MODEL ORGANISMS

# Mouse models challenged

**A systematic comparison of gene expression patterns in human inflammatory conditions and in their corresponding mouse models raises troubling questions.**

Although there are few who would argue that a mouse is the same as a man, the mouse is the most important mammalian model organism in biomedical research. It is used—very effectively in many cases—to study basic biology in conditions of health and disease. For human conditions in particular, how well do mouse models do?

There are many cases where human biology is not precisely recapitulated in the mouse: telomere erosion is not easily studied in this model, for instance. But there have been few, if any, systematic comparative studies of human conditions and their mouse models. The large group of researchers that constitutes the Inflammation and Host Response to Injury, Large Scale Collaborative Research Program has recently reported such a study for several inflammatory conditions.

Researchers in the group had conducted several genome-scale studies on human and mouse inflammatory conditions over the past years; they now have used some of the resulting datasets in their comparative study. Specifically, they compared patterns of gene expression in three human conditions—trauma, burn or exposure to low-dose endotoxin in healthy volunteers, all of which involve systemic inflammation—with expression patterns in mouse models of these conditions. In both species, the gene expression data were from white blood cells obtained in serial blood draws at different time points after injury or intervention.

An examination of the almost 5,000 genes that changed significantly between normal and disease conditions in human, and that were also assayed in the mouse models, showed no correlation between mouse and human conditions either in how much the expression changed or in the direction in which it changed, for any of the three inflammatory conditions. If the researchers focused on the 100 genes that changed the most between normal and disease states, they saw a slight increase in the correlation between species but it remained low ($R^2$ of 0.11–0.28). Patterns from different mouse models also did not correlate very well with each other.

In contrast, in spite of the substantial heterogeneities in the human trauma and burn patient populations—in demographics, severity of injury, treatment and outcome—there was a strong correlation in gene expression patterns between these groups. Even the endotoxin-treated healthy volunteers, for example, had patterns that correlated better with those of burn and trauma patients than those of the corresponding mouse models.

Likewise, the biological pathways modulated in each of these conditions correlated more strongly between the human-derived datasets than between datasets for a particular condition in the two species. Finally, the timing of the transcriptional response also varied between mouse and man. In particular, the researchers observed that the time it takes for gene expression patterns to return to normal is much longer in the human than in the mouse.

A comparison with independently published gene expression datasets on other human and mouse inflammatory diseases recapitulated the researchers' essential conclusion: gene expression patterns in human inflammation do not correlate well with patterns in the mouse models used to study this condition.

Do these results call into question all biomedical research on the mouse? Certainly not. There is little doubt that at the molecular level there are many congruencies between the species, and there are plenty of mouse mutants that phenotypically resemble their human counterparts. If one considers that the environments in which the mouse and human immune responses have evolved were (and are) quite different, it is conceivable that mouse models for immune conditions are particularly prone to diverge from those for the human.

The work is nevertheless a challenge that should prompt a more critical examination of the mouse as a tool to study human disease. It is also a sobering reminder of what most thoughtful biologists already know: your biological conclusions are really only as good as the methods that get you there.

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RESEARCH PAPERS
Seok, J. *et al.* Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc. Natl. Acad. Sci. USA* **110**, 3507–3512 (2013).