Commentary

Excess circulating angiopoietin-2 levels in sepsis: harbinger of death in the intensive care unit?

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Abstract

The early recognition and management of sepsis remain the greatest challenges in the field of critical care medicine. Endothelial injury is one of the hallmarks of sepsis, leading to capillary leak, microcirculatory dysfunction, organ failure, and eventual death in many critically ill patients. The angiogenic growth factors, angiopoietin (angpt)-1 and angpt-2, act upon the Tie-2 receptor in opposing roles. Angpt-2 has been found in abundance in septic patients when compared with healthy controls. In the study by Kümpers and colleagues in the previous issue of *Critical Care*, angpt-2 levels correlated with markers of tissue hypoxia, disease severity, and mortality in septic adults. However, the temporal kinetics of the angiopoietins were not assessed. It remains to be seen whether angpt-2 levels will function solely as an early marker of sepsis or whether the manipulation of the angpt/Tie-2 system will become a rational therapeutic target for the management of sepsis.

In the previous issue of *Critical Care*, Kümpers and colleagues [1] demonstrated a direct correlation between increased peripheral blood levels of the vascular growth factor, angiopoietin (angpt)-2, and mortality in 43 critically ill adults with sepsis. Endothelial injury is one of the main hallmarks of sepsis, leading to capillary leak, microcirculatory dysfunction, organ failure, and eventual death in many critically ill patients [2]. Angpt-1 and angpt-2 are two of the best-characterized members of a family of endothelial-derived vascular growth factors necessary for both normal and pathologic angiogenesis and vasculogenesis. Both angpt-1 and angpt-2 appear to bind to the tyrosine kinase receptor, Tie-2, found primarily on the luminal surface of endothelial cells [3]. Recent studies have also shown that the Tie-2 receptor may be found on certain populations of peripheral blood monocytes [4], although the function and role of the Tie-2 receptor in the host innate immune response remain relatively unexplored. Angpt-1 and angpt-2 appear to have directly opposing roles during health and disease states. Angpt-1 is a Tie-2 agonist and promotes endothelial stabilization and quiescence, whereas angpt-2 is a Tie-2 antagonist and promotes endothelial activation, destabilization, and inflammation [3]. As such, the relative balance between angpt-2 and angpt-1 at the Tie-2 receptor may be more relevant to the pathobiology of sepsis than the absolute levels of the individual growth factors [5,6].

Several studies have demonstrated increased peripheral blood levels of angpt-2 in critically ill patients with sepsis [5,7-9], multiple trauma [10,11], acute lung injury (ALI) [7,12,13], and cardiopulmonary bypass [6] when compared with healthy controls. More importantly, increased angpt-2 levels appear to be associated with adverse outcomes [5,6,9-12]. For example, the study of Kümpers and colleagues [1] showed that increased peripheral blood angpt-2 levels correlated with surrogate markers of tissue hypoxia, disease severity, and mortality in 43 critically ill adults with sepsis. Also of note, consistent with the opposing roles of angpt-2 and angpt-1 on the Tie-2 receptor, peripheral blood levels of angpt-1 were significantly lower in the patients with sepsis compared with healthy controls. Unfortunately, in the study of Kümpers and colleagues, similar to the aforementioned studies, the temporal kinetics of angpt-1 and angpt-2 were not assessed as blood samples were collected upon the first day of admission to the intensive care unit only. Angpt-2 is stored in the Weibel-Palade bodies within endothelial cells [14] in a more or less prepackaged form. It is therefore not surprising that angpt-2 levels are increased early in response to endothelial activation or injury. Whether angpt-2 levels remain increased in critically ill patients with

ALI = acute lung injury; angpt = angiopoietin.

sepsis has not been directly addressed and is a question for future investigation. It is certainly tempting to speculate that peripheral blood angpt-2 levels would be an ideal biomarker of early endothelial activation and injury. Similarly, whether angpt-1 levels remain decreased in critically ill patients who eventually succumb to their illness is an interesting question. Angpt-1 may be a biomarker of endothelial recovery; however, given its purported anti-inflammatory role, angpt-1 would appear to be an attractive therapeutic target as well. To this end, several studies have suggested that manipulating the ratio of angpt-2 to angpt-1 by augmenting angpt-1 levels may represent an ideal therapeutic strategy for patients with sepsis and ALI [15].

Important translational laboratory studies are necessary to show that increased angpt-2 levels in critically ill patients are more than just an epiphenomenon. The role of angpt-2 in the pathobiology of sepsis and ALI needs to be further elucidated by using *in vitro* cell-based studies and animal models of critical illness. Similarly, the presence of the Tie-2 receptor on certain subpopulations of peripheral blood monocytes [4] suggests a larger role for angpt-2 in the host innate immune response. Finally, manipulation of the angpt/Tie-2 system may be a rational therapeutic strategy for the management of critically ill patients with sepsis and ALI. All of these questions remain an active focus in several laboratories, including our own.

Competing interests

The authors declare that they have no competing interests.

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