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Mouse models fail to reproduce inflammatory genomic response to serious injuries

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Existing mouse models do not appear to accurately reproduce the human genomic response to serious traumatic injury, including major burns, according to an article appearing in *PNAS* Early Edition.

The report from a national consortium investigating the role of inflammation in the body's response to injury finds little correlation between the human response to burns, trauma or a bacterial toxin and that of currently used mouse models for those conditions. The authors note that their results cannot be applied to the use of mouse models for other research purposes.

"Our findings question the validity of using mouse models to mimic inflammatory conditions in humans," says Shaw Warren, MD, of Massachusetts General Hospital (MGH), co-lead author of the report. "An additional finding is that the whole-genome responses to these conditions in humans correlated well with each other, suggesting that treatments developed for an inflammatory disease from one cause might also work for inflammatory diseases with different causes."

The study is part of the Inflammatory and Host Response to Injury consortium (www.gluegrant.org), established in 2001 to investigate how the human body responds to injury, with particular attention to factors that set off excessive, uncontrolled inflammation. Based at the MGH, the program includes investigators from 20 academic research centers

around the country and is led by Ronald G. Tompkins, MD, ScD, Sumner M. Redstone Professor of Surgery at MGH and co-corresponding author of the current report.

In 2011, the group reported finding that serious injuries set off a "genomic storm" in the human body, altering around 80 percent of normal gene expression patterns. The current study drew on information from that study and others conducted by the consortium to compare the human genomic response to inflammatory disease with that of mouse models. The investigators from MGH, the Stanford University Genome Technology Center and several other research centers combined data from four of their studies of genomic responses to systemic inflammation: two in burn or trauma patients and volunteers treated with a bacterial toxin that produces brief flu-like symptoms and two studies of the responses in mouse models of the three conditions.

While the responses among human patients were very similar, showing highly significant changes in the expression of more than 5,500 genes, there was very little correlation with the expression patterns of corresponding genes in the mouse models. Not only was the human genomic response to inflammatory injury much greater – affecting the expression of more than three times as many genes as in the models – but it also lasted longer, up to six months in humans compared with a few days at most in mice. To confirm their findings, the investigators analyzed data from an additional 20 studies of acute inflammatory disease – 10 in humans and 10 in mice – and found a similar lack of correlation between the response of human patients and the mouse models. In all the human studies, the genomic responses were very similar, despite differences in patient age, gender, type and severity of injury or illness, treatment and outcomes.

"Mice have been used in biomedical research for well over 50 years, in part because of the cost, size, convenience, ease of genetic manipulation

and social acceptability. But it is often forgotten that mice appear to be much more resistant to inflammation and infection than humans," says Warren, an associate professor of Pediatrics at Harvard Medical School. "By studying and understanding the mechanisms by which mice differ from humans, we may be able to develop treatments that help make humans more resistant to damaging inflammation. We also hope that our article will start a broader discussion among scientists, research organizations, journals and granting and regulatory agencies as to the value of mouse models in different specific circumstances."

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