The identification of therapeutic strategies exploiting the metabolic alternations of malignant cells is a relevant area in cancer research. Here, we discuss a novel computational method, based on the COBRA (COntrest-Based Reconstruction and Analysis) framework for metabolic networks, to perform this task. Current and future steps are presented.

The understanding of metabolic alterations in cancer cells constitutes a major topic in oncology. Different works support that these alterations contribute to cell transformation and tumor progression and, therefore, the investigation of cellular metabolism as a therapeutic strategy has received much interest in the last years. Holistic systems medicine approaches, driven by varied biological and clinical data and computational modeling, are promising to systematically exploit metabolic disorders of tumor cells and identify metabolic vulnerabilities to be targeted.

One of the most relevant paradigms within computational systems biology is the COBRA (COntrest-Based Reconstruction and Analysis) framework. Thanks to the efforts of this growing community, there are publicly available high-quality human genome-scale metabolic networks, such as Recon2, which stores thousands of metabolites, reactions and genes reported in human cells (illustrated in Fig. 1). Based on them, we can mathematically analyze different metabolic questions related to human health. In particular, the COBRA approach introduces context-specific constraints on a space of possible metabolic behaviors and allows the prediction of different metabolic phenotypes, including growth rate and gene essentiality. Growth rate is modeled as the flux through the biomass reaction, namely by blocking the synthesis of at least one essential metabolite for cellular proliferation.

The COBRA approach is considered promising to elucidate novel drug targets in cancer. Using "omics" data, different COBRA methods aim to exploit the concept of synthetic lethality in order to elucidate cancer-specific essential genes. To illustrate this, consider Fig. 1, where g1, g2 and g3 are synthetic lethal genes, since their simultaneous inhibition disrupts the production of metabolite A, essential for tumor cell proliferation and included in the biomass equation. Assuming that genes g1 and g2 are not expressed in the tumor sample under consideration, g3 is an essential gene in this context; in other words, g3 is a cancer-specific metabolic essential gene. Interestingly, cancer-specific metabolic essential genes provide potential drug targets that can be further examined by experimental groups.

Our group recently developed a novel COBRA method to find cancer-specific metabolic essential genes. We showed that our approach presents several advantages with respect to existing approaches in the literature. Firstly, our approach returns more objective and unbiased results, since gene expression data is mapped onto the reference metabolic network, avoiding the use of context-specific metabolic reconstructions, which take heuristic decisions to reconcile omics data and add unnecessary noise. Second, our algorithm is more informative, since it captures the synthetic lethality underlying cancer-specific essential genes. In the toy example in Fig. 1, our algorithm would return that g3 is a cancer-specific essential gene, but, additionally, that g1, g2 and g3 are synthetic lethal genes. This information is lost with existing algorithms. In the context of personalized medicine, this is valuable to decide which patients could respond to potential therapies; in the example, the activity of genes A and B defines the lethality of the knockout of gene g3. Third, our approach presents a substantially higher sensitivity to predict
cancer-specific essential genes than competing methods, according to a side-by-side comparison based on genome-scale loss-of-function screens provided by the Project Achilles. Overall, these three elements make our approach a sensible contribution to the field of cancer systems biology.

From the mathematical perspective, the prediction of synthetic lethality is based on the concept of minimal cut sets (MCSs), developed by Steffen Klamt and colleagues, and previous theoretical work by our group, which builds on linear optimization, duality theory and linear algebra. Originally, these methods were constructed for reaction knockout perturbations. In our work, we extended this method to the gene level, introducing the concept of genetic minimal cut sets (gMCSs), a more appropriate concept for cancer studies. We are currently working to include our algorithm in the COBRA Toolbox, an open-source software in Matlab environment that stores a number of methods for the reconstruction and analysis of genome-scale metabolic networks. This will facilitate a simple and intuitive use of our algorithm in the Systems Biology community.

Our computational framework was successfully applied to evaluate the lethality of ribonucleotide reductase catalytic subunit M1 (RRM1) in multiple myeloma (MM), a hematological cancer that remains an incurable disease. However, we expect that our algorithm can be used for other questions in cancer. Currently, we are applying our algorithm to identity drug targets in prostate cancer, different leukemias and tamoxifen-resistant breast tumors, with some promising (yet unpublished) results. In addition, we plan to include drug perturbations in our model in order to, for example, predict the effect of drugs targeting metabolic enzymes and pose possible synergistic strategies to reinforce the treatment.

The identification of silent enzymes, either inherited inactive or lost by the tumor, is indispensable to find metabolic vulnerabilities in cancer. In our work, we used microarray gene expression data; however, the use of genomic data, such as mutations or copy number variations is even more interesting to exploit synthetic lethality. With the proliferation of DNA-seq and RNA-seq data, we anticipate a suitable environment where our COBRA method could be used more accurately to identify metabolic drug targets.

Disclosure of interest

The authors report no conflict of interest.

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