Genomic responses in mouse models greatly mimic human inflammatory diseases

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Mouse models of human diseases are essential research tools that are widely used in the medical sciences to increase our understanding of the pathogenesis and pathophysiology of various diseases, and to search for cures. Despite the widespread use of mice as animal models of disease, in 2013, Seok et al. reported that mouse models poorly mimic human inflammatory diseases, such as severe burn injury, sepsis, and acute infection, in terms of gene expression (*PNAS* 2013, 110(9), 3507-3523), which has been cited more than 400 times since its publication only 18 months ago. Their article led to great commotion, not only among scientists, but also in the popular mass media, including The New York Times and CBS News, reigniting controversy as to whether mouse models are effective for medical research. In response to the article, Dr. Francis S. Collins, director of the National Institutes of Health (NIH), revealed plans to develop "tissue chips" as alternatives to animal models of human disease.

Professor Tsuyoshi Miyakawa from the Fujita Health University, and Associate Professor Keizo Takao, from the National Institute for Physiological Sciences in Japan, applied more appropriate and more sensitive methods for detecting similarities of gene expression patterns than that applied in the original PNAS paper to reanalyze the same datasets used in Seok et al. Professor Miyakawa said, "One of the authors of Seok et al. stated in an interview with the NY Times (*) that when the article was rejected by *Nature* and *Science*, they received comments such as 'It has to be wrong'. I had the same impression as the reviewers." Drs. Miyakawa and Takao then reanalyzed the data used in

the Seok et al. paper, and found inadequate methods in the original analyses, leading them to a conclusion totally opposite to that of Seok et al.

Seok et al. compared the expression levels of genes that were altered in a particular human disease condition between humans and mice, regardless of whether the genes were changed in the mice. A comparison of the genomic response between humans and mice, including those genes altered in one species but not in another, obscures the correlation between homologous genes of humans and mice to nearly zero, as demonstrated by Seok et al.

In Seok et al., comparison of the gene expression patterns between human burn and mouse models of burns, trauma, sepsis, and infection revealed Pearson's coefficient of correlation (R) that ranged from 0.14 to 0.28, and the percentage of genes whose expression changed in the same direction was 55% to 61%, indicating no correlation at all. In the present report, based on the same datasets used in Seok et al., the R values ranged from 0.36 to 0.59, and 77% to 93% of the genes changed in the same directions between the human disease and mouse model. Furthermore, in the present paper, the authors conducted more sophisticated non-biased statistical analyses of the similarity between gene sets of humans and mice utilizing the bioinformatics tool NextBio. Non-parametric ranking analysis using NextBio demonstrated that the pattern of the gene expression changes in mouse models was highly similar to that in human burn conditions with extraordinarily high confidence (overlap p-value = 1.2×10^{-35} - 6.5×10^{-11}).

Many molecular pathways are commonly dysregulated in human diseases and mouse models. Numerous pathways, however, are not commonly affected in human diseases and mouse models. Focusing on the commonalities between human diseases and mouse models will allow us to derive useful information for studying the pathophysiology and

pathogenesis of human diseases, and for developing treatments.

More information: * Kolata G (2013) Health testing on mice is found misleading in some cases. NY Times. Available at www.nytimes.com/2013/02/12/sci … ead-report-says.html. Accessed January 17, 2014.

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