MOLECULAR & CELLULAR ONCOLOGY
2018, VOL. 5, NO. 1, e1389672 (3 pages)
https://doi.org/10.1080/23723556.2017.1389672

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AUTHOR'S VIEW

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COBRA methods and metabolic drug targets in cancer

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

ARTICLE HISTORY
Received 29 September 2017
Revised 3 October 2017
Accepted 5 October 2017

KEYWORDS
cancer; constraint-based reconstruction and analysis; drug targets; essential genes; genetic minimal cut sets; metabolic networks; personalized medicine; synthetic lethality

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.[1] 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 (COnstraint-Based Reconstruction and Analysis) framework.[2] Thanks to the efforts of this growing community, there are publicly available high-quality human genome-scale metabolic networks, such as Recon2,[3] 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.[4] Growth rate is modeled as the flux of an artificial reaction, typically named the biomass equation, which involves the metabolic requirements (essential metabolites), in terms of building blocks and energy, to produce biomass (Fig. 1). The biomass equation enables in-silico gene essentiality and synthetic lethality analysis at metabolic level. Thereby, essential and synthetic lethal genes are defined as knockout strategies that disrupt the flux through the biomass reaction, namely by blocking the biosynthesis 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 g_1, g_2 and g_3 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 g_1 and g_2 are not expressed in the tumor sample under consideration, g_3 is an essential gene in this context; in other words, g_3 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.[5] We showed that our approach presents several advantages with respect to existing approaches in the literature.[6] 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 g_3 is a cancer-specific essential gene, but, additionally, that g_1, g_2 and g_3 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 g_3. Third, our approach presents a substantially higher sensitivity to predict

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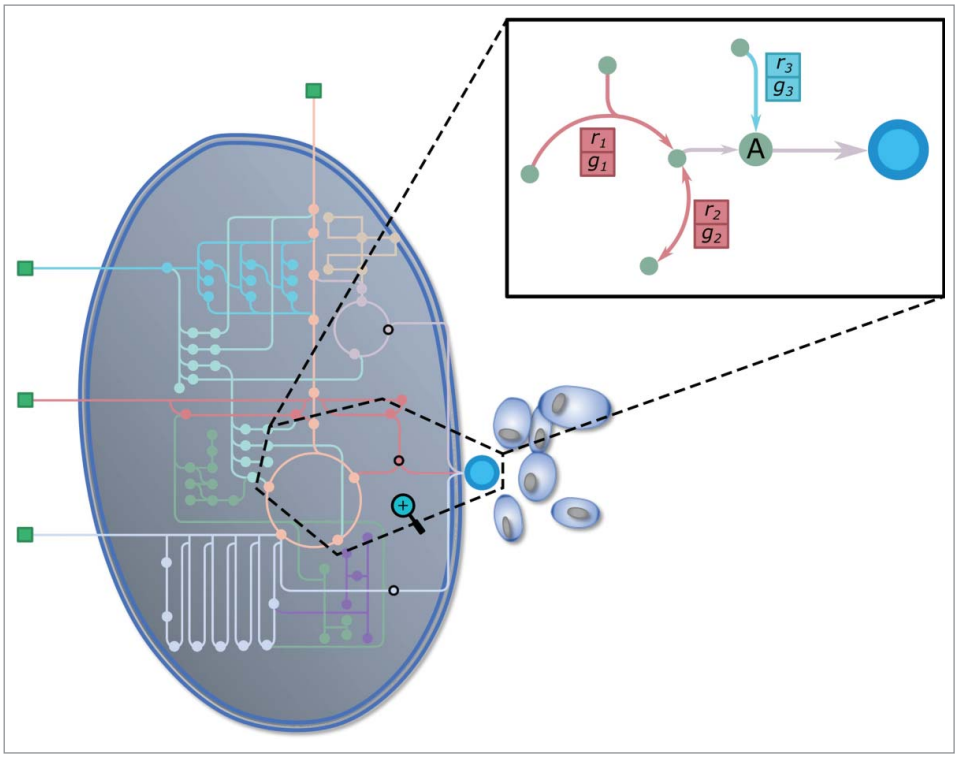

Figure 1. COBRA (COnstraint-Based Reconstruction and Analysis) approach and genetic minimal cut set (gMCSs). We show different ingredients in a genome-scale metabolic model: the green squares represent nutrients in the growth medium, lines are reactions and dots are metabolites, while the outlined circles constitute essential metabolites for cell proliferation (integrated in the biomass equation). In the zoomed in panel, g_1, g_2 and g_3 genes, which catalyze univocally r_1, r_2 and r_3 reactions, respectively, form an example gMCS. These genes are synthetic lethal for the biosynthesis of the biomass precursor metabolite A. Using available transcriptomics data, we assume that g_1 and g_2 are not expressed (red color) while g_3 is expressed (blue color). In this context, g_3 would be a cancer-specific essential gene and, therefore, a potential drug target.

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.[7] 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,[8] and previous theoretical work by our group,[9] 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,[10] 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.

Acknowledgments

I.A. was supported by the Basque Government under Grant <PRE_2016_2_0044>. This work was supported by the Minister of Economy and Competitiveness of Spain under Grant <BIO2016-77998-R>; ELKARTEK Programme of the Basque Government under Grant <KK-2016/00026>; Centro de Ingeniería Biomédica (University of Navarra); Instituto de Salud Carlos III under Grants <PI10/01691>, <PI13/01469>, <PI14/01867>, <PI16/02024>, <RTICC RD12/0036/0068>; CIBERONC under Grant <CB16/12/00489> (Co-finance with FEDER funds); ERA-NET programmes TRANSCAN-2 JTC EPICA by the "Torres Quevedo" Subprogramme under Grants <PTQ-11-04777>, <PTQ-14-07320 I.D.M>; Gobierno de Navarra under Grant <40/2016>; and

Fundació La Marató de TV3 <20132130-31-32>. We would like to thank Jacobo Paredes for his helpful comments on Fig. 1.

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