Concerns over interspecies transcriptional comparisons in mice and humans after trauma

We have read with interest the study by Seok et al. (1) describing transcriptional responses of the immune systems of humans and mice. The authors perform Affymetrix GeneChip-based microarray assays on blood samples collected from blunt trauma, burn, and endotoxemia patients and mouse models of these pathologies. They report little correlation between human and murine genomic responses. Furthermore, the authors assert that mouse models of human disease are of questionable value due to the low biological similarity they observed.

This paper raises some legitimate issues regarding mouse vs. human differential and temporal responses at a gross whole blood level to biological perturbations occurring in other tissues. However, we are concerned that the failure to examine more than a single immune-polarized mouse strain, the lack of correction for differentially abundant cell types, and the use of data analysis approaches that did not consider these factors in an additive fashion strongly limit the conclusions that can be drawn from the data. We question the value of broad comparisons between genetically diverse patients and a single strain of mice. Male C57BL/6 inbred mice, which were used exclusively, have minimal genetic variation and are predisposed to Th1-mediated immune responses (2). Inclusion of additional mouse strains should have been considered in the study design to avoid pseudoreplication (3). Therefore, genetic background is the more appropriate unit of replication and not the individual patient or mouse.

Differences between human and mouse responses to traumas are likely exaggerated when time course data are used in aggregate rather than comparing biologically analogous time intervals and individual cell populations. Mouse and human leukocyte populations differ; thus, the majority of observed effects could be attributed to differential cell population margination or cell death rather than pathway-specific alterations of otherwise constant levels of different cell types. The authors apparently compared expression data from total blood leukocytes collected up to 1 y after injury in human patients vs. only 1 wk in murine models. Although it is certainly true that recovery rates between humans and mice differ, it is inaccurate to suggest that the genomic responses are dissimilar when parallel information is not used.

An additional issue is that data were analyzed without consideration of potential error resulting from variations in sensitivity among different probe sets for genes on the microarrays, which may have led to overestimation of expression divergence between species (4, 5). Further, although negative R values can indicate an inverse correlation, the coefficient of determination, R^2, cannot be negative (see figures 3 and 4 and table 1 in ref. 1). Finally, validation of expression levels using complementary methods (e.g., quantitative PCR or Western blotting) was not presented.

We believe these concerns must be addressed before broad conclusions can be drawn from the data. The current conclusions are especially troubling in light of the attention given to this study by the popular media. Although concerns exist regarding the utility of animal models in translating basic research to successful clinical treatments, we believe the current conclusions drawn from this manuscript are of questionable validity.

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The authors declare no conflict of interest.

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