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RAPID COMMUNICATION

A network based efficient drug repurposing strategy for targeting diabesity

Type II diabetes and obesity are two of the most prevalent metabolic disorders effecting a huge population throughout the world. Research over the last decade has unequivocally established considerable molecular links between them and hence they are often described in conjugation as 'diabesity'. The hallmarks of type II diabetes are primarily reduced insulin sensitivity, progressive insulin resistance and consequent hyperinsulinemia.[1] Whereas, hyperinsulinemia promotes a plethora of fat synthesis from excess circulating carbohydrate and hyperactive fat storage mechanisms, ultimately inducing hepatic steatosis, myosteatosis and pancreatic steatosis.[1] This in turn, aggravates the insulin sensitivity further, inflicting more insulin resistance and even more hyperinsulinemia. Needless to mention that the vicious process in turn, promotes uncontrolled weight gain[1] and many secondary metabolic disorders. The prevalent anti-diabetic and anti-obesity medications comes with several limitations ranging from inefficiency to adverse side effects.[2] Here, we report an efficient strategy of repositioning previously approved drugs with novel indication in the context of diabesity by investigating deregulated signalling axes affecting patients with both the disorders. Our approach relies extensively on deciphering the strength of gene association in various interactomes, as it is known that within networks, genes linked to similar disease phenotypes tend to be functionally similar[3] and remain proximal to each other.[4] Moreover, the potential drug targets associated to a disease pathway also cluster proximal to the disease pathways.[4]

To investigate the underlying molecular signalling involved in obesity and type II diabetes, we selected gene expression data from patients inflicted with both these phenotypes (Fig. 1A–I). This was followed by pathway enrichment analysis (Fig. 1A–I) to identify the deregulated signaling axes that forge the link. The pathway enrichment analysis of DEGs provided a mechanistic insight into deregulated signaling axes constituting major domains, such as carbohydrate metabolism, lipid metabolism, fat storage and immune system (Fig. S1), which included insulin receptor signaling, insulin resistance, galactose metabolism, adipocytokine signaling pathways, fatty acid biosynthetic pathways, regulation of inflammatory response and macrophage activation, adipogenesis, response to vitamin D etc. (Table S1). The enriched deregulated genes obtained were further mapped to tissue-specific background networks that were constituted from protein–protein interaction (PPI) and gene co-expression network (GCN) which generated tissue-specific disease modules (Fig. 1A–II). Overall, from the PPI, we found proteins such as TP53, MTOR, STAT3, EGFR, MYC, HDACs, etc. show high number of connectivity within the disease network (Fig. S2A), suggesting the possible role of cancer, FOXO mediated transcriptional regulation aging, mTOR signaling and epigenetic regulation. Similarly, from the GCN on the other hand, we observed that candidates like BTK, SPI1, SYK, ITGB2, HCK, UCP2 and PTPN6 are among those which show maximum connectivity in the network (Fig. S2B), signifying a probable involvement of immunomodulation, cancer malignancy and lipid metabolism. To create disease relevant modules from these networks, we applied walktrap algorithm over the tissue specific background networks. We subsequently performed overrepresentation analysis (ORA) with the genes populated in these disease modules. The overrepresented signaling axes further revealed pathways related to metabolic disorders, anti-inflammatory response and cytokines production, vitamin D metabolism, LDL clearance, regulation of lipid metabolism by PPARα, mitochondrial dysfunction, accumulation of triglycerides, fatty acyl intermediates, and chromatin modifying enzymes (Table S3 and Fig. S3A–C). Therefore, we could conclude the importance of adipocyte dysfunction, deregulation of lipid metabolism and inflammation in pathophysiology of diabesity. We also identified some intriguing signaling axes like FOXO mediated transcriptional axes related to aging, mTOR signaling, regulation of p53 activity, programmed cell death, cellular senescence, circadian clock, deregulated autophagy such

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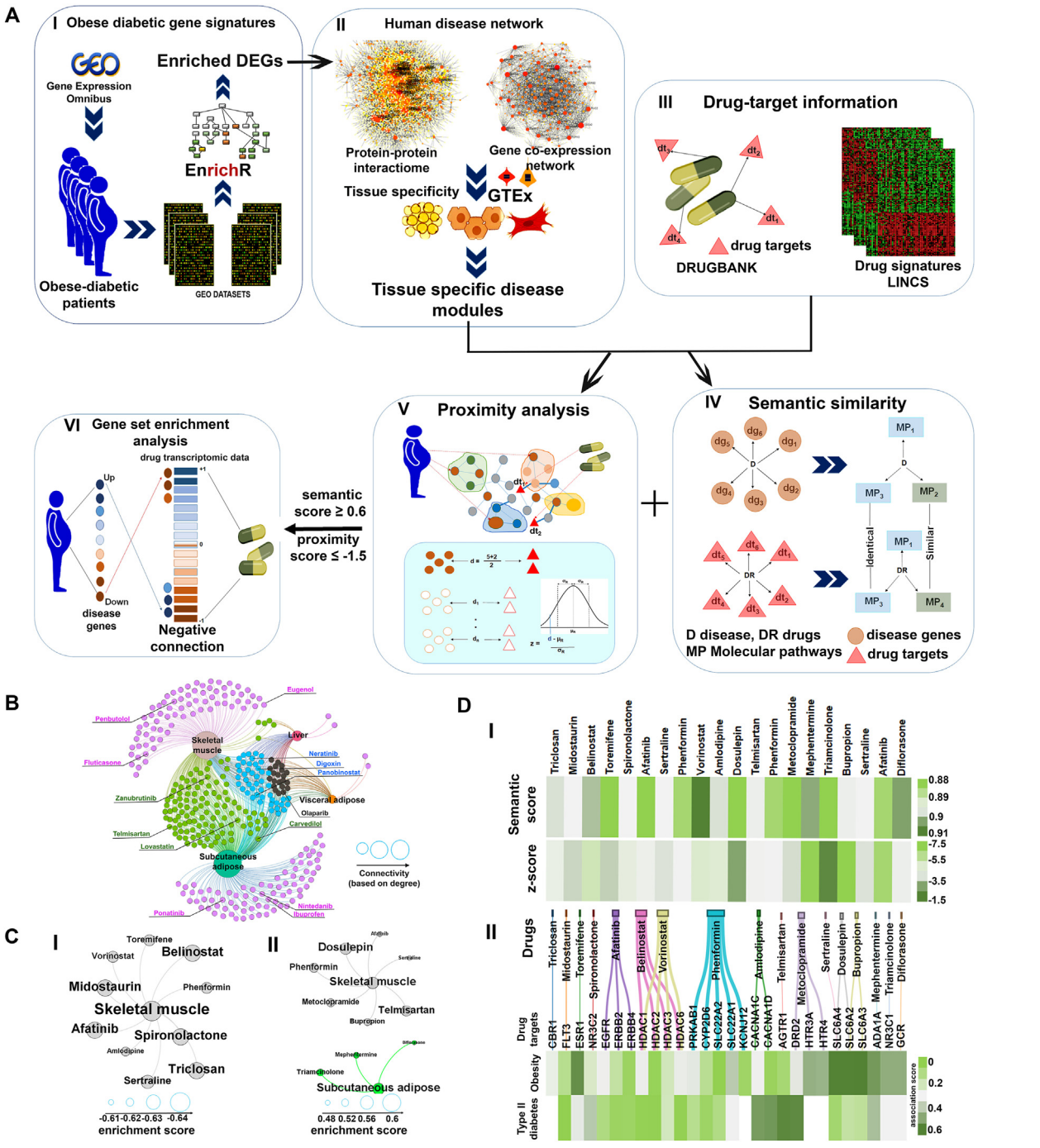

Figure 1 Framework adopted for the study and the potential drug candidates along with their scores. **(A)** (I) The diabesity-associated genes were obtained from patients inflicted with both obesity and diabetes followed by pathway enrichment analysis. (II) The disease genes were subsequently mapped to tissue specific protein—protein interactome and Gene Coexpression Network to generate tissue specific disease modules. (III) Drug targets and drug perturbed gene signature were retrieved from DrugBank and LINCS database respectively. The drug—disease associations were established by performing (IV) semantic similarity and (V) network proximity analysis between disease relevant genes and drug targets. These associations were further consolidated by (VI) gene set enrichment analyses which considered only those drugs capable of reversing the disease signature. **(B)** A subnetwork highlighting tissue specific drug associations connecting 403 drugs to adipose (subcutaneous and visceral), liver and skeletal muscle relevant deregulated pathways. Nodes are sized according to the degree of connectivity within the subnetwork. **(C)** Subnetworks highlighting top 10 drugs with highest enrichment scores whose (I) upregulated gene sets, and (II) downregulated gene sets were significantly enriched in the down- and up-regulated disease gene signatures. Nodes are sized according to the z scores. **(D)** (I) Heat maps depicting semantic scores (upper panel) and proximity z-scores (lower panel) of these drugs. (II) Sankey diagram depicting the connectivity of these drugs with their targets (upper panel) and heat maps depicting the distribution of association score (AS) of these targets with obesity and type II diabetes as a measure of the extent of clinical exploration of them in the context of the mentioned diseases.

as mitophagy and pexophagy, PI3K/Akt signaling in cancer, and neurodegenerative pathways in Alzheimer's disease models from the analysis.

The strength of similarity and proximity in function between approved drug (with targets obtained from drug bank and drug signatures obtained from LINCS) (Fig. 1A—III) and disease relevant pathways/genes was measured by semantic analysis and through network proximity calculations (Fig. 1A—IV, V) respectively. The drugs with high semantic scores indicating greater functional similarities were from a wide variety of classes including HDAC inhibitors, kinase inhibitors, glitazones, immune modulators, statins, β-blockers (Table S4). Apart from some well explored targets, we also obtained the classes of kinase inhibitors like fostamatinib (SYK), zanubrutinib (BTK), bosutinib (SRC/ABL1) which are less explored in the context of obesity and diabetes. Drug-disease association as scaled by the proximity scores, identified the potential candidates like HDAC inhibitors, tyrosine kinase inhibitors, statins, sulfonylureases, biguanide, PARP inhibitors, anti-arrhythmic agents, antihypertensive agents, glucocorticoid, etc (Table S4). Among these group kinase inhibitors and glucocorticoids are potentially interesting implying the possible role of immunomodulation to target diabesity. Using a criteria of high molecular semantic similarity (semantic score $\geq$ 0.6) and network proximity (z-score ≤ -1.5) we could list a total 400 drugs targeting various tissues (Fig. 1B). We found that drugs like pemetrexed, trimipramine, benzylpenicilin and simvastatin were found to be both functionally associated (high semantic score) and proximally connected (high proximity score) (Fig. S5-I, II) to disease phenotype across majority of the tissues studied. Identifying significant associations based on semantic similarity and network proximity, although extremely effective, fails to determine if an association is positively or negatively correlated with the disease phenotype. To address this issue, we next performed gene set enrichment analysis (GSEA) of drug-perturbed gene sets (obtained from LINCS) on obese-diabetic patient signatures (Fig. 1A—VI). Our analysis was based on the signature reversion principle[5] that prioritizes drugs, whose signature is negatively enriched with the disease-associated gene signature. From the analysis we found that drugs which could reverse both the upregulated and downregulated disease specific gene signatures (GSEA score = 2) were mostly targeting skeletal muscle (Fig. S6A). Whereas drugs which could reverse either of the up- or down-regulated gene signature associated with the disease (GSEA score = 1) were distributed among all the 4 tissues with the majority being the skeletal muscle (Fig. S6B). Many of the drugs belonging to kinase inhibitors and immunomodulators such as dasatinib, afatinib, sorafenib, baricitinib, etc. were less explored as depicted by their association scores (AS $\leq$ 0.2, Fig. S6C and Table S5). We also observed that the above drugs could connect with most of the metabolic domains through targets like SRC, ABL1, PDGFRB, KIT, FYN EGFR, MTOR, LCK (Fig. S7 A—D). Drugs which could exert strongest signature reversal capacity were afatinib, phenformin and sertraline etc. that were significantly enriched in the down- and up-regulated disease gene signature (Fig. 1C—I, II and D—I, II). Based on further refinement following (i) high ES_{dn} (ES $>$ 0.4) and low ES_{up} (ES < -0.5), (ii) AS $\leq$ 0.2 for both obesity and type II diabetes, (iii) high semantic score ($\geq$0.8) score, and (iv) low proximity z-scores, we could get a prioritized list of drugs (afatinib, fostamatinib, baricitinib, sorafenib, panobinostat and nicotinamide) which are well connected to most of the deregulated metabolic modules through important targets (Fig. S8I-VI; Fig. S9). To summarize, our study offers a powerful, network-based systems pharmacology pipeline for the rapid identification of potential repurposable drugs for diabesity which could potentially be extrapolated to study other diseases.

Author contributions

S.D. collected the data and carried out the analyses according to the adopted computational pipeline. T.N. carried out semantic similarity and proximity score analysis and edited the manuscript. S.R. and D.C. helped preparing the figures in the manuscript. D.D. framed the research question, approved the computational pipeline, analysed the data, supervised throughout the work and wrote the manuscript. All the authors approved the final version of the paper.

Conflict of interests

The authors declare that they have no conflict of interest.

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Data availability

The datasets used for this research purpose can be obtained from NCBI GEO (link). The analysed datasets along with corresponding R scripts may also be available from the corresponding author upon a reasonable request. The Supplementary files have been provided. VolcanoR (http://45.8.90.25:3838/volcanoR/), EnrichR (https://maayanlab.cloud/Enrichr/), NetworkAnalyst (https://www.networkanalyst.ca/), DrugBank (https://go.drugbank.com/), Drug Central (https://drugcentral.org/), OpenTargets (https://platform.opentargets.org/), ChEMBL (https://www.ebi.ac.uk/chembl/).

Code availability

The codes are available in the github repository 'Diabesity_drug_discovery' (https://github.com/Debo-Lab/Diabesity_drug_discovery).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.02.015.

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