Dissecting Inflammatory Complications in Critically Injured Patients by Within-Patient Gene Expression Changes

John Storey

Lewis-Sigler Institute for Integrative Genomics of Princeton University, U.S.A.

Trauma is the number one killer of individuals 1-44 years old in the United States. The prognosis and treatment of inflammatory complications in critically injured patients continue to be challenging, with a history of failed clinical trials and poorly understood biology. New approaches are therefore needed to improve our ability to diagnose and treat this clinical condition. We conducted a large-scale study on 168 blunt-force trauma patients over 28 days, measuring ~400 clinical variables and longitudinally profiling leukocyte gene expression with ~800 microarrays. Marshall MOF clinical score trajectories were first utilized to organize the patients into five categories of increasingly poor outcomes. We then developed an analysis framework modeling early within-patient expression changes to produce a robust characterization of the genomic response to trauma. A quarter of the genome shows early expression changes associated with longer-term post-injury complications, captured by at least five dynamic co-expression modules of functionally related genes. In particular, an early down-regulation of MHC-class II genes and up-regulation of p38 MAPK signaling pathway were found to strongly associate with longer-term post-injury complications, providing a discrimination among patient outcomes from expression changes during the 40-80 hour window post injury. The genomic characterization provided here significantly expands the scope by which the molecular response to trauma may be characterized and understood. Additionally, the quantitative approach we have introduced is potentially applicable to future genomics studies of rapidly progressing clinical conditions.