ABSTRACT

Cardiovascular diseases and their main underlying pathology, atherosclerosis, are the leading cause of death. Statins, a mainstay of prevention, only reduce cardiovascular mortality by an estimated 27% [1]. Therefore, there is a pressing need for new therapies to combat atherosclerosis and to prevent its acute complications, heart attacks and strokes. Atherosclerosis is known to involve pathogenic responses of macrophages, a subset of innate immune cells that are of particular interest as a potential therapeutic target. Given the health and socioeconomic burden of cardiovascular diseases, drug repurposing is a promising and cost-effective approach to identify new therapies. There are thousands of FDA approved drugs that are off-patent and whose potential effects in various off-label disease contexts remain to be elucidated. Using measurements of these drugs' effects on the transcriptome of HUVEC cells obtained from the Connectivity Map database [2], we hypothesize that candidate atheroprotective drugs can be identified through a rank-based statistical test adapted from the test proposed by Subramanian et al. [3]. A preliminary analysis using query sets of genes obtained by transcriptome profiling of human coronary artery disease (CAD) [4] has identified several candidate drugs including brinzolamide, nic迫切, and zaprinast. Future work will focus on screening additional gene sets and on molecular pathway analysis of candidate drugs.

METHOD (cont.)

3.) Calculate significance of score through a permutation test

METHOD

RESULTS

Figure 3. The permutation test. The P value calculated is the probability that a random query set will have a higher score deviation from zero than the drug's query set.

Figure 4. Evaluating the permutation test. Across all drugs, -log(P) values are correlated with absolute enrichment scores in a "volcano plot" of statistical significance vs E-score.

Figure 5. Filtering for high-scoring drugs. Drugs are filtered with a P value cutoff of 0.05 for both up and down enrichment scores derived from both "up" and "down" gene sets. Requiring a negative E-score for the "up" gene set and a positive E-score for the "down" gene set provides an additional filter for beneficial responses. Drugs that passed both filters are shown in blue.

Drugs that may inhibit atherosclerosis-associated gene expression changes

Table: Drugs that may inhibit atherosclerosis-associated gene expression changes

Conclusions and Future Directions

We have created a viable method of scoring drug responses against disease-associated gene sets. The analysis of statistical significance vs E-score (Fig. 4) shows that our permutation test is a good measure of the statistical significance of the enrichment score. Our preliminary analysis has yielded some promising results with zaprinast, valproic acid and brinzolamide appearing near the top of the list. These preliminary results indicate the discovery potential of screening drug/transcription databases with disease-associated gene sets to uncover novel applications for off-patent drugs.

In future work, we will test the hypothesis that through analysis of gene sets from multiple studies, drugs with cardiovascular indications or functions will meet our filtering criteria more frequently than expected by chance. We anticipate that along with this expected result, a handful of other drugs will appear in the top of the rankings as well. The most promising candidate drugs will then be experimentally investigated to determine their effects on gene expression in primary mouse and human macrophages.

References


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