A Methodology for Predicting Tissue-specific Metabolic Roles of Receptors Applied to Subcutaneous Adipose

Judith Somekh

Department of Information Systems, University of Haifa, Haifa, Israel

Email: judith_somekh@is.haifa.ac.il
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Abstract

The human biological system uses 'inter-organ' communication to achieve a state of homeostasis, through the response of receptors, located on target organs, to the binding of secreted ligands from source organs. Albeit years of research, the roles these receptors play in tissues is only partially understood. This work presents a new methodology based on the enrichment analysis scores of co-expression networks fed into support vector machines (SVMs) and k-NN classifiers to predict the tissue-specific metabolic roles of receptors. To facilitate supervised learning, a list of known metabolic and non-metabolic receptors was constructed using a semi-supervised approach following literature-based verification. Our approach confirms that pathway enrichment scores successfully classify the metabolic receptors in adipose subcutaneous. We also show that the k-NN method outperforms the SVM method. Finally, we analysed ~ 700 receptors to predict novel metabolic roles of receptors which can enhance biological understanding and the development of new receptor-targeting drugs.

Receptor dysregulation underlies the etiology of many human diseases and prescription drugs are designed to affect the regulation of these receptors. This work presents a new methodology to predict the tissue-specific metabolic roles of receptors.

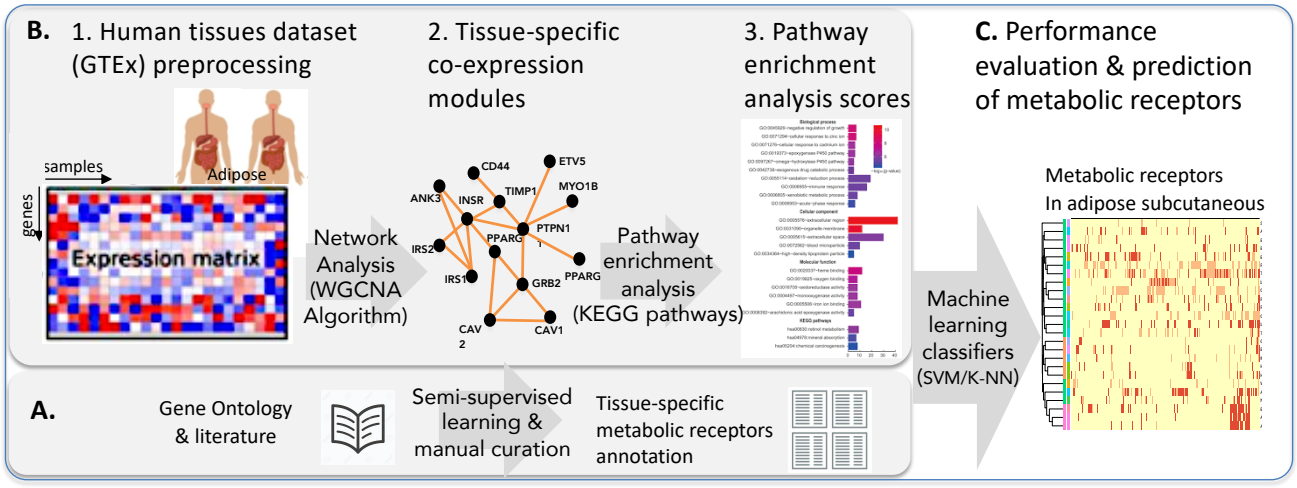

Figure 1. Schematic view of the new computational methodology.

The methodology incorporates three steps A, B and C (see in Fig. 1) and is based on our detection that metabolic receptors expression is coordinated. We applied our method to the GTEx gene expression data[2] of subcutaneous adipose tissue. In Step A, a labelled list of metabolic and non-metabolic receptors was constructed combining the literature and a semi-supervised learning approach. We used the SVM PU (positive unlabelled) bagging algorithm[3], to add an additional 37 metabolic receptors as positive examples, which we verified using the literature/Gene Ontology database. As the negative examples two distinct groups were used: (1) 61 cytokine receptors derived from KEGG DB and (2) 55 receptors inferred by the PU bagging algorithm[3] and validated. In Step B, the pre-processed GTEx data was used for co-expression network analysis utilizing the Weighted Gene Co-expression Network Analysis (WGCNA) algorithm[1] and followed by biological pathway enrichment analysis to annotate the networks. We used the enrichment scores of the receptors related networks to train SVMs (Support Vector Machines) and k-nearest neighbour (k-NN) classifiers and compared their performance using 10-fold cross-validation. Table 1 presents the performance of the classifiers for predicting genes representing metabolic and non-metabolic receptors. The k-NN/SVM classifiers are highly successful (accuracy > 0.9) in classifying metabolic receptors. In Step C, we used the SVM/k-NN classifiers to test ~700 receptors and to predict novel metabolic roles for 21 receptors in adipose. Our methodology established the first step in using gene expression data to predict the roles of receptors in tissues.

Table 1. Comparison of performance evaluation of linear SVM and k-NN classifiers (using the Euclidian distance) for metabolic receptors classification in subcutaneous adipose tissue.

	Method	Negative group	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy	MCC
1	k-NN	inferred	50	55	0	2	0.96	0.96	**0.98**	0.96
2	SVM	inferred	44	55	0	8	0.85	0.87	**0.93**	0.86
3	SVM/	cytokines	42	60	1	10	0.81	0.86	**0.9**	0.81

	k-NN									

References

1. Langfelder, P. & Horvath, S. WGCNA: An R package for weighted correlation network analysis. BMC Bioinformatics 9, 559 (2008).
2. Ardlie, K. G. et al. The Genotype-Tissue Expression (GTEx) pilot analysis: Multitissue gene regulation in humans. Science (80). 348, 648–660 (2015).
3. Mordelet, F. & Vert, J. P. A bagging SVM to learn from positive and unlabeled examples. Pattern Recognit. Lett. 37, 201–209 (2014).