Traumatic Brain Injury Induces Bone Marrow Dysfunction by Altering Bone Marrow Cellular Composition and Transcriptomic Profile

Anannya Das, Sagar Vyavahare, Nicholas S Moore, Abbas Jarrahi, SONU KUMAR GUPTA, Yujiao Lu, Mehek Sharma, Carlos Isales, Marco Corbo, Krishnan M Dhandapani

INTRODUCTION:
Traumatic brain injury (TBI), caused by an external mechanical force to the head, results in both acute and long-term impairments in cognitive function. According to the Centers for Disease Control and Prevention (CDC), the combined healthcare burden of fatal and non-fatal TBIs in the United States was estimated at $40.6 billion in 2017. While the bone marrow (BM) plays a critical role in tissue repair and the systemic response to injury, the impact of TBI on BM function remains poorly understood. Emerging evidence from our group and others suggests that TBI induces systemic immune dysregulation, including alterations in BM homeostasis, which may contribute to multi-organ complications and diminished quality of life.
METHODS:
This study aimed to characterize the effects of TBI on BM cellular composition and transcriptional changes using single-cell sequencing. We employed a controlled cortical impact (CCI) model of traumatic brain injury (TBI) in four-month-old male C57BL/6 mice (n = 3/group, CCI vs. sham). After 48 hours, BM cells were collected from the long bones and underwent single-cell RNA sequencing (scRNA-seq) at MedGenome (Foster City, California, USA). Data were analyzed using the 10X Genomic platform to perform alignment and UMI counting.
RESULTS:
We identified 17 distinct cell populations in the BM. Among these, four cell types exhibited statistically significant changes in abundance post-TBI: classical monocytes ($p = 0.020$), macrophages ($p = 0.019$), memory CD8+ T cells ($p = 0.043$), and progenitor cells ($p = 0.022$). Within these four cell types, we found several dysregulated genes compared to the sham group. Within the classical monocytes, we identified 194 dysregulated genes, comprising 119 upregulated and 75 downregulated genes. Within macrophages, we identified 161 dysregulated genes, comprising 46 upregulated and 115 downregulated genes. Within memory CD8+ T cells, we found 887 dysregulated genes, with 618 upregulated and 269 downregulated. Within progenitor cells, we identified 156 dysregulated genes, comprising 87 upregulated and 69 downregulated genes. Of interest, ELANE was upregulated in all cells. TSC22D3 and DDIT4 were also upregulated, and MT-CO3 and MT-ATP8 were downregulated in all cell types except memory CD8+ T cells. Additionally, FN1 was upregulated in macrophages and memory CD8+ T cells, and PTRN3 was upregulated in classical monocytes and progenitor cells.
DISCUSSION AND CONCLUSION:
Our findings reveal TBI-induced alterations in both the cellular composition and transcriptional landscape of BM. The upregulation of TSC22D3 (a glucocorticoid-induced leucine zipper protein) and DDIT4 suggests possible roles in inflammation and HIF-1α signaling, respectively. Downregulation of mitochondrial genes MT-CO3 and MT-ATP8 may indicate impaired redox homeostasis following TBI. The observed increase in FN1, an extracellular matrix glycoprotein associated with wound healing and inflammation, further supports the pro-inflammatory state of the brain microenvironment following TBI. This is the first study to comprehensively profile BM responses at the single-cell level following TBI. Our results highlight the potential role of BM-derived immune and progenitor cells in mediating post-TBI systemic inflammation and identify novel molecular targets for therapeutic intervention.