Cellular & Molecular Immunology (2013) 10, 373–374

www.nature.com/cmi

RESEARCH HIGHLIGHT

Translating translational research: mouse models of human disease

Amanda M Burkhardt[1,2] and Albert Zlotnik[1,2]

Cellular & Molecular Immunology (2013) **10,** 373–374; doi:10.1038/cmi.2013.19; published online 12 August 2013

Translational research has become increasingly popular in recent years. Within the field of medical research, animal models are considered valuable research tools that provide insight into the complex world of human diseases. Inbred animals eliminate several of the challenges of human studies and allow researchers to conduct disease research on, arguably, the most controlled model system possible. The ease with which animal models allow us to advance research often leads us to ignore the possibility that these studies may only provide limited translational potential to humans. Seok and colleagues of the 'Inflammation and Host Response to Injury Large Scale Collaborative Research Program' have recently published an impressive study[1] that specifically addresses this question, that is, the degree to which results of mouse models of inflammation mimic corresponding human diseases. And their results raise serious questions.

Their study analyzed changes in gene expression in several conditions (burns, trauma and endotoxemia) that involve inflammatory responses between cohorts of human patients and corresponding mouse models. The authors identified 5544 genes that change significantly in human inflammatory disease and subsequently determined that 4918 of these genes had murine orthologs. These 4918 'shared' genes were then compared by several different bioinformatic and biostatistic methods to determine whether the gene expression changes observed in the human conditions studied were also observed in the corresponding mouse model.

Their results yielded two distinct trends in gene expression response to inflammatory trauma. First, the gene expression profiles for the human inflammatory diseases analyzed generally showed a very high correlation in expression patterns. In contrast, the different mouse models studied showed very low correlation between each other. Secondly, there was very low correlation observed between genes expression changes in human patients and the genes expressed in the 'corresponding' mouse model.

They also observed additional differences in gene expression between human patients and their corresponding mouse model, including significant differences in the 'recovery time' required for gene expression to get back to 'background' or 'normal' expression patterns following the initial inflammatory trauma. Mice can recover normal gene expression patterns (from the initial induced trauma) in hours to days, while humans do not revert to a normal gene expression profile for at least 1–6+ months. Taken together, these data suggest that mouse models are not an accurate portrayal of what actually occurs in human inflammatory diseases.

To ensure that the observed results were not specific to just the human diseases and their matched mouse models that were originally selected for validation, the authors expanded the panel of diseases and performed the same gene expression analysis. They found the same trends that were observed with the initial diseases and corresponding mouse models, including large differences in gene expression patterns between the human patients and the matched mouse models for sepsis, acute respiratory distress syndrome and infection. The human genomic response for these additional diseases correlated with the three diseases initially analyzed; and the mouse diseases continued to show low correlation between the gene expression patterns of the different inflammatory models. The fact that three additional inflammatory diseases and their 'representative' mouse models follow the same pattern observed originally further strengthens the conclusions of the study.

The authors acknowledge that the differences observed between human and mouse responses may be due to evolutionary differences between the two species, differences in cellular composition of tissues and/or the fact that the mice used in research experiments were inbred. An example of these differences can be found in the evolution of the chemokines, which are soluble mediators involved in inflammatory responses.[2] The chemokines have been classified into inflammatory and homeostatic. The former mediate leukocyte recruitment during inflammatory responses, while the latter are expressed in specific tissues in the absence of exogenous stimuli. Importantly, there are significant differences between mouse and human inflammatory chemokines, including

[1]Department of Physiology and Biophysics, School of Medicine, University of California, Irvine, Irvine, CA, USA and [2]Institute for Immunology, University of California, Irvine, Irvine, CA, USA
Correspondence: Albert Zlotnik, Ph.D., 3034 Hewitt Hall, Institute for Immunology, University of California Irvine, Irvine, CA 92697.
E-mail: azlotnik@uci.edu

extreme cases where a given chemokine exists in one species but not the other. In contrast, homeostatic chemokines exhibit strong conservation between species. This can be explained by the important role that inflammation plays in resistance to infectious agents. Therefore, the differences between mouse and human chemokines likely reflect the divergent 'infectious experience' of the mouse and human ancestors of the present species. Conversely, the strong conservation observed in the homeostatic chemokines reflects their important roles in critical processes, such as development.[3] A corollary is that inflammation, as a process, has diverged more than others during evolution.[2] A recent study comparing human psoriasis to mouse models reached a similar conclusion.[4] It is therefore possible that the conclusions of Seok *et al.*[1] found the poorest correlation between mouse and human studies because they focused on inflammatory responses.

In contrast to the poor correlation observed between mouse and human models of inflammation, the authors draw attention to the fact that the heterogeneity of their human patient population did not affect the trends observed; the cohort of patients used for each human disease analyzed were not controlled groups. Rather, the factors that are predicted to make direct human studies complex because they cannot be controlled as easily as age-and sex-matched inbred mice did little to skew the observed trends. In other words, despite the heterogeneous genetic backgrounds of the human subjects studied, it was possible to identify a 'genetic signature' that reflects their responses to the inflammatory processes that were the focus of the study.

The consistency of the human gene expression data despite the heterogeneity of the patient population is an important observation. What these data indicate, as has been observed in many human disease gene expression studies (see Refs. 5–7 for examples), is that human diseases exhibit a molecular or genetic signature that transcends age, gender, ethnicity and treatment regimen. The findings of Seok *et al.*[1] support this notion, that is, that human patients without exact matching characteristics can yield reliable gene expression data. These conclusions reflect the view that human diseases are mediated by the overactivity of certain genetic/signaling pathways that result in the over/underexpression of specific genes. These are the changes that represent a 'molecular signature' characteristic of each human disease.

This study provides an important caveat to animal model research: mice are not humans, and there are limitations in the extrapolations we can make from mouse models. Importantly, this study also demonstrates that we now have the gene expression technologies and tools that can be used to validate animal models and ensure that they represent their corresponding human disease. This provides an opportunity to critically evaluate animal models and identify those that more faithfully represent a human disease. This is a welcome development that should help us better translate the results of biomedical research from preclinical to clinical stages, or put another way, from bench to bedside.

1 Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W *et al*. Genomic responses in mouse models poorly mimic human inflammatory diseases. *Proc Natl Acad Sci USA* 2013; **110**: 3507–3512.
2 Zlotnik A, Yoshie O. The chemokine superfamily revisited. *Immunity* 2012; **36**: 705–716.
3 Perlin JR, Talbot WS. Signals on the move: chemokine receptors and organogenesis in zebrafish. *Sci STKE* 2007; **2007**: pe45.
4 Swindell WR, Johnston A, Carbajal S, Han G, Wohn C, Lu J *et al*. Genome-wide expression profiling of five mouse models identifies similarities and differences with human psoriasis. *PLoS ONE* 2011; **6**: e18266.
5 Selman M, Pardo A, Barrera L, Estrada A, Watson SR, Wilson K *et al*. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. *Am J Respir Crit Care Med* 2006; **173**: 188–198.
6 Hever A, Roth RB, Hevezi P, Marin ME, Acosta JA, Rojas J *et al*. Human endometriosis is associated with plasma cells and overexpression of B lymphocyte stimulator. *Proc Natl Acad Sci USA* 2007; **104**: 12451–12456.
7 Hevezi PA, Tom E, Wilson K, Lambert P, Gutierrez-Reyes G, Kershenobich D *et al*. Gene expression patterns in livers of Hispanic patients infected with hepatitis C virus. *Autoimmunity* 2011; **44**: 532–542.