

## COMMENTARY

# SkM-ing information from traumatized tissue

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Trauma is the leading cause for lost disability-adjusted life-years around the world in people younger than age 50 years.<sup>1</sup> Bleeding is a major cause of death in trauma, with 30% to 40% of fatalities attributable to bleeding, the vast majority occurring in the first 24 h.<sup>2</sup> For many critically injured patients, this period is one of the first opportunities to improve outcomes. Immediate hemorrhage needs to be controlled and resuscitation implemented to maintain tissue perfusion; however, efforts in these areas may be limited by impaired hemostasis. Early resuscitation and hemostasis may impact microvascular perfusion, which in turn may contribute to late mortality through the development of multiorgan failure.

The term trauma-induced coagulopathy (TIC) has been used to describe the complex derangements in hemostasis occurring because of trauma,<sup>3</sup> and TIC results in absence of clot formation or formation of clots of reduced strength. Enhanced activation of the coagulation system and thrombin generation are common to many coagulopathies. Endothelial dysfunction, likely driven by microvascular hypoperfusion, leads to increased activated protein C, overexpression of tissue plasminogen activator, and heparan sulfate release, impairing hemostasis and activating fibrinolysis. Reducing fibrinolysis in trauma through the early use of tranexamic acid has been an effective way to reduce mortality.<sup>4</sup> In animal models, the combination of trauma and hypotensive shock are required to induce this pattern of TIC, with either alone being insufficient.<sup>5,6</sup> The changes in hemostatic proteins may be accompanied by acidosis and hypothermia, both of which further impair procoagulant enzymes and are independent risks for mortality.<sup>6</sup> Platelet dysfunction can

also arise in the setting of TIC, resulting in loss of platelet adhesion under flow and responsiveness to platelet agonists.<sup>7</sup>

Trauma-induced coagulopathy is not constant; it changes over time. Early coagulation failure is replaced by a procoagulant state as the coagulation system recovers and rebounds with the acute systemic inflammatory response. Increased levels of plasminogen activator inhibitor-1 likewise may switch from a hyperfibrinolytic state to a hypofibrinolytic state, the timing of which is variable.<sup>8</sup> TIC is also not uniform; the nature of the coagulopathy varies depending on several patient factors, including preexisting coagulation status, age, comorbidities, the mechanism of injury, and the extent and type of organs injured.<sup>3</sup> Understanding the underlying pathophysiology is critical for developing appropriate goal-directed strategies to reduce bleeding, particularly given the difficulties in conducting clinical trials in trauma.

In this edition of *the Journal*, Coleman and colleagues investigated the association of plasma skeletal muscle myosin (SkM) and coagulopathy in trauma, with intriguing results.<sup>9</sup> In previous work, the authors have shown that skeletal muscle myosin activates thrombin through the formation of a myosin-FVa-FXa complex.<sup>10</sup> Release of additional myosin as a result of muscle trauma could conceivably contribute to the activation of coagulation in trauma. A similar model has been proposed with brain trauma and the release of procoagulant brain-derived microparticles contributing to brain injury-induced coagulopathy.<sup>2</sup>

The results in the current paper,<sup>9</sup> although intriguing, are not conclusive. Caution should be exercised in interpreting the results

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of observational studies alone, and the observed lack of difference between the control and trauma populations suggests that the release of SkM may not be a significant factor in trauma. However, the finding that coagulopathy was associated with lower levels of myosin needs further exploration. If myosin drives coagulopathy, then higher levels might be expected in patients exhibiting extensive coagulopathy. Instead, the opposite was seen, with myosin seemingly positively associated with increased hemostatic capacity. This is what we expect from canonical coagulation proteins, with consumption of the clotting factors leading to reduced levels. It raises the possibility that myosin may also be consumed in the process of clot formation.

It is also of interest that myosin levels were positively associated with increased clot amplitudes and angles in viscoelastic testing. These parameters are usually associated with stronger fibrin-platelet clot meshwork,<sup>11</sup> and in clinical practice are usually considered to represent the sum of fibrinogen and thrombin-activated platelets. The conventional myosins consist of a dimer of heterotrimers, and three isoforms of SkM comprising intact SkM (520 kDa), heavy meromyosin (350 kDa), and the SkM S1 fragment (130 kDa) occur. Separation of SkM by SDS polyacrylamide electrophoresis followed by western blotting with an antibody against human SkM results in visible bands corresponding to 240–260 kDa, 160 kDa, and 95 kDa SkM fragments, corresponding to full-length heavy chain, HMM, and the S1 fragment, respectively. Previous work by the same group has shown that plasmas from individual blood donors vary in the presence and absence of three distinct SkM MW band patterns, based on the presence or absence of different MW SkM heavy chain isoforms.<sup>12</sup> If myosin can contribute similarly, it raises the possibility to intervene in critical bleeding; however, an understanding of trauma- and patient-specific myosin features would be important.

The advantage of viscoelastic testing in assessing the sum of factors leading to hemostasis is also a limitation when it comes to elucidating physiologic mechanisms. The amplitude of clot strength may be reduced by a deficiency of components but also by increased fibrinolysis. The association between lower myosin levels and increased fibrinolysis is not readily explained by a myosin-FVa-FXa prothrombinase. There is evidence of myosin stabilizing fibrin<sup>13</sup>; however, the present study is unable to determine whether a reduction in an antifibrinolytic effect or a procoagulant effect are contributing to TIC, or whether myosin is a bystander protein with levels associated with, but not integral to, coagulopathy in trauma.

Nonetheless, the possibility of a role of SkM in coagulation and trauma-induced coagulopathy is intriguing. Recently, SkM has been reported to possess an intrinsic thrombin activation potential via FXI A3 domain binding.<sup>14</sup> SkM also indirectly promotes coagulation via obligatory phospholipid contamination with tissue factor.<sup>15</sup> Thus, SkM isoforms with potentially distinct affinities for FXI A3, or phospholipids bearing tissue factor, may indeed correlate with some of the variability observed in coagulation following trauma.

But as with all good research, the findings here raise many questions that must be addressed to better evaluate SkM as a sentinel of TIC. For example, does the release of SkM isoforms into the

bloodstream correlate with the muscular anatomy, mode, and severity of trauma, leading to the spectrum of Full-SkM levels in the plasma, or are there intrinsic biological differences between trauma victims leading to the dichotomous outcomes *in vitro*? To what extent are measurable SkM isoforms simply a surrogate marker rather than a true biomarker of coagulopathy? And beyond SkM, are there other components of the trauma coagulum such as tissue factor-loaded microparticles and citrullinated histone H3, which may confound the global coagulation results reported by Coleman and colleagues?<sup>9</sup>

#### CONFLICT OF INTEREST

All authors declare that they have no relevant conflicts of interest.

#### AUTHOR CONTRIBUTION

P.J. Crispin, P.Y. Choi, and E.E. Gardiner cowrote and reviewed the manuscript together. All authors approved the final draft.

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