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Type	Oral communication
Session	Biological Networks
Title	Gene co-expression networks identify mediators of inter-tissue interactions
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Motivation

Biological systems can be often dissected in multiple components: different organs, tissues or cell types that, at different levels, interact with each other and contribute in defining the system’s properties and behaviour. These interactions are manifest also at the gene expression level, with the expression of a gene in one cellular compartment influencing gene expression in the other. For nearby compartments, this can be explained by direct cell-cell contacts or by paracrine signals that activate signalling cascades in the target cells. For tissues or organs that are far apart, hormones might be the vehicles.
Despite their well-recognized role, studying experimentally these communications is laborious, and mostly limited to the analysis of one signal-receptor interaction at a time.
Gene co-expression networks have been widely employed and proven valuable in inferring genome wide gene interactions, but have been exclusively applied to individual tissues or to samples comprising a non-separable admixture of cell types. Nevertheless, the principle of co-expression networks could be extended to the study of inter-cellular communication, to provide a simple way of selecting genes mediating inter-tissue interactions, which could be then assessed experimentally.

Methods

We adapted the WGCNA algorithm (Weighted Gene Co-expression Network Analysis) to study inter-tissue interactions, modifying the metric used to define nodes’ distance. As for WGCNA, nodes in the network are genes, while edges indicate co-expression of pairs of genes across samples.
As input, our method requires the transcriptomic profiles of matched samples from the same experimental subjects, deriving from two or more cellular compartments, tissues or organs. It then builds a gene adjacency matrix based on genes’ inter-tissue pairwise correlations, which it uses as input for WGCNA, finally identifying modules of tightly connected genes. To avoid artefacts due to coordinated gene expression induced by external factors acting on both tissues, self-loops are imposed to zero. In addition, we defined two metrics, which we call kext and kint, based on the weighted inter-tissue or intra-tissue degree, respectively, and indicating the influence of each gene on within- or between-tissue communication. Modules and genes with high kext / kint represent good candidates as central mediators of interactions.

Results

We showed that our method accurately quantifies brain inter-region communication, using two independent multi-region transcriptome datasets, by comparing it with functional connectivity measurements. The correlation between two biological signals of such different kind, gene co-expression and functional connectivity, but representing the same phenomenon, inter-region communication, gave us confidence on the reliability of the method and motivated us to apply it to additional contexts. In particular, we chose to study tumor-microenvironment interactions in breast cancer using data from laser capture microdissected tumors, separating stromal and epithelial compartments. Analysing seven independent datasets we identified genes belonging to the Gene Ontology categories of “G-protein coupled receptors signalling pathway” and “receptor regulator activity” as consistently enriched amongst the top drivers of inter-compartment gene interactions.
In conclusion, with our method we can quantify the communication strength between tissues at the gene expression level and identify potential mediators of inter-tissues interactions.

Info

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Figure	
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Availability	-
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