LETTER

Reply to Osterburg et al.: To study human inflammatory diseases in humans

Osterburg et al. (1) raise questions from our recent publication (2). First, in our program, a single mouse strain, C57B/6, was selected because it has been the most commonly used in the field for decades. Furthermore, all strains of mice are remarkably resistant to LPS relative to humans. If anything, C57B/6 mice are less resistant and therefore potentially closer to the human response than many other mouse strains (3). Last, figure 4 and table 1 of ref. 2 show that our results are consistent with those of other independent mouse studies and not specific to strain, model, or investigator.

Osterburg et al. (1) question whether the choice of time intervals was appropriate. Gene recoveries in mouse models differ markedly compared with those in complex human diseases. In general, time course comparisons are much more rigorous than single time point or cross-sectional studies in capturing the similarities and differences in the gene changes between humans and mice (4). We performed the time course comparison and compared multiple characteristics of the response in humans and mice, including directionality and maximum magnitude of the changes (figures 1, 4, and S1 and table 1 of ref. 2), the response time and recovery time of the changes (figures 2*B* and S5 of ref. 2), and time course patterns (figures 2*A*, S6, and S7 of ref. 2). For both species, the gene response time occurred within the first 6–12 h (figure S5 of ref. 2).

Regarding the technical and statistical issues raised by Osterburg et al., instead of comparing the raw expression values from the microarrays between human and mouse, the comparisons were performed on the changes of expression values between disease conditions and controls within each species, where the same array platform was used for each of the species. The annotation of $-R^2$ was explained in the figure 3 legend and table 1 of ref. 2.

The myriad of ways that mice differ from humans including the different time intervals and the fact that mouse and human leukocyte cell populations differ raise the important question as to whether it is appropriate to try to adjust the model system to more closely compare similar features. To try to adjust or somehow correct for the mouse–human differences either in cell number, time course, or in any other way would introduce artifact. In our study, for example, had we adjusted the leukocyte populations, the genomics would not have reflected the in vivo condition.

Our article provides data for what most investigators already know from their experiences: current mouse models poorly reflect human inflammatory diseases. We are not damning all mouse models. Rather, we propose that the scientific community raise the bar to require model systems to more accurately reproduce the molecular features of human inflammatory disease and we should reprioritize our infrastructure, resources, tools, and methodologies to study human inflammatory diseases in humans.

Ronald G. Tompkins[a], H. Shaw Warren[a], Michael N. Mindrinos[b], Wenzhong Xiao[a,b], and Ronald W. Davis[a,1]

[a]Departments of Surgery, Medicine, and Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114; and [b]Stanford Genome Technology Center, Stanford University, Palo Alto, CA 94305

1 Osterburg AR, et al. (2013) Concerns over interspecies transcriptional comparisons in mice and humans after trauma. *Proc Natl Acad Sci USA* 110:E3370.

2 Seok J, et al.; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program (2013) Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA* 110(9):3507–3512.

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4 Storey JD, Xiao W, Leek JT, Tompkins RG, Davis RW (2005) Significance analysis of time course microarray experiments. *Proc Natl Acad Sci USA* 102(36):12837–12842.

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The authors declare no conflict of interest.

[1]To whom correspondence should be addressed. E-mail: dbowe@stanford.edu.