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Early Transfusion with Mesenchymal Stem Cell Derived Extracellular Vesicles: A New Transfusion Strategy for Life-Threatening Hemorrhage and Traumatic Brain Injury

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Abstract

Background:

Life-threatening hemorrhage and traumatic brain injury (TBI) have a significantly increasing global burden and remain leading causes of preventable deaths. Effective interventions may protect the brain against ongoing damage and improve the long-term outcomes. A growing area of interest is transfusion of cell-based therapies, particularly with bone marrow-derived mesenchymal stem cells (MSC). Transfusion using MSC derived extracellular vesicles (EVs) have shown to improve neurologic outcomes in animal models of life-threatening hemorrhage, stroke, and TBI. However, the precise mechanisms remain poorly characterized. In the present study, we aimed to elucidate some of the key cerebral genes, pathways, and networks that were modulated after transfusion of EVs in a porcine model of hemorrhagic shock (HS) and TBI.

Methods:

Swine were subjected to HS (40% blood volume) and severe TBI (8-mm cortical impact). After 1 hour of shock, animals were randomized (n=4/group) to treatment with either lactated Ringer's (LR) or LR+EV. Both groups received fluid resuscitation after 2hours of shock, and autologous packed red blood cells 5 hours later. After 7-days, brains were harvested and RNA-sequencing was performed. The transcriptomic data was imported into the iPathway pipeline for bioinformatics analyses.

Results:

5,273 genes were differentially expressed in the LR+EV group vs. LR alone (total 9,588 measured genes). Genes with the greatest up-regulation were involved in synaptic transmission and neuronal development and differentiation, while down-regulated genes were involved in inflammation. Gene Ontology terms experiencing the greatest modulation were involved in inflammation, brain development, and cell adhesion. Pathway analysis revealed significant modulation in the glutamatergic and GABAergic systems. Network analysis revealed down-regulation of inflammation, and up-regulation of neurogenesis, and neuron survival and differentiation.

Conclusions:

In a porcine model of HS+TBI, EV transfusion was associated with an attenuation of cerebral inflammatory networks and a promotion of neurogenesis and neuroplasticity. These transcriptomic changes could explain the observed neuroprotective and neurorestorative properties associated with EV transfusion. EV transfusion reduces the hyper-inflammatory response and may have great promise in improving outcomes in concurrent life-threatening hemorrhage and severe TBI. Further testing of this novel strategy and its implications in transfusion medicine are warranted.