than prophylactically. While the therapeutic interval was short, this treatment model highlights the possibility that a Tie-2 agonist could be a feasible therapy for the microvascular dysfunction of sepsis. Second, although MAT.Ang-1 was described previously, this study represents its first therapeutic trial in this setting. Third, the *in vivo* imaging of skeletal muscle provides an interesting window into microvascular function and a novel demonstration of the potential therapeutic effects of manipulation of the Ang1/2 axis.

At the same time, many questions about the effects of this modified Ang-1 compound remain unanswered. In the current paper, only effects on skeletal muscle vasculature and expression of cytokines and angiogenic factors were assessed. What might lung intravital microscopy, which has become a valuable scientific tool in models of acute lung injury, reveal about the effects of MAT.Ang-1 on the pulmonary vascular bed and leukocyte trafficking in the lung? More broadly, what are the effects of MAT.Ang-1 on organ injury and mortality in experimental models of sepsis? How does MAT.Ang-1 affect the immune response, including bacterial counts, in live bacterial models? Perhaps most importantly, how do different approaches to manipulating the Ang-1/2 axis compare in the same experimental sepsis models?

While many questions remain, this work by Alfieri and colleagues adds to the growing weight of literature highlighting the potential value of targeting the vascular endothelium in sepsis and will certainly pique the interest of the many researchers who are continuing the decades-long quest for the holy grail of a targeted sepsis therapy.

#### Abbreviations

Ang, angiopoietin; COMP.Ang-1, cartilage oligomeric matrix protein-angiopoietin-1; IL, interleukin; LPS, lipopolysaccharide.

#### Competing interests

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#### Author details

<sup>1</sup>Department of Pediatrics, University of California, San Francisco, San Francisco, CA 94143, USA. <sup>2</sup>Departments of Anesthesia and Medicine, University of California, San Francisco, San Francisco, CA 94143, USA.

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