A Better Understanding of Why Murine Models of Trauma Do Not Recapitulate the Human Syndrome*

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*See also p. 1552.

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Objective: Genomic analyses from blood leukocytes have concluded that mouse injury poorly reflects human trauma at the leukocyte transcriptome. Concerns have focused on the modest severity of murine injury models, differences in murine compared with human age, dissimilar circulating leukocyte populations between species, and whether similar signaling pathways are involved. We sought to examine whether the transcriptomic response to severe trauma in mice could be explained by these extrinsic factors, by utilizing an increasing severity of murine trauma and shock in young and aged mice over time, and by examining the response in isolated neutrophil populations.

Design: Preclinical controlled in vivo laboratory study and retrospective cohort study.

Setting: Laboratory of Inflammation Biology and Surgical Science and multi-institution level 1 trauma centers.

Subjects: Six to 10-week-old and 20- to 24-month-old C57BL/6 (B6) mice and two cohorts of 167 and 244 severely traumatized (Injury Severity Score > 15) adult (> 18 yr) patients.

Interventions: Mice underwent one of two severity polytrauma models of injury. Total blood leukocyte and neutrophil samples were collected.
Measurements and Main Results: Fold expression changes in leukocyte and neutrophil genome-wide expression analyses between healthy and injured mice (p < 0.001) were compared with human total and enriched blood leukocyte expression analyses of severe trauma patients at 0.5, 1, 4, 7, 14, and 28 days after injury (Glue Grant trauma-related database). We found that increasing the severity of the murine trauma model only modestly improved the correlation in the transcriptomic response with humans, whereas the age of the mice did not. In addition, the genome-wide response to blood neutrophils (rather than total WBC) was also not well correlated between humans and mice. However, the expression of many individual gene families was much more strongly correlated after injury in mice and humans.

Conclusions: Although overall transcriptomic association remained weak even after adjusting for the severity of injury, age of the animals, timing, and individual leukocyte populations, there were individual signaling pathways and ontogenies that were strongly correlated between mice and humans. These genes are involved in early inflammation and innate/adaptive immunity. (Crit Care Med 2014; 42:1406–1413)

Key Words: blunt trauma; microarray; mouse model; shock

Injuries from trauma continue to be the leading cause of death for persons less than 45 years in the United States (1, 2). Despite recent advances in trauma and critical care, as well as an improved understanding of the basic pathophysiology of severe trauma and its sequelae, morbidity and mortality, especially later following trauma, remain high (3). Although it is generally accepted that murine models do not fully recapitulate the human condition in its entirety, they remain the mainstay for invasive and interventional studies in trauma and burns (4). This reliance on a single species (Mus) has raised considerable concerns about its appropriateness, given the recently published transcriptomic differences to trauma, burns, and endotoxins between humans and mouse (5), in addition to innumerable failed clinical trials based on “cures” in mice derived from monogenic approaches in assumed appropriate models of injury. Criticism of these findings has centered on potential nongenomic differences between murine and human trauma, including the severity of the injuries, the differences in comparative age between humans and mice, the differences in the baseline blood leukocyte patterns between mice and humans, and the focus on the total leukocyte genome rather than on those cell-specific genes and pathways involved in inflammatory and immune responses. In the present report, we specifically examined whether more precisely matching the murine model to human trauma in terms of comparative age, severity of injury, timing of sample collection, type of circulating leukocyte population (neutrophils), and subanalysis of combinations of these would improve the transcriptomic correlations between the two species. Of note, we have recently reported that by increasing the severity of the traditional murine trauma model (6) to one that is multicompartamental, including hemorrhagic shock, long bone fracture, soft-tissue damage, and a cecectomy, we are better able to recapitulate the early plasma inflammatory cytokine and chemokine responses and the phenotypic leukocyte changes following severe human trauma (7).

MATERIALS AND METHODS

Human Subjects

Two populations of trauma patients were included: the first whose blood was collected and processed to conduct genome-wide expression analyses on whole blood leukocytes (1, 8), and the second whose blood was processed to conduct expression analyses on isolated blood neutrophils, monocytes, and lymphocytes. The first consisted of 167 severely injured trauma patients, who are 18–55 years old, who were enrolled from 2003 to 2006, along with 35 healthy age, gender, and ethnicity-matched control subjects (1). These entry criteria included those who suffered from severe blunt trauma with Injury Severity Score (ISS) more than 15, systolic hypotension (<90 mm Hg), or elevated base deficit more than or equal to 6 mEq/L and requirement for blood transfusion within 6 hours of injury. Patients with traumatic brain injuries were excluded. All subjects were treated under study protocols using standard operating procedures to minimize treatment variation (9) and at centers with institutional review board approval. In the second set of patients which was used for the leukocyte subset analysis, 244 severely injured trauma patients who are 16–90 years old (2006–2010), with the same inclusion and exclusion criteria as above, were compared with 57 healthy, matched controls. Blood neutrophils, monocytes, and lymphocytes were isolated as previously reported (10, 11), and genome-wide expression was determined. The patients were taken from the “Inflammation and Host Response to Injury Large-Scale Collaborative Research Program.” This study was reviewed by the Institutional Review Boards at Massachusetts General Hospital and the University of Florida and was approved.

Murine Models

Male C57BL/6J mice from either Jackson Laboratory (Bar Harbor, ME) (young, 6–10 wk) or the National Institute of Aging (old/aged, 20–24 mo) were housed in pathogen-free facilities and acclimated at least 1 week prior to use under protocols approved by the University of Florida Institutional Animal Care and Use Committee. As previously described, using inhalational anesthesia, groups of mice underwent one of two models of trauma and shock (7). All mice underwent unilateral or bilateral femoral artery cannulation followed by shock induced by removing enough arterial blood to be maintained at a mean blood pressure of 30 mm Hg (±5 mm Hg) for 90 minutes while awake. Mice were subsequently resuscitated with a crystalloid solution at four times the blood volume drawn. Next, mice were reanesthetized and underwent either a one centimeter laparotomy to simulate the traditional model of trauma-hemorrhage (TH) or a more severe model including a one centimeter laparotomy with cecectomy combined with medial thigh dissection with femur fracture and...
muscle tissue damage (polytrauma) (7). After injury, the mice were administered buprenorphine (0.2 mg/kg bodyweight) prior to arousal from anesthesia and every 12 hours afterward until they were killed. Mice were euthanized after 2 hours and on postoperative days 1 and 3, and blood was collected for analysis. Blood samples from naïve 6- to 10-week-old and 20- to 24-month-old animals were used as murine controls. To determine whether old mice required a unique control group, we ran blood leukocyte genomic analyses between naïve young and old mice, and it was determined by cluster analyses that expression patterns from the two ages of mice could not be distinguished. Therefore, control samples were combined as one control group (data not shown). Four mouse replicates were used for each group as mice are expected to be genetically similar and exhibit reduced heterogeneity compared with the human population.

Gene Expression Profiling
As previously published, human total blood and enriched leukocytes were isolated, and RNA was extracted and hybridized onto either the Affymetrix HU133 Plus 2.0 or the HH1/2/3 GeneChip (Affymetrix, Santa Clara, CA) (12) according to the manufacturer’s recommendations (7, 8). For human neutrophil isolation, microfluidics was used to capture all polymononuclear leukocytes bearing carcinoembryonic antigen-related cell adhesion molecules-8, as previously described (11). Briefly, captured PMNs were lysed and total RNA was extracted and analyzed in the same manner as described above for total leukocytes. For lymphocytes and monocytes, enriched populations of human lymphocytes and monocytes were isolated from peripheral blood samples using a two-step negative immunoselection protocol, consisting of binding antibody to unwanted cells then using density centrifugation removal of those cells, followed by enriching the remaining populations with antibody-bound bead columns (10).

Murine total blood leukocytes were isolated using the exact same procedures as for human blood samples. Murine PMNs were isolated by Ficoll-dextran isolation as previously described (11). Total cellular RNA was extracted as for the human samples and hybridized to the Affymetrix Mu430 2.0 GeneChip (Affymetrix) according to the manufacturer’s recommendations.

Statistical Methods
Significant genes were selected by identifying trauma-responsive genes in humans (167 patients) versus human control subjects (35) at a p value of less than 0.001. For genes that were represented by multiple probesets, the probeset with the highest expression value was used for analysis. Once the trauma-responsive significant genes were identified (Table 1), fold changes were calculated between mean values from human patients and control subjects. The same approach was used for the determination of the gene expression patterns from individual leukocytes from the 244 trauma patients in the second cohort. Next, the corresponding mouse orthologues to the human trauma-responsive genes were identified (Table 1). Fold changes were calculated on the mouse orthologues between mice that had undergone injury and naïve control mice.

Pathway Analysis
After identifying genes whose expression changed significantly from control (p < 0.001), we then performed a pathway analysis on the condition with the highest correlation at each human time point. We identified the top 100 up- and down-regulated genes in the humans and their corresponding mouse orthologues and analyzed them for interactions and relationships using Ingenuity Pathway Analysis (IPA) (http://www.ingenuity.com). IPA was also used to identify the most overexpressed canonical pathways and the most highly up- and down-regulated genes.

RESULTS
Injury Severity, but Not Sample Timing or Age, Improves Gene Expression Correlations Between Murine and Human Trauma
For human trauma, we used existing data from 167 trauma patients obtained from the Inflammation and Host Response to Injury, Large-Scale Collaborative Research Program (Glue Grant) who had total blood leukocyte genome-wide expression determined (8). Human trauma patients had blunt trauma without brain injury, an ISS more than 15, systolic

<table>
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<tr>
<th>Human Time Point (d)</th>
<th>Human Probe Sets at p &lt; 0.001</th>
<th>Mouse Orthologues</th>
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<tbody>
<tr>
<td>0.5</td>
<td>31,847</td>
<td>11,720</td>
</tr>
<tr>
<td>1</td>
<td>31,239</td>
<td>11,585</td>
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<tr>
<td>4</td>
<td>30,643</td>
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<td>21</td>
<td>21,763</td>
<td>9,475</td>
</tr>
<tr>
<td>28</td>
<td>21,492</td>
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For human total leukocyte gene expression from the 167 patients after severe trauma, an analysis of variance analysis was run on discrete age ranges (16–32 vs > 32–55 yr and 16–44 vs > 44–55 yr), and we found that gene expression was not different. The 244 trauma patients were divided into groups of those less than or equal to 55 years and those greater than 55 years.

Spearman correlations were calculated to assess the correlation between changes in gene expression in murine and human samples in multiple subgroup analyses, including age, leukocyte subset, and timing of injury. Because of the large number of correlations conducted, a conservative Bonferroni correction was used to adjust the α probability of p value of less than 0.05.
hypotension (< 90 mm Hg), or elevated base deficit more than or equal to 6 mEq/L, and requirement for blood transfusion within 6 hours of injury. Blood samples were collected in the first 12 hours and at days 1, 4, 7, 14, 21, and 28 after trauma, during hospitalization. In comparison, we used two murine trauma models: the traditional murine trauma model used in earlier studies where C57BL/6 (B6) mice underwent 90 minutes of shock (mean arterial blood pressure of 30 mm Hg) and resuscitation via femoral artery cannulation followed by a midline abdominal laparotomy (TH) (13, 14), and a more recent model of polytrauma where the TH model was supplemented with a cecectomy and femur fracture with muscle tissue damage (PT) (7). Blood samples were collected at 2 hours and 1 and 3 days. Genome-wide expression analysis was performed on total leukocytes and enriched blood neutrophil populations. Murine trauma was induced in both 6- to 10-week-old animals (equivalent to a 14- to 20-year-old humans) and in 20- to 24-month-old animals (equivalent to 55- to 70-year-old humans) (15).

We first examined the human probe sets whose expression changed at p value of less than 0.001 at individual time points (between 21,492 and 31,847) and subsequently identified their mouse gene orthologues (between 9,475 and 11,720) (Table 1). Focusing on these genes, we compared the changes in gene expression of total blood leukocytes in a traditional TH model of murine trauma with human blunt trauma, and we see weak correlations, regardless of the timing of the measurements (Fig. 1). These findings confirm those of Seok et al (5) demonstrating sporadically significant correlations between human trauma and murine TH and in some cases significant inverse correlations. However, because of the large number of genes included in the correlation, the biological significance of statistically significant correlations ranging from 0.05 to 0.1 is essentially zero. These weak correlations are independent of the age of the mouse, employing either a juvenile mouse (6–10 wk) or an older mouse (20–24 mo). We also distinguished gene expression between adults under the age of 45 years versus those 45–55 years old from the initial dataset (8) and found no improvement in the genome-wide correlation in gene expression with either juvenile or aged mice (data not shown).

We then examined the effect of model severity on how well the human and mouse genomic changes correlate following severe trauma. We found that by increasing the model severity alone, we were able to improve the correlation in genome-wide expression between murine PT and human trauma, as evidenced by improved Spearman correlations (Fig. 1); however, the improvements were modest.

We then examined the effects of age and timing on the correlations using the more severe PT model and found that there was no consistent improvement in the correlation between mouse and human genome-wide expression based on the timing of the blood sampling nor were the genome-wide correlations in expression improved by inducing severe polytrauma in aged mice (data not shown).

Analyzing and Comparing Circulating Human Leukocyte Subsets to Murine Samples Improves Gene Expression Correlations
It is well known that the dissimilarities in the cellular composition of the circulating leukocytes between mice and humans may underlie some of the differences seen when comparing the murine and human responses to trauma (Fig. 2A) (5, 16, 17). To explore whether exploiting these differences would improve the correlation between human trauma and murine models, we performed subgroup analysis comparing murine total leukocytes to enriched human T cells, monocytes, and PMNs. The human patients in this previously unpublished analysis consisted of 244 blunt trauma patients with the same inclusion criteria listed previously in whom neutrophils, monocytes, and T cells were isolated, and genome-wide expression was performed on enriched cell populations. In this second cohort obtained from the Glue Grant between 2006 and 2010, we compared the expression of murine total leukocytes to each human isolated leukocyte and performed a direct comparison of murine and human circulating neutrophils. This subgroup analysis was able to improve the correlation by three-fold as compared with the best value for the TH model for the majority of the correlations, and these best correlations with their optimal adjustments are illustrated in Figure 3.

Performing a More Restrictive Analysis on Matching Enriched Cell Populations Improves Spearman Correlations Between Human Trauma and Murine Trauma Models
We then compared the expression of enriched murine neutrophils following the PT model with human neutrophils at the same time points, and there was no improvement in the correlations over the comparison between mixed leukocyte populations (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A841). However, when a more restrictive analysis was performed examining only those genes whose expression had a greater than 1.5-fold change, we were able to significantly improve the best Spearman correlations between neutrophil enriched populations (0.21–0.43, respectively) (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/CCM/A841).

Although Overall Genome-Wide Expression Between Murine Models of Trauma and Humans May Be Modest, Functional Analysis Reveals That Selected Individual Gene or Pathway Responses Are More Similar
A general criticism of using a broad, genomic approach may be that it has limited significance if the investigator has a specific interest in individual genes or pathways. Even in the absence of overall correlations in gene expression, the expression of selected individual gene or pathway responses may be very similar. For example, when examining the top 100 responsive genes to trauma in humans over time, we observed that 80–99% of the same genes were also up-regulated following murine PT (Fig. 3), thus indicating that the majority of top responsive
genes are behaving similarly in both mice and humans after injury. Not surprisingly, many of these genes were involved in early inflammatory processes and innate immunity. This was confirmed by functional analysis using IPA which revealed that the majority of these pathways were involved in early inflammatory responses and activation of innate immunity (Fig. 3). They included up-regulation of nuclear factor-κB, mitogen-activated protein kinase, and Janus kinase/signal transducer and activator of transcription signaling pathways associated with cytokine signaling and down-regulation of T-helper cell differentiation pathways.

DISCUSSION

Although there has been recent criticism about the validity of murine models of trauma and burns (5), most investigators in the field recognize the critical role they have played. Despite this persistent question regarding the appropriateness of using murine models to study human trauma and burns, there remains considerable evidence that murine models have proven useful for evaluating other inflammatory processes in humans, most notably in the development of anti-inflammatory and anti-immunity drugs for rheumatoid arthritis (e.g., etanercept, anakinra, abatacept, tocilizumab, and tofacitinib) (18). However, rheumatoid arthritis is a chronic low-grade human inflammatory condition caused by autoimmunity, and not the “genomic storm” of severe injury (8), which may also help to explain the failure to translate these identical therapies in the acute injury setting.

Understanding the limitations of murine studies is essential as the majority of new drugs target specific genes and pathways, and differences between mice and humans can lead to inconsistent or incorrect conclusions. Similar to Seok et al (5), we have illustrated that the overall total murine leukocyte transcriptomic response to severe injury and shock is dissimilar to humans when using current rodent models of trauma appropriately limited because of animal welfare concerns. Only modest
improvements can be made by humanely increasing the severity of the injury and specifically looking at certain times post injury and focusing on individual human leukocyte populations.

Undoubtedly, the one determinant that can be best improved upon is the severity of the traumatic injury, as moving from a simple TH model to a model of polytrauma significantly improves the overall genome-wide correlations. Regardless, overall comparison of total blood leukocytes is still suboptimal, and recognizing the limitations of these models is essential. However, the results are not all gloom and doom. Focusing on specific genes or cell signaling pathways can still prove valuable in predicting what the human response would be under similar conditions. For example, in Figure 3, we list immune-related pathways and genes of interest garnered from an analysis comparing the top 100 up-regulated and top 100 down-regulated genes in humans to their murine orthologues. Here, we show that canonical pathways including acute phase response signaling, interleukin (IL)-10, IL-6, and JAK/STAT signaling all behave in a similar manner in both mice and humans following trauma. Similarly, we list genes involved in early inflammatory responses and activation of innate immunity, such as ARG1, MMP9, and SOCS3 that behave in the same manner. Efforts to validate the comparative responses of individual genes or pathways in these models might improve their acceptance by the scientific and medical communities.

At the genome-wide response in total circulating leukocytes under the best of circumstances, less than 10% of the variation in human gene expression could be predicted by changes in the mouse genome. Mouse models may fail to surpass this level for multiple reasons, including, but not limited to, species differences, differences in homogenous versus heterogeneous responses, and differences in the severity of their injuries. For example, the murine PT is a nonlethal model and the genomic response is returning to baseline by 3 days (data not shown). As there was no consistent difference in the correlation between mouse and human genome-wide expression based on the timing of the blood sample collection, the fact that the correlations of PT day
3 mice did not significantly decline when compared with later time points post human trauma sampling may indicate that earlier time points in murine models may still reflect subacute and chronic ICU patients at some level. Alternatively, in the human studies, approximately one third of the cohort had an uncomplicated outcome and were discharged from the ICU within 5 days, while roughly, another one third either were hospitalized for organ failure for longer than 14 days or died (1, 8). Thus, the lack of time dependence may reflect the heterogeneity of the human population.

However, this was not necessarily true for specific gene pathways and ontologies. In fact, of those genes that changed the most in the human blood leukocytes after trauma, 88–100% of the murine orthologues changed in a similar direction. Similarly, the most overrepresented pathways and ontologies were those involved in cytokine signaling and inflammation in humans after trauma and were generally recapitulated in the mouse, as listed in Figure 3.

It is not clear as to why gene expression from total murine leukocytes at certain time points better reflect gene expression in specific human leukocyte populations in the early and later phases after trauma (Fig. 3). An overall pattern emerged that the genomic response of murine total circulating leukocytes best reflects the human T-cell response in the early phases after severe injury, whereas later time points in both mice and humans better correlate to expression by human myeloid cells (data not shown). This may be a reflection of the myeloid response associated with sepsis and trauma that is associated with the persistent inflammation immunosuppression catabolism syndrome (19). Regardless, the transcriptomic differences or similarities between mice and humans cannot be easily explained by differences or similarities
in the prevalent type of circulating leukocyte after injury (Fig. 2B). In general, the genome-wide correlations between mice and humans are improved after accounting for the severity of the injury model, sampling intervals, and differences in leukocyte populations with time, although they remain modest at best (Fig. 4).

Despite more precisely matching the murine model of injury to the injury sustained in human trauma patients, another limitation remains: the fact that severely injured human trauma patients receive continued ICU care, including, but not limited to, mechanical ventilation, blood transfusions, placement of invasive central catheters, and Foley catheters, whereas the mice are merely resuscitated and then receive ongoing pain management. Indeed, although blood leukocytes are undoubtedly important cells in the immune response, they most certainly are not the sole cell type to help orchestrate the immune response. Many other immune tissues and cell types are involved in a septic or traumatic insult. These may be equally important as blood leukocytes and may even show stronger correlations to humans; hence, the investigation into appropriate murine models that reflect the human condition should continue.

CONCLUSIONS

In conclusion, the findings suggest that murine biology cannot be assumed to accurately represent the entire complexity of the human response, and thus, murine research should not be used indiscriminately without validation a priori. Investigators must strive within sufficient capacity to develop rodent models that best mimic human insults and pathology. However, mouse models can suitably reflect specific components of the human response, and these physiologic or pathophysiologic functions can be examined, assuming that there is an appropriate understanding of the limitations of the data obtained, as well as reasonable validity of the model under investigation.

REFERENCES


