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KERIS: kaleidoscope of gene responses to inflammation between species

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ABSTRACT

A cornerstone of modern biomedical research is the use of animal models to study disease mechanisms and to develop new therapeutic approaches. In order to help the research community to better explore the similarities and differences of genomic response between human inflammatory diseases and murine models, we developed KERIS: kaleidoscope of gene responses to inflammation between species (available at http://www.igenomed.org/keris/). As of June 2016, KERIS includes comparisons of the genomic response of six human inflammatory diseases (burns, trauma, infection, sepsis, endotoxin and acute respiratory distress syndrome) and matched mouse models, using 2257 curated samples from the Inflammation and the Host Response to Injury Glue Grant studies and other representative studies in Gene Expression Omnibus. A researcher can browse, query, visualize and compare the response patterns of genes, pathways and functional modules across different diseases and corresponding murine models. The database is expected to help biologists choosing models when studying the mechanisms of particular genes and pathways in a disease and prioritizing the translation of findings from disease models into clinical studies.

INTRODUCTION

A cornerstone of modern biomedical research is the use of mouse models to explore basic disease mechanisms, evaluate new therapeutic approaches, and make decisions to carry new drug candidates forward into clinical trials. However, few of these human trials have shown success (1–4). Through the Inflammation and Host Response to Injury Large-scale Collaborative Research Program (Glue Grant), we have studied the genomic response to systemic inflammation in a large number of patients, human volunteers and murine models. We systematically evaluated, on a molecular basis, how well murine disease models mimic human inflammatory diseases, and reported previously (5) that, although acute inflammatory stresses from different etiologies resulted in highly similar genomic responses in humans, overall the corresponding mouse models did not correlate well with human and each another. In addition, the comparison of significantly regulated pathways between these human diseases and murine models showed that the correlations varied depending on the individual pathway and the model (5). Vibrant discussions occurred in the research community on the merits and limitations of animal models and how to better translate findings from disease models to clinical studies (6–14). For example, Lin *et al.* reported the comparison of gene expression patterns between humans and mice in 13 normal tissues using RNA-sequencing, and showed overall 'considerable RNA expression diversity between humans and mice', 'likely reflecting the fundamental physiological differences between these two organisms' (14).

Exiting online resources, such as Integrated interactions database (IID) (15), and MouseNet (16) aim at discovering disease-associated genes and underlying mechanisms for human diseases or phenotypes by comparing the gene expression between human and other species. However, these databases focus on the comparisons on the baseline levels in different tissues and cell types between human and model organisms.

Successful translation of findings from model systems to clinical research is increasingly dependent on rigorous computational analysis of large datasets and critical evaluation of the results. Because virtually every drug and drug candidate functions at the molecular level, a disease model shall be carefully examined to see whether it mimics or fails to mimic the molecular behavior of key genes, key pathways, or the genome-wide level thought to be important for the relevant human disease. To help the research community to better explore the similarities and differences between human diseases and murine models and to better translate findings of disease models, here we present KERIS, a comprehensive resource for the genome responses between human inflammatory diseases and murine models. By incorporating data from well-curated studies of six most common inflam-

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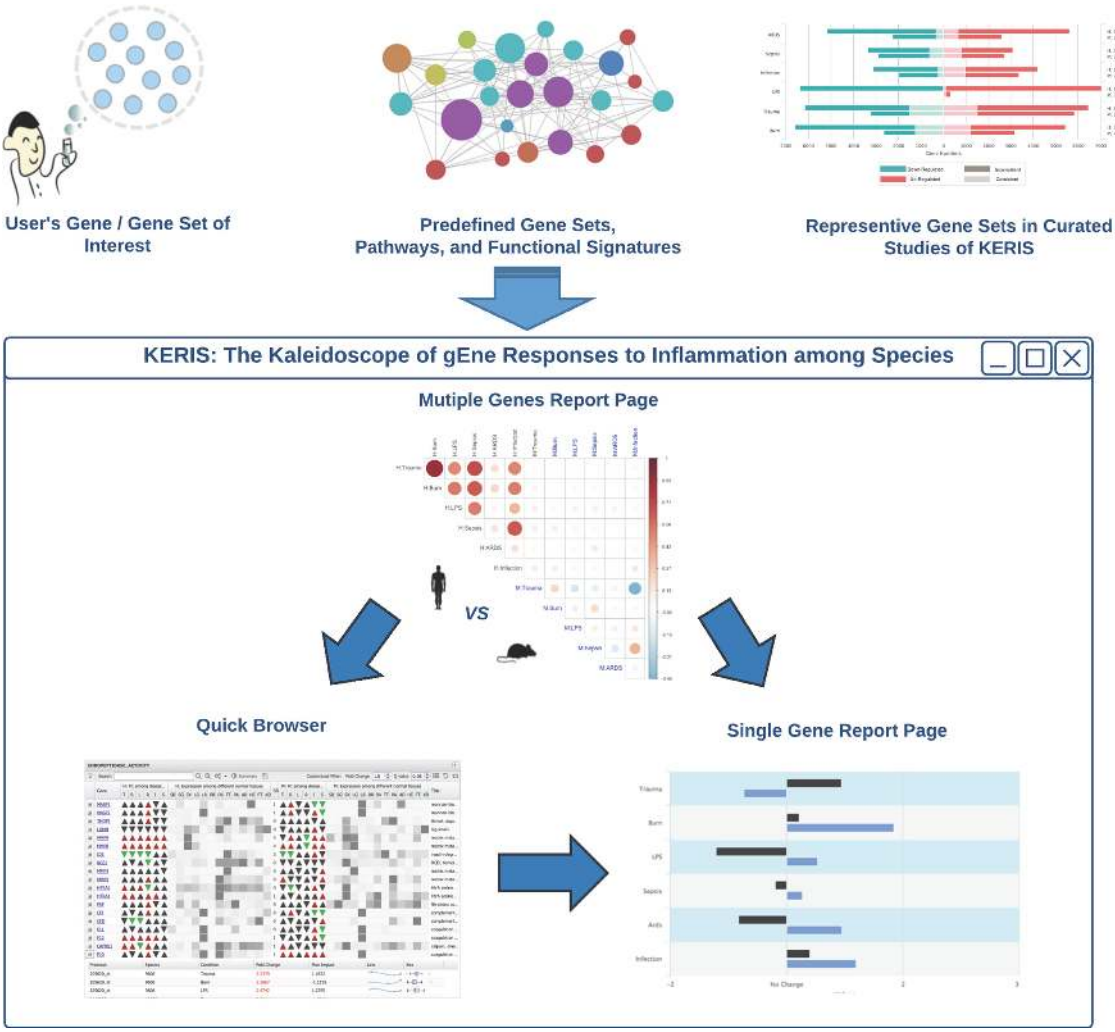

Figure 1. Overview of the KERIS database. Researchers can query KERIS by gene or gene set, or browse representative gene sets and pathways curated in KERIS. The multiple genes report page provides results of statistical analysis of the genomic response of the multiple genes among different diseases and mouse models. The single gene report page provides detailed comparisons of the response of the gene in each disease and each model, and of the baseline expression levels of the gene in different tissues of human and mouse. Quick browser provides comprehensive data of the gene set and many additional functions to examine further the data in KERIS.

matory diseases including 2257 samples, and the expression profiles of 13 tissues in human and mice by RNA sequencing (14), researchers can systematically explore genes, pathways (17,18) or gene sets (19) of interest on both response levels among different human diseases and corresponding murine models and baseline levels among different tissues between human and mouse (Figure 1). The results from these aforementioned comparisons are likely complementary in helping biologists evaluating murine models when investigating particular genes or pathways/genesets of human diseases. In addition, KERIS presents in the summary pages overall results and selected examples of the comparisons between patients and models to facilitate researchers utilize data in KERIS. For all the user queries, the results of analysis are generated in real time on the computational servers and are shown using interactive and user-friendly visualization tools in KERIS.

MATERIALS AND METHODS

Data resources

Genomic responses in different human inflammatory diseases and corresponding murine models. The Inflammation and Host Response to Injury, Large Scale Collaborative Research Program has completed multiple studies on the genomic responses to systemic inflammation in patients and human volunteers as well as murine disease models (18,20–23). These datasets include genome-wide expression analysis on white blood cells obtained from serial blood draws in 167 patients up to 28 days after severe blunt trauma (20), 244 patients up to 1 year after burn injury, and 10 healthy humans for 24 h after administration of low-dose bacterial endotoxin (18), as well as expression analysis on analogous samples from well-established mouse models of trauma, burns and endotoxemia (16 treated and 16 controls per model) (21–23). In order to systematically compare the similarities and differences in gene response between pa-

Table 1. Datasets for the genomic responses among different human inflammatory diseases and related murine models in KERIS

Species	Condition	Experiment	Platform	# Samples
Human	Trauma	GSE36809	GPL570	857
Human	Burn	GSE37069	GPL570	590
Human	Infection	GSE30119	GPL6947	143
Human	Sepsis	GSE13904	GPL570	227
Human	LPS	GSE3284	GPL570	110
Human	ARDS	GSE10474	GPL571	34
Mouse	Trauma	GSE7404	GPL1261	144
Mouse	Burn	GSE7404	GPL1261	144
Mouse	Infection	GSE20524	GPL8321	72
Mouse	Sepsis	GSE19668	GPL1261	50
Mouse	LPS	GSE7404	GPL1261	144
Mouse	ARDS	GSE52684	GPL13912	30

tients and murine models in different human inflammatory diseases, we further sought and evaluated additional well curated studies of patients and corresponding mouse models from Gene Expression Omnibus (GEO) (24) for several other severe acute inflammatory diseases [sepsis, acute respiratory distress syndrome (ARDS) and infections], and integrated these datasets in KERIS. The biological findings from the comparisons have been published (5). All the gene expression datasets in KERIS have been deposited in GEO under the accession numbers listed in Table 1.

Baseline expression levels of genes in different tissues of human and mouse. The baseline gene expression data were calculated based on the RNA-seq data of 13 paired mouse-human samples under one experimental protocol generated by Lin *et al.* (14) The 13 tissues include, SB: small bowel, SG: sigmoid, SX: spleen, LG: lung, LR: liver, BR: brain, OV: ovary, TT: testis, PA: pancreas, AD: adrenal, HE: heart, FT: fat, and KD: kidney.

Analysis of gene expression data

The fold changes of each gene measured were calculated between patients and controls in human studies or between treated and control groups in mouse model studies. For time course data, the trajectory of longitudinal expression of each gene was obtained by a cubic spline function, and the mean expression of the controls was considered as the baseline expression. The maximum deviation of the trajectory line from the baseline was referred to as the maximum fold change or simply, the fold change of the gene between patients and healthy controls. The significance of the longitudinal gene expression change was estimated using EDGE (25) by 1000 random permutations for time course studies. False discovery rate (q-value) was calculated for case–control studies.

Analysis of RNA-seq and calculation of shannon entropy

The expression matrix was from the study of Lin *et al.* (14). Briefly, the fastq data of RNA-sequencing were aligned using Tophat (26) to ENSEMBL genome build Homo sapiens GRCh37.58 or Mus musculus GRCm38.68 (27). Cufflinks was used to derive FPKM values with gtf files of Gencode Release 14 (28) or Mus_musculus.GRCm38.68.gtf (29) for humans and mice, respectively. This dataset was used to calculate the baseline gene expression abundances in different tissues and to compare the expression patterns between human and mouse in normal tissues.

We also calculated Shannon entropy (H) for each gene according to Schug *et al.* (30) with the expression data. H is a parameter commonly used to assess the specificity of gene expression, with lower values signifying expression in a smaller fraction of the total set.

Human–mouse orthologs

The orthologs between human and mouse that include ∼15 106 protein-coding genes were generated by the mod ENCODE and mouse ENCODE consortia (31).

RESULTS

Website implementation

The backend of KERIS was implemented using the Django web framework with PostgreSQL as the database, and Celery as the distributed task queue to organize R and Python toolkits on computational servers. We developed a scalable database structure to save flexible expression matrix into PostgreSQL data table using the feature of variable-length multidimensional arrays, which allows an open database architecture for indexing and integrating new studies into the current data matrix and provides a high-performance data structure for further analysis in R or Python. The online API was built on Django REST framework. The frontend of KERIS was implemented with Sencha Ext JS, Highcharts and jQuery Javascript libraries. This enables KERIS to provide more meticulous, feature-rich, and interactive online visualization applications. The entire KERIS application is hosted at Massachusetts General Hospital.

Querying KERIS

Query a gene. The main page of the KERIS website accepts a gene or protein ID and returns reports on the response levels of the gene among different inflammatory diseases and mouse models. The input can be a gene name or its alias. The entry is submitted to NCBI using the NCBI eQuery API. If the query matches multiple candidates, a table of the candidates is returned so the user can select the gene(s) of interest. On the single gene information page, a user can get information about the queried gene in terms of its genomic response level among different diseases and

models, and its baseline expression levels among different tissues between human and mouse.

Query a gene set. A user can query a custom gene set of interest by entering the gene names or aliases and receive comprehensive results of statistical analysis. The entries are submitted to NCBI using NCBI eQuery API. If the queried gene set has more than 10 genes, one will be directed to the multiple genes report page; otherwise one will receive the comprehensive data of all the queried genes in the quick browser, since when the number of genes is too few, some of the summary statistics might lose its significance. On the multiple genes report page, a user can find several visualization plots and reports about the gene set on its response levels between different diseases and models, and the baseline expression levels in different tissues. These include the scatter plot, principle component analysis (PCA), box plots of the fold changes, correlations between different conditions, percentage of genes changed to the same directions, and plots and correlation of the expression in different tissues.

Query a pathway. A user can also query KERIS using a name or keyword of a specific pathway and see results and analysis report. Pathways are treated as pre-indexed gene sets in the system. As of June 2016, pathways are collected from KEGG (17), GSEA (19), and other knowledge bases such as Ingenuity Pathway Analysis (18). Here a query tool allowing approximate string matching is provided for the user to search and identify the correct pathway of interest. When a curser is mouse-over the pathway input area, there is a drop-down menu that automatically updates the recommended pathways based on the keyword entry from the user, and a user can click on the pathway name of interest to go to multiple genes report page of the specific pathway.

Examples. KERIS was developed to help biologists evaluating relevant animal models when investigating particular genes or gene sets (pathways) in a human disease. Figure 2 shows a few examples of data query and visualization implemented in KERIS toward this objective. Here, we query the response of IL-3 signalling pathway between different inflammatory diseases and models. First, scatter plot of the fold changes of genes of the pathway (Figure 2A) can be examined between each disease condition and corresponding model, such as JAK2, which is upregulated in both human burns and the murine burn model, and PIK3CG, which is upregulated in human trauma but downregulated in the murine trauma model. Second, clicking on the point of PIK3CG leads to the detailed information on the gene of interest, for example, the bar plot of its fold changes (Figure 2B). Note that, in burns and LPS, the PIK3CG gene is upregulated in both human patients and mouse models, in contrast to trauma. Third, the Spearman correlations of the fold changes of genes of the pathway in diseases and models can be compared (Figure 2C). This reveals that a subset of murine models (M:Burn, M:Sepsis, and M:Infection) have substantially higher correlations with human diseases than the other models (M:Trauma, M:LPS, and M:ARDS). Finally, the IL-3 pathway is compared with other pathways in the heatmap of Spearman's rank correlation coefficients (Figure 2D).

Similarly, if a user would like to investigate the Th1 vs Th2 pathway response to human infections and would like to evaluate, among the murine models, which model might show the closest response to human, the user can type 'th2' in the pathway search form, and choose from the list of gene sets returned in the drop-down menu. For example, in the multiple genes report page for the 'Biocarta Th1/Th2 pathway' (http://www.igenomed.org/immune/summary?pathway=M6705), the user can examine the PCA plot and the heatmap of correlations, and find that different human inflammatory diseases such as Burns, Trauma and Sepsis show highly similar genomic responses for this pathway, while the mouse Infection and mouse Trauma model mimic the human infection response to a certain extent. In contrast, the mouse LPS model shows a negative correlation.

Browsing KERIS

Summary page. The page shows summary results and selected examples of the comparison of the genomic response between patients and murine models. Here we present the global statistical results of the database and a few significant or representative findings as demonstration examples. (i) Comparison of the number of differentially expressed genes between human inflammatory diseases and corresponding mouse models. From this summary, researches could get all the differentially expressed genes (DEGs, q-value$<$0.05 and absolute fold change$>$1.2) numbers in specific diseases and the consistent or inconsistent DEG numbers between human and related murine model. (ii) Numbers of differentially expressed genes that changed to the same directions over a number of different human inflammatory diseases and mouse models: Six human inflammatory diseases and their corresponding mouse disease models were analyzed. For each condition, DEGs between disease and control groups were identified. For each species, the union of the six sets of DEGs was included in further analysis. The report shows that $\sim$1600 genes were differentially expressed to the same directions among all six human inflammatory diseases, but there were no genes consistently changed among the six corresponding disease models in the mouse. (iii) Heatmaps of the Spearman's rank correlation of individual pathways between human burn vs other inflammatory diseases and related mouse models on selected pathways (e.g. Figure 2D). (iv) Receiver operator characteristic (ROC) curve for the translatability of gene response between Burn and Trauma within/across human and mouse. (v) Comparison of the correlations of genes between human and mouse in 13 normal tissues and in six inflammatory disease conditions. (vi) Boxplots of the tissue specificity scores of genes differentially expressed in a varying number (zero to six) of human inflammatory diseases and related mouse models.

Quick browser. A convenient application to quickly explore the data in KERIS by browsing or custom querying the database (Figure 3). The quick browser provides comprehensive data of the response levels among different dis-

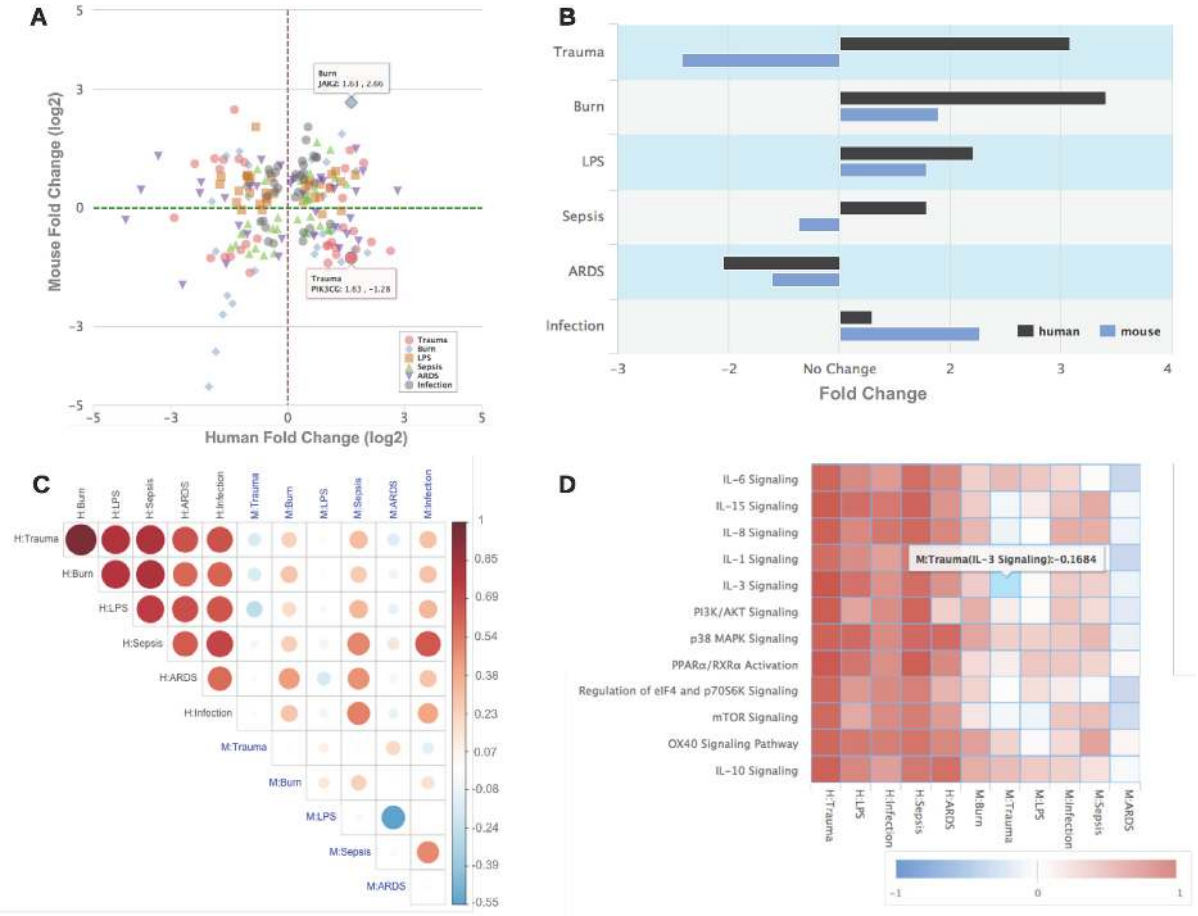

Figure 2. Comparisons of the response between different diseases and models. (**A**) Scatter plot of fold changes between different conditions of a queried gene set. Shown as an example is IL-3 signalling pathway. A user can hover over a point of interested in the figure and click on it to get detailed information about that gene (e.g. PIK3CG as shown in Figure 2B), also they can click on a disease condition to show or hide the response of all the genes under the condition. (**B**) Bar plot of the fold changes of the expression level of a gene (PIK3CG, as an example). Note that, in trauma, the PIK3CG gene is upregulated in human patients and downregulated in mouse trauma model, and in burns and LPS, the gene is upregulated in both human patients and mouse models. (**C**) Heatmap of Spearman correlations of the fold changes of a queried gene set in diseases and models. IL-3 pathway is shown as an example, where a subset of murine models (M:Burn, M:Sepsis, and M:Infection) have substantially higher correlations with human diseases than the other models (M:Trauma, M:LPS, and M:ARDS). (**D**) Shown is the heatmap of Spearman's rank correlation coefficients for selected pathways between human burns and other inflammatory diseases and between human burns and mouse models of inflammatory diseases. One can click on a pathway name to get detail analysis reports about that gene set (e.g. IL-3 pathway as shown in Figure. 2A).

eases and related murine models, the baseline expression levels among different tissues between human and mouse, and the functional annotation information of the genes; in addition, it provides a variety of additional tools. There are four search modes for user to query directly in the browser: single gene search mode; multiple gene search mode; customized filter mode; and random walk mode. The first two return information of the queried gene or gene set. The customized filter mode allows users to filter genes by multiple properties with custom cut-offs, for example, to find the gene set that significantly up regulated among trauma and burns in both human patients and corresponding murine models using the cutoffs of fold change ≥ 2 and q-value ≤ 0.05. The random walk mode retrieves a random, predefined gene set related to a specific pathway or functional signature from GSEA, KEGG or Ingenuity. A user can show/hide/sort specific columns or drag them to different location to customize the grid view, download the XML file of all the information in current view for further analysis, or use the built-in tools to do the summary analysis in KERIS or using other online resources such as KEGG and DAVID (32).

DISCUSSION

Concluding remarks

We have developed the KERIS database of the gene response in acute inflammatory diseases and murine models studies by the Inflammation and Host Response to Injury Glue Grant and other research programs, and implemented online analysis tools and visualization system to help the users to gain deeper insights into the genomic responses. The database includes the largest datasets to date on the gene response in human acute inflammatory diseases. As the first integrated resource for systematical exploration of the relations between human diseases and murine models, we expect this work to stimulate discussions in the scientific community on how to evaluate and improve murine

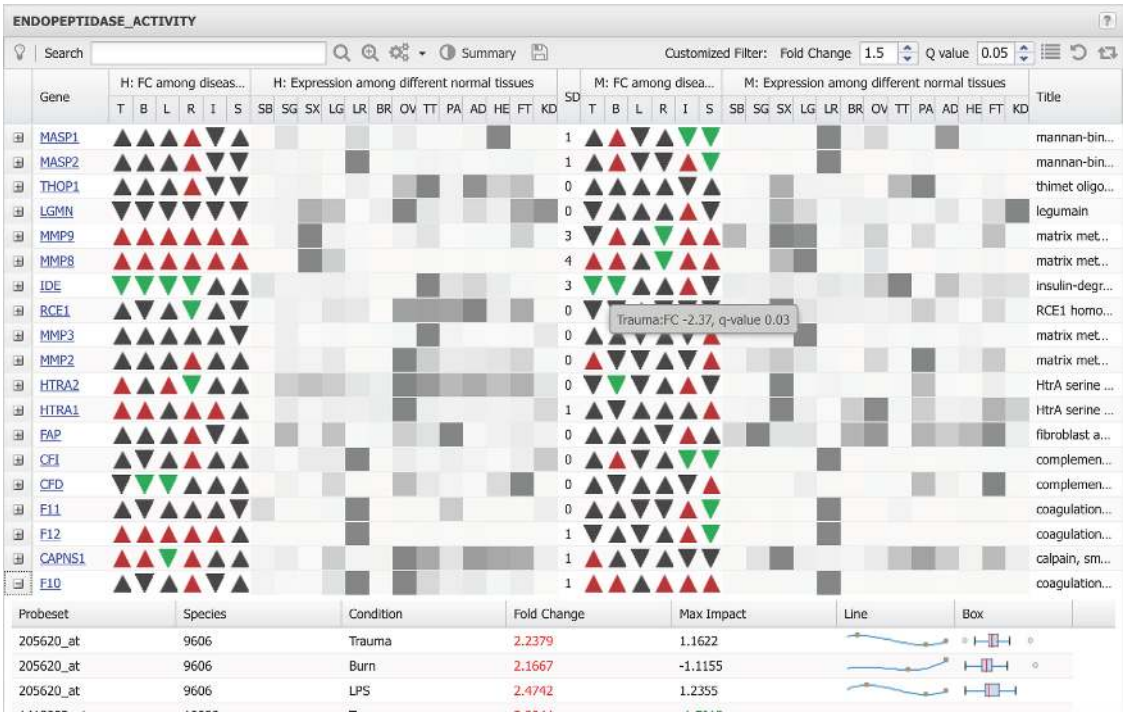

Figure 3. Quick browser of a queried gene set. Shown are the directions of changes of the genes in each disease and murine model (red: significantly upregulated, green: significantly downregulated, black: not significant), and the heatmap of the expression levels of these genes in different human and mouse tissues (black: high, white: low). A user can quickly query or filter genes directly in the browser and customize the grid by showing/hiding/sorting specific columns or dragging them to a different location. Quick browser also provides other functions such as quick tips, outputting the data, and linking to other online resources.

models of human inflammatory diseases, to help biologists choosing models when studying the mechanisms of particular genes and pathways in a disease, and to help prioritizing the translation of findings from disease models into clinical studies. In addition, the large-scale human datasets curated in the database will facilitate further studies of the consistent gene response patterns in these inflammatory diseases, to discover new functional mechanisms and to identify potential drug targets.

Future development

Addressing limitations. While currently KERIS provides the *P*-values and Fold Changes of testing the differences between different groups (e.g. disease versus control) within each species, it does not yet include results, such as *P*-values, of statistical testing on the differential responses between human disease (patients versus normal controls) and mouse disease models (treated versus untreated). Rigorous statistics is currently challenging because of the multiple differences in designs of the clinical studies versus animal experiments. Ongoing effort aims at solving this problem and provide the statistical tests necessary for interpreting the significance of the differences between species.

Resources on more cell types, species and inflammatory diseases. Additional large scale datasets will be curated and integrated into KERIS. First, although human and mouse share common overall structure of their immune systems, they differ in the composition of their blood leukocytes. Human blood is neutrophil rich whereas mouse blood has a preponderance of lymphocytes (33). The Glue Grant has collected data of the genome responses in monocytes, neutrophils and T cells of patients and murine models; these data and results will be integrated into KERIS. Second, comparing to humans that are sensitive to infections, mice are tolerant to infections. We will curate the genome responses of other species and extract the molecular response patterns of these additional species to infections. Third, we will analyse additional inflammatory diseases and models from well-curated studies and integrate into the KERIS database.

In-silico toolkit for model validation. To aid researchers better evaluate disease models, we will develop online tools for model validation which will calculate the similarity and difference of the expression features between a custom study and curated studies of patients of inflammatory diseases and disease models in KERIS. Researchers can then upload the expression profile of their study of a disease model to KERIS to assess the detailed comparisons of the genomic response between the model and studies in KERIS.

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