Annals of Surgery

Response to: Comment on The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients

--Manuscript Draft--

Manuscript Number:	
Full Title:	Response to: Comment on The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients
Article Type:	Response to Letter
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Manuscript Region of Origin:	UNITED KINGDOM
Additional Information:	
Question	**Response**
Have all coauthors viewed and approved of this version manuscript?	Yes - All coauthors have seen & approved
Do you or any of your coauthors have any potential conflicts of interest you need to declare?	The authors declare there are no conflicts of interest.
Was this submission funded by an outside agency (e.g., business, government agency, etc.)	No funding was received in support of this work.
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Response to: Comment on The S100A10 Pathway Mediates an Occult Hyperfibrinolytic Subtype in Trauma Patients

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We thank Dr Moore and colleagues for their interest in our article[1] and for their thoughts on the interpretation of our findings. The authors highlight in their letter the relative knowledge gaps and need for additional studies to improve our understanding of the temporal changes in the fibrinolytic system following trauma with which we fully concur. However, we challenge their interpretation and conclusions regarding the potential role of S100A10 and its utility as a future therapeutic target.

Viscoelastic hemostatic assays (VHAs) are a relatively blunt tool for the detection of fibrinolysis and it is unclear precisely what VHA-hypofibrinolysis represents in the fibrinolytic system *in-vivo*. We and others[2] have identified trauma patients with low-VHA fibrinolysis to be a heterogeneous subgroup, in terms of injury characteristics, levels of fibrinolysis biomarkers and clinical outcomes, with some suggesting it may represent a protective or adaptive response[3]. Moore et al. have questioned our proposal that tissue-bound S100A10 fibrinolysis receptor is a mechanistic candidate for hyperfibrinolysis whilst simultaneously lowering VHA fibrinolysis *ex-vivo*. We concur that further research is required to explore the role of S100A10 *in-vivo* and in particular its role at the endothelial surface - an area of investigation which has been hampered by the inherent limitations of currently available VHA assays. However, the known pathophysiology of Acute Promyelocytic Leukemia provides biological plausibility for our assertion of severe hemorrhagic complications due to excessive fibrinolysis characterized by normal levels of tissue plasminogen activator (tPA) but high surface expression of S100A10[4].

We would not expect S100A10 spiking of healthy blood to increase Plasmin-α2-antiplasmin complex (PAP) or D dimers (DD) since the detection of fibrinolysis with ROTEM requires plasmin production *ex-vivo* and S100A10 is known to lyse plasmin thus in the absence of tPA e.g. in healthy subjects or trauma patients with low maximum lysis (ML) and high DD, no plasmin can be generated. A number

of studies have identified S100A10 as a key plasminogen receptor and a major regulator of cellular plasmin generation.[5] The accumulation of fibrin in the tissues of the S100A10-null mouse as well as the reduction in fibrinolysis further highlight the importance of S100A10 in fibrinolysis.[6] The carboxyl-terminal lysine of the plasminogen receptor, S100A10 is not the sole lysine residue involved in acceleration of tissue plasminogen-dependent plasminogen activation[7] although it is unknown if tranexamic acid (TXA) in the context of TBI and S100A10 mediated lysis or a specific S100A10 inhibitor is most effective in reversing fibrinolysis.

In focusing solely on hyperfibrinolysis leading to early death from uncontrolled hemorrhage, we believe this misses the wider implications of our study, particularly in the setting of traumatic brain injury (TBI). Central in our findings was that the low ML high DD cohort represents polytrauma patients with a preponderance of severe TBI. We were not able to examine cause of death but in the ML low DD high (raised S100A10) patients, the Kalpan-Meier curves are suggestive of patients dying of severe TBI (24-72 hours) rather than acutely from hemorrhage. The rate of massive transfusion in this subgroup is plausible given the significant bleeding that is known to occur with severe TBI requiring operative intervention. Progression of intracranial hemorrhage following TBI is recognized as a major contributor to secondary brain injury and poorer outcomes, with fibrinolytic activation identified as a major contributor to hemorrhage progression[8].

S100A10 is in essence a receptor which promotes fibrinolysis and is expressed widely within the brain. Current evidence suggests that the antifibrinolytic TXA can reduce intracranial hemorrhage progression in TBI[9] and when administered empirically in the prehospital phase to patients with suspected TBI improves survival without increasing the rate of thromboembolic events.[10] Pending the results of the CRASH-3 trial due to be released shortly, these results suggest a beneficial role for

targeted TXA administration in patients with a TBI, to reduce non-hemorrhage related deaths and to reduce the burden of morbidity associated with major bleeding and TBI.

The precise mechanism for TBI associated fibrinolysis and relative role of S100A10 with respect to other mediators of fibrinolysis is at present not clear. We propose S100A10 as one possible explanation given its patterns of tissue expression in the brain, *in-vitro* effects and correlation with elevated D-dimers. Defining VHA-hypofibrinolysis at admission is problematic and temporal trends are likely more important in understanding fibrinolysis and associated outcomes as suggested by Dr Moore and others in their recent review on fibrinolysis shutdown in trauma.[11] Detailed serial biomarker studies are clearly required to ascertain the significance of the many plasminogen receptors that are currently known and key pathways which both drive and inhibit fibrinolysis. In addition delineation of local versus systemic effects of S100A10 and other mediators of lysis both in TBI and non-TBI polytrauma are required. These areas remain the subject of ongoing investigation both by our research team and others. The imminent publication of the CRASH-3 trial is sure to spark a further period of welcome and intense scientific debate, whether it demonstrates a positive or negative effect of anti-fibrinolytic therapy in TBI.

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