

COMMENTARY

CXCR3 blockade: a novel anti-sepsis approach?

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Abstract

Blockade of the CXC chemokine receptor 3 (CXCR3) attenuates inflammation and improves survival in a murine model of near lethal polymicrobial sepsis. However, given the multitude of cellular responses and inflammatory mediators that orchestrate sepsis syndrome, more detailed investigations will be required before a complete understanding of the mechanism(s) of CXCR3 blockade and its therapeutic potential are revealed.

In the previous issue of *Critical Care*, Herzig and colleagues [1] set out to determine whether blockade of the CXC chemokine receptor 3 (CXCR3) attenuates inflammation and improves survival in a murine model of near lethal polymicrobial sepsis. Their results show that concomitant CXCR3 blockade and antibiotic therapy significantly improves survival when administered prior to and even shortly after sepsis. This study is a natural extension of the authors' prior work that demonstrates that CXCR3 blockade impedes lymphocyte trafficking, decreases systemic cytokine production and improves sepsis survival [2]. From this body of work, the authors conclude that CXCR3 inhibition should be considered a potential target for anti-sepsis therapies.

Although the authors' results are compelling, the conclusion that CXCR3 signaling is detrimental in polymicrobial sepsis must be accepted with caution. Others have previously investigated the impact of CXCR3 and its ligand, CXCL10, with strikingly dissimilar results, depending upon the model employed. In contrast to Herzig and colleagues' report, several prior investigations have found that CXCR3 and CXCL10 were necessary for survival in adult and neonatal murine polymicrobial sepsis models. Kunkle, Standiford and colleagues [3,4] in separate reports demonstrated that CXCL10 blockade

worsens survival in sepsis and pneumonia. Cuenca and colleagues [5] showed that CXCL10 concentrations increase in the peritoneum and blood of septic neonatal mice, that CXCL10 blockade and CXCR3 blockade worsen survival, and that adjuvant augmentation of CXCL10 is protective from sepsis mortality. In two consecutive reports, Kelly-Scumpia and colleagues from our laboratory implicated type I interferon production in general, and CXCL10 production specifically, as a prerequisite for hematopoietic cell function and adult mouse survival in a low-lethality polymicrobial sepsis model [6,7]. In most of these latter studies, the lethality of the sepsis models was considerably less than used by Herzig and colleagues. The disparity between Herzig and colleagues' findings [1] and those of prior reports [3-7] may well be dependent upon the magnitude of the early inflammatory response, and should raise concern that CXCR3/CXCL10 signaling is more complex than previously suggested, and undoubtedly plays both beneficial and adverse roles in outcome to sepsis.

When Herzig and colleagues' results are juxtaposed against the backdrop of known CXCR3/CXCL10 functions, and more importantly the historical landscape of failed clinical trials with inhibitors of inflammation, several questions become paramount. What are the theoretical advantages of CXCR3/CXCL10 as a therapeutic target compared with other inflammatory targets? Importantly, does severe murine peritoneal sepsis recapitulate human sepsis sufficiently to reasonably expect similar results in humans with severe sepsis and septic shock? And most importantly, what can we learn about the mechanism of protective immunity by CXCR3/CXCL10 action?

Given the ever growing complexity and reticular nature of human sepsis, is it wise to continue to pursue single therapeutic interventions for the multidimensional sepsis syndrome [8,9]? In a 21st century landscape stained by the history of failed therapeutic interdiction [10], the authors should be applauded for their demonstration that CXCR3 blockade begun 6 hours after the onset of sepsis is beneficial to survival. The fact that CXCR3 inhibition after the onset of sepsis improves survival gives the potential therapy a practical and broad appeal. Herzig and colleagues' findings clearly show the detrimental side

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of exaggerated CXCR3 signaling in severe sepsis with high mortalities. In the clinical setting, there is little disagreement that what we call 'severe sepsis' is presently so vaguely defined that our study populations are too heterogeneous to optimize therapeutic efficacy. Although the authors demonstrate a 40% improvement in survival, the harsh fact remains that existing individual animal models are rather poor surrogates of human sepsis [8,10-12]. Even though the cecal ligation and puncture model is generally accepted to best replicate human peritoneal sepsis (the 'gold standard' to many), several clinical intangibles, such as pre-existing comorbidities, age, continuous fluid resuscitation, nutritional support, antibiotic therapy, and operative intervention, make human sepsis more complex, and routinely difficult to replicate in mice [13]. Juxtaposed with the murine versus human sepsis conundrum stands the mortality disparity between the authors' cecal ligation and puncture model, which was 90% across the board and 50% in the group that showed a benefit, compared to an overall mortality of approximately 25% in human sepsis [8,14,15].

Compared to other, older anti-inflammatory therapeutic targets, CXCR3 is a relative new-comer with only a handful of studies dealing with its role in polymicrobial sepsis. More detailed investigations are warranted to better understand the receptor's scope of action and full therapeutic potential. In their prior report, Herzig and colleagues partially addressed this issue by implicating CXCR3 blockade in reducing peritoneal lymphocyte recruitment and interleukin-6 and macrophage inflammatory protein 2 production [2]. However, given the multitude of cellular responses and inflammatory mediators that orchestrate the sepsis syndrome, more detailed investigations are required before we will truly understand the mechanism of CXCR3 blockade and its therapeutic potential. However, Herzig and colleagues are to be congratulated on advancing the field, and drawing attention to the important role that individual chemokines play in sepsis survival.

Abbreviations

CXCR3, CXC chemokine receptor 3.

Competing interests

The authors declare that they have no competing interests.

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