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Angiopietin-2 in sepsis: A “*thera-gnostic*” tool to tailor treatments?

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We appreciate Zhang et al.’s [1] commentary placing our recent study [2] in the context of how angiogenesis factors may modulate the sepsis phenotype. We share their enthusiasm that Angiopietin-2 (Angpt-2) represents a compelling target for future investigation, and we appreciate their interest in RNA interference (RNAi) as a viable therapeutic approach. The commentary from Zhang et al. also offers an opportunity to address three points for further consideration.

First, pre-formed Angpt-2 protein is stored in endothelial cells and is thought to be released into the circulation by early events of systemic inflammation—e.g., induction of TNF α . In turn, released Angpt-2 protein then potentiates the inflammatory response of the endothelium. However, this paradigm fails to explain why the sickest individuals often exhibit a progressive elevation of circulating Angpt-2 as their clinical status deteriorates over days toward death [3]. In this light, our recent study provides first-in-kind evidence that sustained biosynthesis of Angpt-2, not simply release of pre-formed protein, is itself pathological in sepsis. Angpt-2-directed RNAi reduced mortality whether it was administered before or after the induction of experimental sepsis. This new observation also stresses the need to investigate mechanisms that regulate ANGPT2 gene expression in inflammation.

Second, heterogeneity—both between affected individuals and within the time course experienced by a single patient—continues to confound efforts to develop novel treatments in sepsis. Personalized treatments may thus be highly desirable. Angpt-2 concentration is easily measured in the blood, and its elevation is strongly associated with other measures of

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vascular leakage and with hard outcomes such as the future risk of shock or death [3]. Measurement of circulating Angpt-2 may thus be a promising approach for identifying septic patients whose molecular pathophysiology is driven by vascular leakage. More broadly, Angpt-2 measurements may be used in future trials not only as an inclusion criterion, but also as a means to follow response to therapies targeting the vasculature (whether or not such therapies directly target Angpt-2 itself).

Lastly, Zhang et al. introduce the concept of a dual-axis vascular therapy, suggesting that combined inhibition of Angpt-2 and VEGF signaling may yield benefits beyond either approach applied singly. While pre-clinical studies offer encouragement regarding such an approach [4], one might worry about the emergence of vascular toxicity from compound approaches as well [5]. A careful assessment of the risks and benefits is highly desirable.

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