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- Genomic Controlled Phenotypic Response to Severe Injury

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AWARDS

American Trauma Society: William S. Stone Award
Shock Society: Scientific Achievement Award
University of Washington, Department of Surgery: Distinguished Alumnus Award
American Heart Association: Lifetime Achievement Award
American Surgical Association: Flance-Karl Research Award
Accreditation Council of Graduate Medical Education: Parker J. Palmer Courage To Teach Award

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The Global Burden of Surgical Disease is increasingly recognized as a major impact on the economic health of any country. Within surgical disease, trauma is a major contributor, costing the United States over $250 billion per year. However, since trauma overall consists primarily of minor injuries, and patients at any given institution mostly do well, a sense of accomplishment and under-recognition of the true impact of major trauma is frequently assumed by physicians, the public and our legislators. This, combined with the great challenges involved in developing a high quality detailed physiologic dataset of the impact of severe trauma, has led the non-combatant into believing the war has been won.

Trauma remains a major cause of death and morbidity in America. It is the number one cause of mortality among 1–45-year-olds and is the overall number one cause of loss of productive years of life in America. Death due to injury occurs in three peaks: 1) at the scene; 2) during the acute resuscitation phase; and 3) late, after one to two weeks of ICU support, secondary to multiple organ failure and sepsis. My research focuses on each of these phases. Prevention provides the best means to minimize deaths at the scene and minimize ultimate morbidity. Trauma system developments and improvements in acute care, including optimal resuscitation, will reduce early deaths during the resuscitation phase and minimize subsequent morbidity. Finally, elucidation of the genomic and molecular responses to severe injury will identify treatment targets to prevent the dysregulated autodestructive inflammatory response causing organ dysfunction and death following trauma.

Harborview Injury Prevention and Research Center

I am Senior Advisor to the Harborview Injury Prevention and Research Center (HIPRC). The HIPRC is linked closely with the Northwest Regional Trauma Center at Harborview Medical Center. The goal of the HIPRC is to diminish the impact of trauma on people's lives and to draw analyses based on the effectiveness of the Northwest Regional Trauma Center's injury prevention and trauma treatment programs. Established at HMC in 1985, the HIPRC is a component of the University of Washington and the Schools of Medicine and Public Health.

Current projects include identifying the risk factors for injury while developing new techniques for the application of epidemiology in the field of trauma research. Further goals are to develop and utilize systematic, high-quality data systems to document the types, causes, treatment and consequences of injuries in a wide variety of settings. A particular focus is on assessment of outcomes and the impact of trauma system development. In addition, development and assessment of new, more effective means to resuscitate and treat injured patients along the entire spectrum of care, from pre-hospital to rehabilitation, is ongoing.

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Relationship Between Trauma Center Volume and Outcome

The premise underlying regionalization of trauma care is that optimal outcomes can be achieved at greatest efficiency if care is restricted to relatively few dedicated trauma centers. Implicit in this premise is that higher patient volumes will lead to greater experience, and this experience translates into better outcomes. This relationship appears to hold for other areas of surgical care involving complex procedures but, in contrast, there is no such relationship when less complex procedures are evaluated. Previous studies evaluating the relationship between institutional volume and outcomes in trauma patients are difficult to interpret because of multiple logistical issues.

Two distinct cohorts of trauma patients were evaluated, including penetrating abdominal injury and multisystem blunt trauma with, at a minimum, head injury and lower extremity long bone fracture, treated at 31 academic Level I or Level II trauma centers across the United States that participate in the University HealthSystem Consortium. Results indicate that a strong association exists between trauma center volume and outcome, with significant improvements in mortality and length of stay, but only when the volume exceeds at least 600 cases per year. These benefits were only evident in patients at the highest risk for adverse outcomes, and not in the vast majority of lesser-injured patients.

Splenic Injury

An ongoing study at the HIPRC investigates geographic variation in the management, outcome and costs of splenic injury. Reducing the variation that exists in health care practice is necessary for both improving health care quality and reducing unnecessary costs. Splenic injury is an appropriate model to study variation in trauma care, as it is a common injury that has undergone a recent evolution in management. The Healthcare Cost and Utilization Project (HCUP) State Inpatient Database (SID) for 2001, 2004, and 2007 was used to detect significant variation in a state-to-state comparison of management and outcomes for 33,131 hospitalized patients with splenic injury. After adjusting for patient, injury, and hospital factors, multivariate regression demonstrated up to a 1.7-fold difference in the use of splenectomy between states, a 2.4-fold variation in mortality, and a 1.7-fold variation in costs. Reducing this variation through the development of and adherence to management guidelines should be a priority for the delivery of cost effective care.

Clinical Trials in the Surgical Intensive Care Unit

We are performing multiple ongoing trials based on the pathophysiologic response of the severely injured patient, many in conjunction with the Division of Pulmonary and Critical Care in the Department of Medicine. In particular, clinical studies and associated basic investigations are focused on acute respiratory distress syndrome (ARDS), which affects critically ill and injured patients.

ARDS is largely responsible for the prolonged intensive care unit and hospital stay, and contributes significantly to mortality in these patients. Management is primarily supportive while the underlying disease process stabilizes and resolves. Attempts to reduce the consequences of ARDS have focused upon: 1) pharmacologic manipulation of the inflammatory response; and 2) modifying positive pressure ventilation techniques to reduce the potential iatrogenic ventilator-associated lung injury. Examples of current studies are:

Modulation of the Inflammatory Response

The potentially auto-destructive excessive immuno-inflammatory response is thought to contribute to the initiation and progression of ARDS and multiorgan failure (MOF) and to ultimately affect patient outcome. Work at Harborview Medical Center (HMC) has shown a high incidence of vitamin C and vitamin E deficiency in trauma patients admitted to the HMC intensive care unit (ICU). Reports from other institutions document a low plasma vitamin C concentration in 28–83% of hospitalized ICU patient populations and 12–21% of all new hospital admissions.

Our HMC study demonstrated that supplementing 3 grams/day of vitamin C and 3000 IU/day of vitamin E in patients with initially low levels resulted in plasma levels within the normal reference range within seven days. Patients not receiving supplements remained in the low or below the reference range. In addition, patients with ARDS have been shown to have high levels of oxidants and suppressed levels of antioxidants, such as vitamin C and vitamin E, in bronchoalveolar lavage (BAL) specimens. We hypothesized that routine supplementation of vitamins C and E would protect against oxidant-induced organ injury in severely injured and stressed patients, and avoid the diffuse insult predisposing to ARDS and other organ dysfunction, along with secondary nosocomial infections such as ventilator-associated pneumonia and wound infections. In a prospective observational study, all trauma admissions to the HMC surgical ICU had three grams of vitamin C or 3,000 IU of vitamin E, divided over three doses per day, started at the time of admission. Otherwise, care was standard and the populations were followed to determine the incidence of ARDS, duration in the ICU, mortality and infectious complications. In addition, we studied BAL samples for evidence of oxidant injury and cytokine production.

The results show that the treatment with anti-oxidant supplementation on admission to the surgical ICU produced a 50% reduction in evidence of oxidant injury in the BAL solution, along with a 50% reduction in the production of inflammatory mediators, while having no detrimental effect on the production of antibacterial mediators of the immune system. Concomitant with this decrease in the intrapulmonary inflammatory response, there was a decrease by 50% in the incidence of ARDS and a significant decrease in the length of stay and ventilator days in these critically ill patients. Concomitant with this decrease in development of ARDS and inflammation was a 50% reduction in mortality in the treated population.

Modulation of the Trauma-Related Macrophage Inflammatory Response to Prevent ARDS, MOFS and Death

A major area of investigation is based on the aberrant host immuno-inflammatory response to trauma and sepsis. This auto-destructive response is thought to be responsible for the induction and persistence of the "malignant systemic inflammatory response" underlying ARDS and multiple organ failure syndrome (MOFS). ARDS and MOFS are the major determinants associated with late death following trauma.

The primary etiology of ARDS and MOFS leading to late mortality following trauma is the clinical "sepsis syndrome," or systemic inflammatory response syndrome (SIRS). This diffuse inflammatory response causes disseminated tissue injury and subsequent organ dysfunction. The long-lived, highly diverse tissue-fixed macrophage is a crucial central coordinator of both the normal and the aberrant host immuno-inflammatory response. The macrophage is both primed and activated by a multitude of stimuli during the inflammatory response.

Until now, therapeutic approaches have focused on control or inhibition of single components of the overall inflammatory response. However, since the inflammatory response is replete with redundancy and feedback amplification mechanisms, it is appealing to take a broader approach to control the inflammatory response and subsequent injury to multiple diffuse organ beds. To achieve this goal in these basic laboratory investigations, we are focusing, in part, on the cellular and molecular mechanisms involved in macrophage signaling and activation by inflammatory stimuli and the subsequent production of multiple inflammatory cytokines.

The goal is to develop therapeutic interventions based on controlling these intracellular transduction pathways and to modulate the over-aggressive macrophage response and the subsequent auto-destructive immuno-inflammatory response. Currently, we are studying the manipulation of cellular signal transduction mechanisms that control inflammatory mediator genes by altering the intracellular levels and release of calcium, the regulation of levels of cyclic AMP and the delineation of regulatory protein kinase signal transduction pathways, particularly the MAP kinase family, including ERK1/2, JNK and r38. In addition, we are investigating signaling processes activated through formation of focal adhesion complexes induced by adherence of the monocyte/macrophage as critical to the host inflammatory cell response.

A major focus is on the ability of antioxidants, such as vitamin E, or cytoskeletal spatial disruption with agents, such as cytochalasin D, to modify the cellular response to inflammatory stimuli. Recent investigations have also demonstrated that hypertonic preconditioning similarly disrupts the signaling pathways in the macrophage. Hypertonic saline has been shown to produce an adequate resuscitation for the severely injured while limiting the excessive inflammatory response. Recent investigations have confirmed that hypertonic saline led to a reduction in ERK1/2 phosphorylation with no effect on r38. This was correlated with an inhibition of stress fiber formation in the macrophages and appears to link to cytoskeletal polymerization for optimal MAP kinase signal transduction and inflammatory mediator production. Thus, hypertonic saline early in the response of the host to reperfusion injury could lead to a reduction in subsequent organ injury and failure. Elucidation and control of these macrophage cellular mechanisms will permit development of future safe therapies to prevent ARDS, MOFS and death in the critically ill surgical patient.

Genomic Controlled Phenotypic Response to Severe Injury

Lastly, to better understand the pathophysiologic phenotype in the severely injured patient, a collaborative study has been developed with the Stanford Genome Institute and Harvard Bio-Statistics Department, and funded by the National Institutes of Health National Institute of General Medical Sciences (NIH-NIGMS) for a consortium and large-scale project grant or "Glue Grant." The intent is to study the entire human genomic response serially across time to the stress of severe injury, resuscitation and subsequent MOF or nosocomial infection. To enable this, the technological developments necessary for reproducible, high quality isolation of RNA, including microfluidics, and analysis via microarray chips have been developed through this consortium. The analysis of gene expression data in clinical medicine has been plagued by a lack of critical tools of accepted methodologies for the analyses of total RNA expression data.

Whole blood obtained from healthy subjects or trauma patients had total RNA isolated from the circulating leukocyte "Buffy coat." cRNA was hybridized to Affymetrix GeneChips, and unsupervised analyses, including hierarchal cluster analysis, were used to measure RNA expression. Subjects for severe blunt trauma and hypotension or acidosis, requiring resuscitation with blood products, were studied at 7 participating institutions with blood sampling at the initial 12 hours and on days 1, 4, 7, 14, 21 and 28 days after injury. Whole blood leukocytes were isolated, and genome-wide expression analyses were performed. Severe trauma alters the expression of >75% of the leukocyte genome over 28 days post injury. The response is highly coordinated and reproducible. Variations in the quantity of blood transfused contribute only modestly to the changes in gene expression. Individuals with a complicated clinical recovery in organ failure demonstrate selective prolonged increases and decreases in the expression of genes involved, primarily in the innate and adaptive immune response, respectively. There is no genomic evidence of either multiple inflammatory events consistent with the second hit, or the delayed expression of adaptive immunity genes associated with a compensatory anti-inflammatory response, which has been commonly portrayed as dogma in this field of investigation. The functional genomic units affected primarily by severe injury are now being identified (Figure 1), and can be utilized as a focus for potential therapeutic intervention to confirm both causal relationship of alteration to subsequent phenotype, and also as a much greater opportunity to identify therapeutic interventions that are likely to succeed in modifying patients' phenotypic response and ultimate clinical outcome.

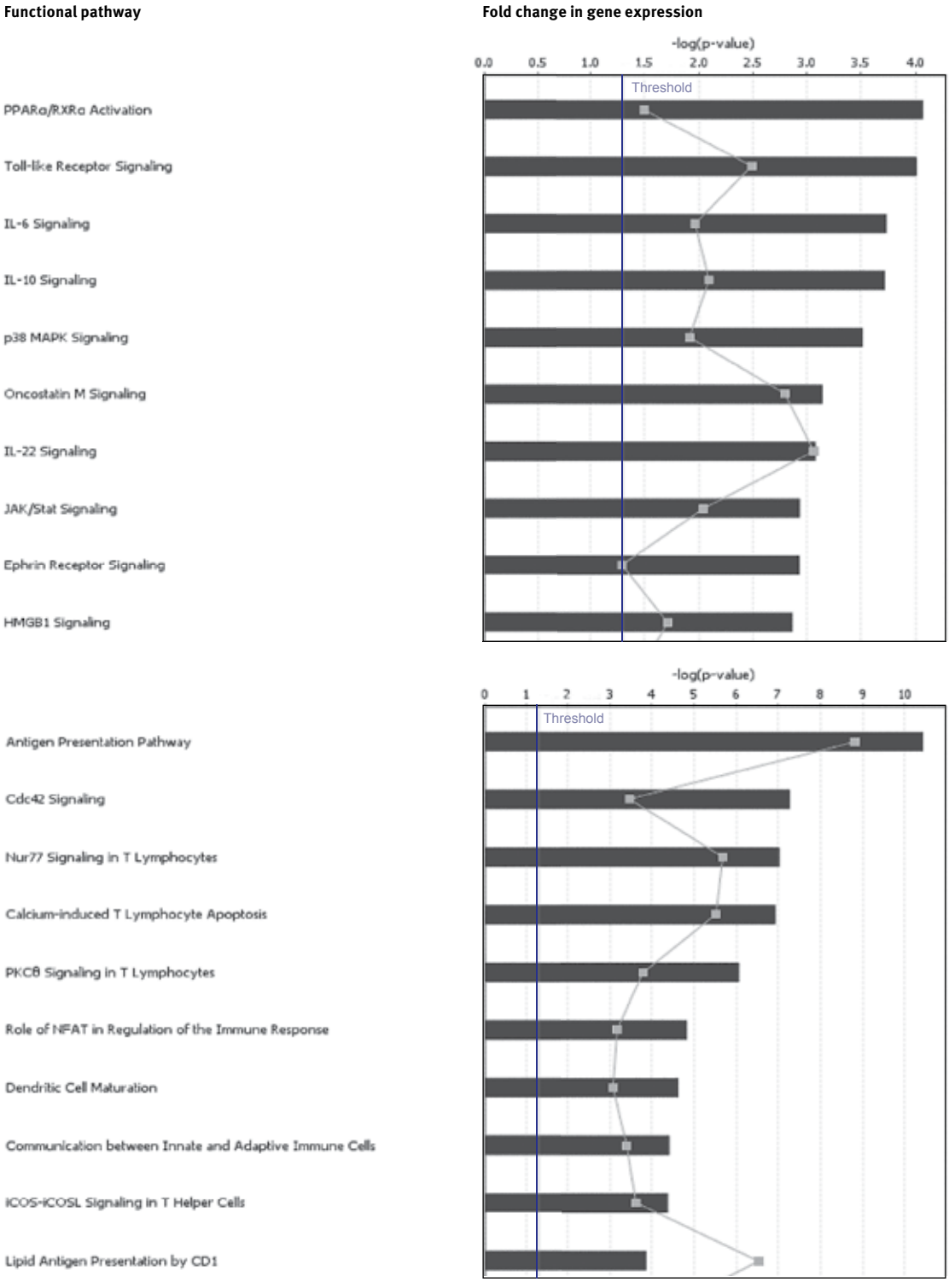

FIGURE 1. The functional genomic pathways that are primarily affected by severe injury

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