Changes in Innate Immunity and the Bone Marrow Transcriptomic Response to Anemia following Severe Blunt Trauma

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Background:
Severe trauma is associated with severe systemic inflammation and neuroendocrine activation that is associated with erythroid progenitor growth suppression and prolonged refractory anemia. Subsequent poor outcomes after trauma are related to both the presence of anemia and the need for transfusion. This study sought to identify a distinct bone marrow transcriptomic response following trauma. We hypothesized that the post-traumatic human bone marrow transcriptomic response would be uniquely altered compared to elective hip replacement patients and healthy controls, with an upregulation of inflammatory activity and downregulation of basal erythropoietic activity.

Methods:
In a prospective observational cohort study, bone marrow was obtained from severely injured trauma patients with hemorrhagic shock and a hip or femur fracture (n=52), elective hip replacement patients (n=33) and healthy controls (n=11). RNA was isolated form the bone marrow using a Purelink RNA mini kit and analyzed for expression of 34 key inflammation and erythropoiesis-related genes on the nCounter MAX Analysis System (NanoString Technologies, Seattle, WA) to determine mRNA copy number. Raw data were normalized using the nSolver Analysis Software Version 4.0. Data presented as log2 fold change relative to healthy controls with significance set at *$p<0.05$.

Results:
Out of the 34 genes assayed, 18 showed significant differential expression between trauma and elective hip replacement cohorts (Figure). These genes encode proteins known to have inhibitory downstream effects on erythropoiesis including ferroportin, interleukin-1 beta (IL-1β), tumor necrosis factor alpha (TNFα), IL-6 receptor, transforming growth factor-beta (TGF-β) receptor, and IL-10, as well as genes involved in innate immunity including toll-like receptor 4 (TLR4) and its associated downstream signaling mediators. In contrast, hip replacement patients had downregulated transcription of erythropoietic inhibitors IL-1β, IL-6, TGF-β, TNFα, and hepcidin with no change in TLR4-mediated signaling factors.

Conclusions:
Differences in the bone marrow transcriptomic response to trauma were identified following severe blunt trauma and elective hip replacement. These differences in the bone marrow transcriptome were related to the innate immune response as well as known inhibitors of erythropoiesis which may explain why blunt trauma patients have a suboptimal erythropoietic response to anemia which can persist long after injury.