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Re: ADAM-17: A potential therapeutic target to prevent organ injury after hemorrhagic shock?

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In Reply

We would like to thank Drs. Xiang and Ryan and for their thoughtful comments in response to our recently published manuscript “Intraluminal tranexamic acid inhibits intestinal sheddases and mitigates gut and lung injury and inflammation in a rodent model of hemorrhagic shock,” in which we demonstrated that orally administered tranexamic acid provided local (gut) and distant (lung) organ injury protection. Additionally, ADAM-17 and TNF α were both significantly decreased locally and systemically by the administration of oral tranexamic acid. ADAM-17 is one member of the ADAM family that is co-expressed with syndecan-1 in the gut and mediates syndecan-1 shedding in the lung.¹ We have also shown the important link between syndecan-1 and ADAM-17 after hemorrhagic shock and resuscitation with plasma.²

The authors raise concern over the potential for ADAM-17 to enhance metabolic rate and therefore potentially worsen injury in the hypoperfused gut. This is based on a report by Gellings et al who examined metabolism in ADAM-17 deficient mice and found a hypermetabolic phenotype.³ In our model, tranexamic acid was delivered at the end of shock, a time when ADAM-17 levels were already increased. Tranexamic acid lessened pathologically elevated levels of systemic and gut ADAM-17. This is a very different situation from a complete absence of ADAM-17 as in ADAM-17^{-/-} mice. As suggested in a recent review by Drey Mueller et al on pulmonary ADAMS, physiologic homeostasis is characterized by checks and balances to avoid excessive or absence of mediators.⁴ These authors report that ADAM-17 promotes permeability, leukocytes migration, and inflammatory mediator production in the lung and also suggested targeting ADAM-17 as a potential therapeutic. However, in line with concerns of Drs. Xiang and Ryan, ADAM-17 may have a beneficial function in chronic lung inflammation. We certainly agree with the authors that further studies are warranted.

The authors further comment on the report by Altshuler et al that supplementing tranexamic acid with glucose may enhance its protection.⁵ While we did not test glucose in our study, this finding is not surprising. We demonstrated a number of years ago that nutrients

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metabolized by the gut, those being glucose and glutamine, are protective to the hypoperfused gut by augmenting the gut's reduced supply of ATP.⁶ Perhaps a better delivery vehicle for tranexamic acid would in fact be a glucose solution rather than water, which is what we and others used in our experimental models.⁷

In summary, we believe that our results support organ protection by orally delivered tranexamic acid in our rodent model of hemorrhagic shock. We agree that prior to any attempts at targeting this complex mediator may be premature, and appreciate the authors insightful comments.

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