CRITICAL CARE

COMMENTARY

The kinetics of T regulatory cells in shock: beyond sepsis

Eirini Christaki* and Eleni Patrozou

See related research by Hein *et al.*, http://ccforum.com/content/14/1/R19

Abstract

During the past decade, there have been an increasing number of studies investigating the precise role of T regulatory cells in human disease. First recognized for their ability to prevent autoimmunity, T regulatory cells control effector $CD4^+$ and $CD8^+$ T lymphocytes and innate immune cells by several different suppressive mechanisms, like cell to cell contact, secretion of inhibitory cytokines and cytolysis. This suppressive function of T regulatory cells could contribute in a similar way to the profound immune dysfunction seen in critical illness whether the latter is due to sepsis or severe injury.

Critical illness, resulting either from infection or from other pro-inflammatory insults, is associated with severe immune dysfunction. However, little is known about how different the dynamics of certain immune (especially suppressor) cell populations are depending on the type of primary insult. Hein and colleagues [1] investigated the role of naturally occurring T regulatory (Treg) cells in 43 patients admitted to the ICU with shock due to sepsis and non-sepsis related etiologies. The discriminating feature of the study is that it included most causes of shock, rather than limiting the scope to sepsis. In more detail, the authors compared the absolute numbers, percentages and kinetics of $CD4^+CD25^+CD127^-$ Treg cells in 26 critically ill patients with septic shock and 17 patients with cardiogenic, hemorrhagic or toxic shock.

Naturally occurring $CD4^+CD25^+$ Treg cells comprise 5 to 10% of $CD4^+$ T cells and play a pivotal role in maintaining immunologic homeostasis by inhibiting autoimmunity and controlling inflammation. Treg cells express the transcriptional regulator forkhead box p3 (Foxp3), which belongs to the forkhead DNA-binding transcription factor family, and is essential for both the development and suppressive function of Treg cells [2]. Although their exact contribution in sepsis and shock has not been completely elucidated yet, evidence from a number of studies suggests that Treg cells act as significant modulators of the innate and adaptive immune response after severe injury [3,4].

After trauma, Treg cell activity increased and was associated with a decreased Th1 pro-inflammatory response, potentially contributing to injury-induced immunoparalysis, both in mice and in humans [5,6]. Moreover, in sepsis, not only the percentage of Treg cells was higher than in healthy volunteers [1,7], but their suppressive activity was enhanced as well, a phenomenon that correlated with increased expression of Foxp3 [8,9]. One explanation for the persistence of Treg cells after injury, despite $CD4^+CD25^-$ and generalized lymphopenia [10], may be explained by their greater resistance to apoptosis [11]. Therefore, it is not surprising that Hein and colleagues [1] reported that the kinetics of Treg cells did not differ significantly between patients with septic and non-sepsis-related shock. Interestingly, survivors from the group of patients with septic shock had higher Treg cell counts and percentages than non-survivors, which remained consistent at all time points. Moreover, higher percentages of Treg cells were associated with lower blood arterial lactate and severity of illness score [1]. This could suggest a protective role of Treg cells in sepsis, although the study's small sample size precludes such a conclusion. It is also worth mentioning that this observation is contrary to the results published by Monneret and colleagues [7], where higher percentages of $CD4^+CD25^+$ cells were associated with worse prognosis in septic shock.

It is always very well received when information extracted from clinical studies is challenged in an experimental model. In the study by Hein and colleagues [1], Treg cell percentage increased early after polymicrobial sepsis, but depletion of $CD25^+$ cells did not affect survival in their model. Data on sepsis outcome from previously published studies that used similar

*Correspondence: Eirini.Christaki@gmail.com
Division of Infectious Diseases, The Warren Alpert Medical School of Brown University, Providence, RI 02906, USA

antibody depleting strategies have been inconclusive [8,9,12]. On the other hand, adoptive transfer of *in vitro* stimulated Treg cells protected mice from lethality in a dose-dependent manner in a polymicrobial sepsis model [13], and decreased Toll-like receptor (TLR)-2- and TLR-4-mediated pro-inflammatory responses in an experimental burn model [14]. At this point, however, a few important points need to be clarified: first, anti-CD25 antibody treatment may not have completely eliminated $CD25^-/Foxp3^+$ or $CD25^{low}/Foxp3^+$ Treg cells [15]; second, anti-CD25 treatment may also eliminate other activated cells that express CD25 [16]; and last, it may be useful to investigate whether antibody depletion, if performed later in the course of shock after the pro-inflammatory insult has amplified the regulatory activity of $CD4^+CD25^+$ Treg cells, could then potentially lead to a different outcome [3].

Even if no great variability exists between the kinetics and activity of Treg cells in different shock states, the sequence and timing of events that lead to the amplification of their suppressive function certainly need to be studied further.

Abbreviations
Treg = T regulatory.

Competing interests
The authors declare that they have no competing interests.

Published: 19 March 2010

References

1. Hein F, Massin F, Cravoisy-Popovic A, Barraud D, Levy B, Bollaert PE, Gibot S: **The relationship between CD4+CD25+CD127- regulatory T cells and inflammatory response and outcome during shock states.** *Crit Care* 2010, **14:**R19.
2. Sakaguchi S: **Naturally arising CD4+ regulatory t cells for immunologic self-tolerance and negative control of immune responses.** *Annu Rev Immunol* 2004, **22:**531-562.
3. Venet F, Chung CS, Monneret G, Huang X, Horner B, Garber M, Ayala A: **Regulatory T cell populations in sepsis and trauma.** *J Leukoc Biol* 2008, **83:**523-535.
4. Kessel A, Bamberger E, Masalha M, Toubi E: **The role of T regulatory cells in human sepsis.** *J Autoimmunol* 2009, **32:**211-215.
5. Ni Choileain N, MacConmara M, Zang Y, Murphy TJ, Mannick JA, Lederer JA: **Enhanced regulatory T cell activity is an element of the host response to injury.** *J Immunol* 2006, **176:**225-236.
6. MacConmara MP, Maung AA, Fujimi S, McKenna AM, Delisle A, Lapchak PH, Rogers S, Lederer JA, Mannick JA: **Increased CD4+ CD25+ T regulatory cell activity in trauma patients depresses protective Th1 immunity.** *Ann Surg* 2006, **244:**514-523.
7. Monneret G, Debard AL, Venet F, Bohe J, Hequet O, Bienvenu J, Lepape A: **Marked elevation of human circulating CD4+CD25+ regulatory T cells in sepsis-induced immunoparalysis.** *Crit Care Med* 2003, **31:**2068-2071.
8. Wisnoski N, Chung CS, Chen Y, Huang X, Ayala A: **The contribution of CD4+ CD25+ T-regulatory-cells to immune suppression in sepsis.** *Shock* 2007, **27:**251-257.
9. Scumpia PO, Delano MJ, Kelly KM, O'Malley KA, Efron PA, McAuliffe PF, Brusko T, Ungaro R, Barker T, Wynn JL, Atkinson MA, Reeves WH, Salzler MJ, Moldawer LL: **Increased natural CD4+CD25+ regulatory T cells and their suppressor activity do not contribute to mortality in murine polymicrobial sepsis.** *J Immunol* 2006, **177:**7943-7949.
10. Venet F, Pachot A, Debard AL, Bohé J, Bienvenu J, Lepape A, Monneret G: **Increased percentage of CD4+CD25+ regulatory T cells during septic shock is due to the decrease of CD4+CD25- lymphocytes.** *Crit Care Med* 2004, **32:**2329-2331.
11. Banz A, Pontoux C, Papiernik M: **Modulation of Fas-dependent apoptosis: a dynamic process controlling both the persistence and death of CD4 regulatory T cells and effector T cells.** *J Immunol* 2002, **169:**750-757.
12. Chen X, Baumel M, Mannel DN, Howard OM, Oppenheim JJ: **Interaction of TNF with TNF receptor type 2 promotes expansion and function of mouse CD4+CD25+ T regulatory cells.** *J Immunol* 2007, **179:**154-161.
13. Heuer JG, Zhang T, Zhao J, Ding C, Cramer M, Justen KL, Vonderfecht SL, Na S: **Adoptive transfer of in vitro-stimulated CD4+CD25+ regulatory T cells increases bacterial clearance and improves survival in polymicrobial sepsis.** *J Immunol* 2005, **174:**7141-7146.
14. Murphy TJ, Ni Choileain N, Zang Y, Mannick JA, Lederer JA: **CD4+CD25+ regulatory T cells control innate immune reactivity after injury.** *J Immunol* 2005, **174:**2957-2963.
15. Couper KN, Blount DG, de Souza JB, Suffia I, Belkaid Y, Riley EM: **Incomplete depletion and rapid regeneration of Foxp3+ regulatory T cells following anti-CD25 treatment in malaria-infected mice.** *J Immunol* 2007, **178:**4136-4146.
16. Scholzen A, Minigo G, Plebanski M: **Heroes or villains? T regulatory cells in malaria infection.** *Trends Parasitol* 2010, **26:**16-25.

doi:10.1186/cc8897
Cite this article as: Christaki E, Patrozou E: **The kinetics of T regulatory cells in shock: beyond sepsis.** *Critical Care* 2010, **14:**132.