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Review

Metabolic Cancer Biology: Structural-based analysis of cancer as a metabolic disease, new sights and opportunities for disease treatment

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ABSTRACT

The cancer cell metabolism or the Warburg effect discovery goes back to 1924 when, for the first time Otto Warburg observed, in contrast to the normal cells, cancer cells have different metabolism. With the initiation of high throughput technologies and computational systems biology, cancer cell metabolism renaissances and many attempts were performed to revise the Warburg effect. The development of experimental and analytical tools which generate high-throughput biological data including lots of information could lead to application of computational models in biological discovery and clinical medicine especially for cancer. Due to the recent availability of tissue-specific reconstructed models, new opportunities in studying metabolic alteration in various kinds of cancers open up. Structural approaches at genome-scale levels seem to be suitable for developing diagnostic and prognostic molecular signatures, as well as in identifying new drug targets. In this review, we have considered these recent advances in structural-based analysis of cancer as a metabolic disease view. Two different structural approaches have been described here: topological and constraint-based methods. The ultimate goal of this type of systems analysis is not only the discovery of novel drug targets but also the development of new systems-based therapy strategies.

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1. Introduction

Cancer is a complex disease which contains multiple types of biological interactions through various physical, sequential, and biological scales. This complexity generates considerable challenges for the description of cancer biology, and inspires the study of cancer in the context of molecular, cellular, and physiological systems. A significant factor contributing to this new synthesis is the observation that several signaling pathways changed in cancer are key regulators of the human metabolic network. This specifies a rational interplay between genetic and metabolic alterations during tumorigenesis without a permanent cause–effect relationship [1]. Otto Warburg first suggested this metabolic modification based on his observations in leukemic cells that altered metabolism of glucose may lead to cancer. This effect is now referred as the "Warburg effect". Since then, different hypotheses (Fig. 1) have been proposed to find the mechanisms responsible for the Warburg effect [2]. However, the metabolic landscape of cancer is still far from understood, and in particular its regulation. Recently, there has been a resurgence of interest in cancer metabolism [1,3,4]. In the last decade, there is a paradigm shift from studying individual enzymes to newer approaches that aims to comprehend altered tumor metabolism as a whole. These new efforts flourish due to increasing availability of high-throughput data from various tumor studies elucidating metabolic concentrations, fluxes and abundance and regulation of the key enzymes. The data can now be analyzed integratively using statistical models to describe cancer metabolism. Beside experimental work, a metabolic network reconstruction is a manually curated, computational framework that empowers the description of gene–protein-reaction relationships [5]. For understanding the metabolic fluxes of a cancer cell, mechanistic genome scale models of cancer metabolism are needed and first attempts are very promising. Mechanistic methods are becoming increasingly feasible not only because of more sophisticated approaches and better data, but also due to hardware improvements enabling to simulate these models on clusters with a couple of hundreds of cores. Several studies have established how such reconstructions of metabolism could guide the development of biological theories and discoveries [6–8].

In this article we have described recent advances in network-based analysis of cancer as a metabolic disease. In the first section, the topological approach has been explained. In the next section, the constraint-based method (as another network-based approach) has been considered.

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Fig. 1. Different mechanism hypothesis for causing the Warburg effect are summarized: (1) tumor environment and stabilization of HIF, (2) post-translational modifications, (3) glutamine metabolism, (4) miRNA, (5) epigenetic changes, (6) nuclear DNA mutations, (7) mitochondrial dysfunction in cancer cells and (8) oncogene activation and loss of tumor suppressor genes [2].

2. Human cancer metabolic models

2.1. Genome-scale metabolic model of human cancer

With the advent of genome-scale metabolic models (GEMs) of various cell types and diseases, a valuable tool to study genetic, epigenetic and metabolic events in combination, has emerged [9]. The convergence of these developments enables the researchers to predict physiological functions and the relevant growth rate of particular human cell types, tissue-specificity and cancer [10–12]. There are four generic reconstructed genome-scale human metabolic networks: Recon1 [13], Recon2 [14], the Edinburgh Human Metabolic Network (EHMN) [15], and HumanCyc [16]. For the study of particular human cell types, tissue-specificity, and cancer; metabolic models have been reconstructed either manually or automatically. Manually reconstructed metabolic models include models of the liver (HepatoNet1 [17]), kidney [18], brain [19], erythrocytes [20], alveolar macrophages [21] as well a model of the core metabolic pathways participating in cancer growth [22]. The first automatic reconstructed metabolic model has been developed by Schlomi et al. for 10 different human tissues [23] as subsets of Recon1. Later they proposed a different algorithm to generate a more flexible and functional tissue-specific model [24].

For human cancer metabolic models, there are two principal models, which have focused on core metabolic pathways outlined by Resendis-Antonio et al. and Vazquez et al. in 2010 [22,25]. In 2011, Shlomi et al. have used Recon1 and a cancer biomass equation in order to provide insights into the Warburg effect [26]. Shortly thereafter, a general genome-scale model of cancer metabolism was constructed based on transcriptomic data from the NCI-60 cell lines. The model was used to assess metabolic drug targets [27]. Agren et al. [28] have developed the INIT algorithm (Integrative Network Inference for Tissues) which relies on the Human Protein Atlas (HPA) as the main evidence source, and on tissue-specific gene expression data [29] and metabolomic data from the Human Metabolome DataBase (HMDB) [30] as extra sources of evidence, leading to build 69 Human Cell Types and 16 Cancer Types. After that, Wang et al. [31] have developed a new approach named metabolic Context-specificity Assessed by Deterministic Reaction Evaluation (mCADRE) in order to build 126 human tissue-specific metabolic models.

To date, different cancer tissue-specific models have been built using data from specific cell lines and tumors. These models have described pathways that differ between tumors. Although these models were successful in predicting cancer specific metabolites and reactions with high accuracy, further curation and integration of data in these models that are subject to specific needs are necessary. In any case, they are still in their infancy which naturally involves more computational work on metabolic models of cancer. The timeline of the genome-scale metabolic models for human normal and cancer tissues has been shown in Table 1.

2.2. Integration of gene expression data into GEMs

Following the introduction of GEMs and the high-throughput approaches for extracting genome-wide expression pattern of a cell (e.g. DNA microarray [32], ChIP-Seq [33] and RNA-Seq [34]), the new challenge for a better prediction of the metabolic activities of different cells appeared; how gene expression data can be integrated into GEMs [35]. First, Covert and Palsson [36] addressed this issue by Boolean approach in 2002. In 2004, Akesson et al. [37] used gene expression data as an additional constraint on metabolic fluxes in yeast. Afterward, different algorithms were developed for tackling this challenge; GIMME [38], E-Flux [39], Moxley [40],

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Table 1
Timeline of the genome-scale metabolic models for human normal and cancer tissues.

Metabolic model		Year	Reference
Genome-scale metabolic network reconstructions	HumanCyc	2005	[16]
	Recon 1	2007	[13]
	EHMN	2010	[15]
	Recon 2	2013	[14]
Cancer-specific metabolic models	2010	[22]	
(core metabolic pathways)	2010	[25]	
Using Recon1 and a cancer biomass equation in order to provide insights into the Warburg effect		2011	[26]
General genome-scale model of cancer metabolism (based on mapping a transcriptomic data from the NCI-60 cell lines)		2011	[27]
Reconstruction of 69 human cell types and 16 cancer types (INIT algorithm)		2012	[28]
Reconstruction of 126 human tissues (mCADRE algorithm)		2012	[31]

MADE [41], RELATCH [42], iMAT [24], tFBA [43], GIMMEp [44], INIT [45], and mCADRE [31]. The conflation of genetic expression data and GEMs leads to a better and deeper understanding of the occurrence of certain changes in gene expression under different conditions [46]. Some methods reduce gene expression levels to binary states (such as GIMME, iMAT, and MADE), whereas methods like the E-Flux tries to map gene expression data into a GEM by constraining the maximum possible flux through the reactions. Integration of gene expression data in genome-scale metabolic network reconstruction has been reviewed by Blazier and Papin in which differences, limitations and advantages of all algorithms explained carefully [47].

3. Topological approach

The topological analysis of biological networks is an important method in systems biology which allows the investigation of large scale networks such as GEMs [48]. Graph theory is the most useful framework for representation of GEMs. A mathematical representation of a network is a graph $G(V,E)$. Its vertex set (V) consists of all nodes. Two nodes are adjacent if an edge exist between which connects them.

There are many parameters which could be calculated by graph theory method such as clustering coefficient, number of connected components, network diameter, network radius, average shortest path length (also known as the characteristic path length), average number of neighbors, network density, number of isolated nodes, number of multi-edge node pairs, number of loop (also called a self-loop), node degree distribution, neighborhood connectivity, different centralities, hub, network motifs, clusters, and so on [48–50].

There is also a need for representation of GEMs in a standard form that could be used for topological analysis. One of the most widely used standards is called Systems Biology Markup Language (SBML) [51]. The SBML is a standard format for describing models in various areas of computational biology, including metabolic pathways, cell signaling pathways, gene regulation, and others. Major releases of the SBML standard are called levels, where level 2 is the most recent. The SBML defines list of species (entities of the model), compartments, parameters and reactions, among others.

In the language of graph theory, metabolic networks consist of two different nodes (metabolites and enzymes). There are different approaches for representation of such networks (Fig. 2) in which the most useful representation will be a bipartite network which is a graph whose vertices could be allocated into two sets U and V such that every edge links a vertex in the set U to one in the set V. The bipartite characteristic of metabolic networks makes it difficult to analyze with topological methods. In addition, it has been shown that metabolite- and enzyme-centric networks can provide extra insights and are therefore relevant for further analysis of the metabolism [48]. However, an additional difficulty, especially for the analysis of enzyme-centric networks, is the presence of currency metabolites which may lead to many biologically meaningless edges in the network. Therefore there is a need to build and investigate undirected and directed metabolite- and enzyme-centric networks, preferably in common and widely used tools/pipelines for the analysis of metabolic systems.

3.1. Construction of metabolite-centric networks

Metabolite-based networks can be constructed in which the metabolites are the nodes linked by the according enzymes [53]. An undirected metabolite-centric network is a dot product of the binary stoichiometric matrix (S_{bin}) and its matrix transpose (S_{bin}^T) [54].

$$M_{\text{undir}} = S_{\text{bin}} \times S_{\text{bin}}^T$$

where the stoichiometric matrix (S) consists of metabolites and reactions of a system. Each metabolite has a row and each reaction has a column in the S.

For construction a directed metabolic-centric network, each column of the S matrix has been parsed and added an edge per every value sign changes (positive to negative or vice versa). It should also consider the reversibility of reactions.

For example, we have we have provided results for a glycolysis model downloaded from the BioModel database (*BIOMD0000000172*). The undirected and directed metabolite-centric networks which have been constructed by aforementioned algorithms are shown in Fig. 3A and B, respectively.

In another approach for construction metabolite-centric networks, ubiquitous metabolites like water, oxygen, ATP and co-factors are not taken into account while studying only the most relevant metabolic fluxes. Pey et al. developed an elaborate concept to construct metabolite-centric networks by setting a link between metabolites only if (i) a reaction exists in which carbon atoms are exchanged, and (ii) at least one reasonable flux path could be reconstructed which accounts for the exact stoichiometry [55].

3.2. Construction of enzyme-centric networks

An undirected enzyme-centric network is a dot product of the transpose of binary stoichiometric matrix (S_{bin}^T) and the binary stoichiometric matrix (S_{bin}) [54].

$$E_{\text{undir}} = S_{\text{bin}}^T \times S_{\text{bin}}$$

For the proper construction of a directed enzyme-centric network, each row of the S matrix has been parsed and added an edge per every value sign changes (positive to negative or vice versa). It has should also consider the reversibility of reactions.

As mentioned before, the problem is more complicated for enzyme-centric networks due to the presence of currency metabolites which means that networks contain a lot of biologically meaningless edges. For example, constructed enzyme-centric networks for the glycolysis model (*BIOMD0000000172*) have been

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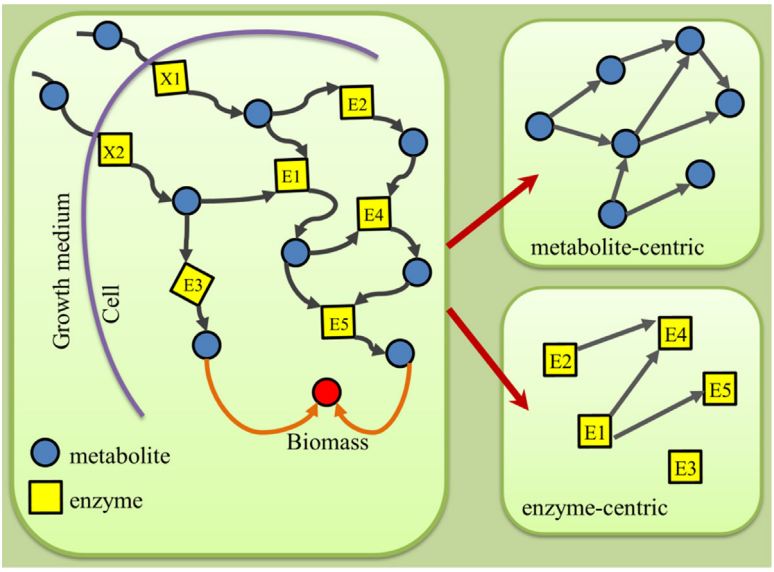

Fig. 2. Three different representations of metabolic networks; (1) considering both metabolites and enzymes in the network also called bipartite network (left), considering metabolites relationships called metabolite-centric (top-right), and considering enzymes relationships called enzyme-centric (bottom-right) [52].

shown in Fig. 3C and D. One could see lots of biologically meaningless edges comparing to the original model due to occurrence of currency metabolites. So, it is necessary to remove currency metabolites before construction. However, currency metabolites could not be defined globally and have to be determined on a reaction basis which require manual work [56]. One possible solution is to provide a given input text file including currency metabolites and use it during the construction process. The algorithm first removes

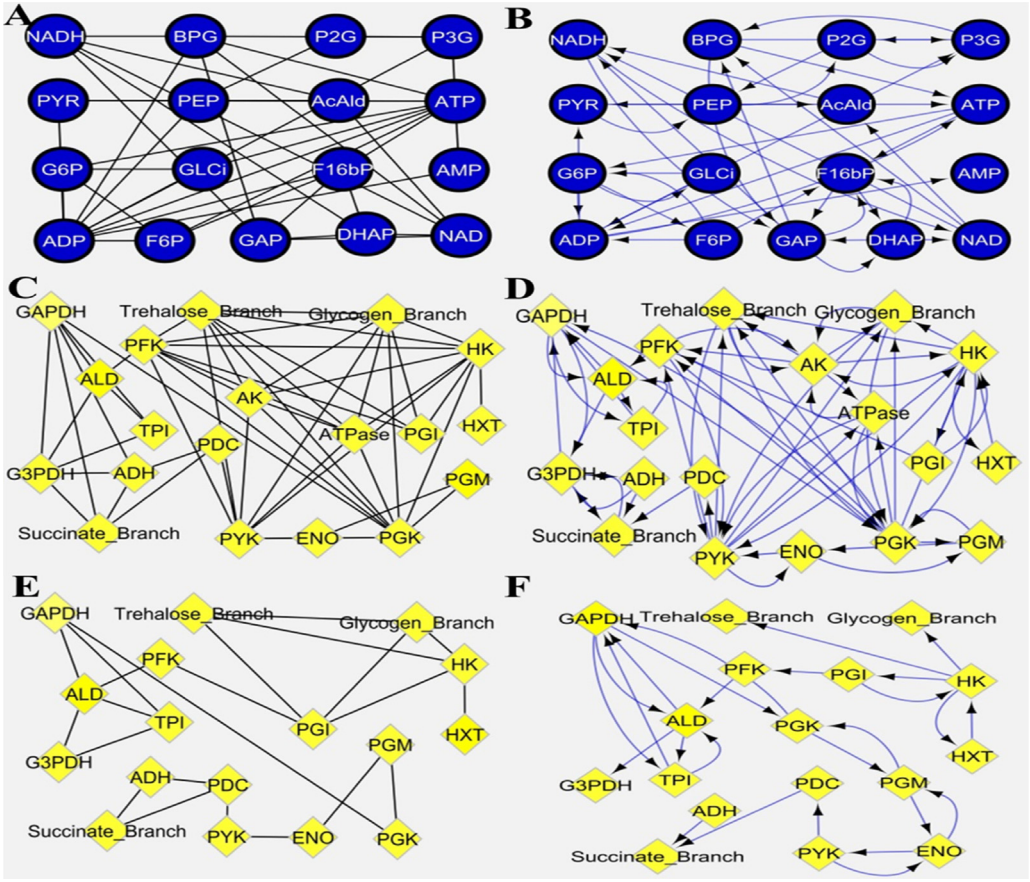

Fig. 3. Metabolite- and enzyme-centric constructed networks based on the glycolysis model (*BIOMD0000000172*); (A) undirected metabolite-centric network, (B) directed metabolite-centric network, (C) undirected enzyme-centric network with presence of currency metabolites, (D) directed enzyme-centric network with presence of currency metabolites, (E) undirected enzyme-centric network after removing currency metabolites using the RCM algorithm and (F) directed enzyme-centric network after removing currency metabolites using the RCM algorithm.

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the metabolites appears in the text file from the *S*-matrix and builds an enzyme-centric network using the new *S*-matrix.

There is also an algorithm called the RCM (Remove Currency Metabolites) which an automatically remove currency metabolites and construct an enzyme-centric network [57]. The algorithm works by deletion the most probable metabolite among all. The selected metabolite will be deleted in the *S*-matrix and its binary *S*-Matrix, and the algorithm continues during a while loop. It is ended if there is not any suspicious case. After that, an undirected or directed enzyme-centric network will be constructed based on the new *S*-matrix. Fig. 3E and F shows constructed undirected and directed enzyme-centric networks using the RCM algorithm for the glycolysis model. However, it is recommended to run an automatic algorithm (such as the RCM) for removing currency metabolites first. Then correct false positives and use the file containing currency metabolites as input for an enzyme-centric construction process.

3.3. Topological works on cancer

Due to the large size of the human genome, and the substantially increased complexity of eukaryotic genetic regulation, inference of topological works in cancer networks presents increased practical and theoretical challenges. Further complexity arises from the different data sources needed for exploring human systems such as primary cell lines, tissue biopsies, immortalized cell lines, and animal models, which each provide defective recapitulation of in vivo cancer biology and changing degrees of experimental malleability. Nonetheless, several efforts to infer regulatory or signaling cancer networks have revealed important information regarding the molecular basis of oncogenesis [58–62]. However, there was less attention to use topological analysis on cancer metabolic networks. But recent development in reconstruction of metabolic models for different cancer tissue-specific networks creates an opportunity to do different graph theory analysis. In a recent study, Asgari et al. [57] have applied a comprehensive topological analysis of 15 recently published genome-scale metabolic models of normal and cancer tissue-specific models to assess the controllability relation between topological parameters and drug targets, with the assumption that the targets of approved anticancer metabolic drugs are driver nodes and therefore control cancer metabolic networks. The centrality analysis showed that drug targets avoid being highly connected enzymes. Motifs, as another local property of networks, have also been examined and there was no difference in metabolic-centric networks of cancer and normal cell types, but there were significant discrepancies in the enzyme-centric networks of cancer cells and their corresponding normal cell types. The number of clusters between cancer and corresponding normal cell networks showed no significant differences, but characterizing drug targets in enzyme-centric clusters showed that most of the drug targets belong in one specific cluster of an enzyme-centric network. Therefore the results indicated that besides primary network parameters, more complex network metrics such as motifs and clusters may be also suitable parameters for controlling the systems providing controllability relationships between topological parameters and drug targets. Also, enzyme-centric networks could be reliable for controlling metabolic systems, although little attention has been paid to such networks in systems control [57].

As another example of topological analysis, it is also possible to do different pattern analysis on metabolic networks which takes the topology of such networks into account. In one study, gene expression data is mapped onto (lattice grid-like) adjacency matrices of metabolic pathways in the PathWave approach to show significant differences between samples of different conditions of neuroblastoma, recognizing a significant switch-like regulation pattern in glutamate metabolism that hints toward deregulated glutamine uptake from the bloodstream [63]. The method was applied in a second cancer study detecting a pattern of up-regulation in cholesterol biosynthesis and down regulation of bile acid degradation in breast cancer hinting for a positive feedback mechanism of estrogen production [64].

Finally, the diverse use of network analysis for studying cancer [65–67], makes it possible to expect performing such an approach for metabolic networks since the interpretation of cancer as a genetic disease has gradually been displaced by that of a metabolic disease in recent years [2,68].

3.4. Topological analysis tools

There are many tools for topological analysis of biological networks. Complete lists of softwares are available on the SBML website (http://sbml.org/SBML_Software_Guide). Tools and libraries such as SBMLToolbox [69], SBToolbox/SBToolbox2 [70], and libSBML [71] are widely used to work with SBML files, but are not GEM-specific and do not provide metabolite-/enzyme-centric networks. Cytoscape is a powerful tool for structural network analysis which comes with many specific plugins [72].

4. Constraint-based approach

4.1. Flux balance analysis

The potential of mathematical computational modeling tools in description, exploration, and prediction of metabolic networks has been realized in recent years [73]. One of the most widely used network analysis approaches is Flux Balance Analysis (FBA), which is based on derivation of the steady-state metabolic capabilities of a system with appropriate constraints and without the need for accurate kinetic data [74]. The main principle of the FBA is that the system will reach a steady-state under any assumed environmental condition that fulfills all the physiochemical constraints of the cell, e.g. the stoichiometric balance of energy and mass [75]. Representing a metabolic network as a stoichiometric set of equations and implying the steady state, it is possible to represent it as a stoichiometric set of equations. The set of coupled ordinary differential equations are then characterized in a matrix format including the stoichiometric (S) and the flux (V) matrices. Since metabolic networks typically have more reactions than metabolites, this leads to an underdetermined system of linear equations containing more variables than equations. Using linear programming is a standard approach to solve under-determined systems. It minimizes/maximizes an objective function as follows:

$$\text{min/max}: \quad \sum c_i \cdot |v_i|$$

$$\text{subject to}: \quad S.v = 0 \quad a_i < v_i < b_i$$

where c is stoichiometric coefficient of metabolite i in the reaction v, and a and b are lower and upper bound of a given reaction, respectively.

Lacking any constraint, the solution for the metabolic fluxes is underdetermined, i.e. an extremely large solution space is present. Applying additional constraints (for example the maximum uptake rate of a given substrate) could lead to allowable solution space and a flux cone corresponding to the metabolic capability could be calculated [76]. The FBA could obtain the optimal set of the flux distribution based on a metabolic optimization objective function such as the maximal biomass production rate.

The FBA does not require kinetic data due to its simple fundamentals and could be computed very quickly. Since its early development about 25 years ago [77], the FBA has shown to be a robust and diverse method to predict the physiologically meaningful steady state in order to obtain a given metabolic objective such

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Table 2
Some of the most useful constraint-based modeling softwares.

Constraint-based modeling tools	Reference
COBRA	[87]
VANTED	[88]
SurreyFBA	[89]
CellNetAnalyzer	[90]
RAVEN	[91]

as ATP production rate or growth rate [74]. It was also demonstrated to be effective in predicting cellular and metabolic phenotypes through various perturbations, such as different growth conditions in *E. coli* and other organisms [78,79]. Last, but not least, the FBA could offer the ability to predict core reactions or pathways of an organisms' metabolism with apparent effects for metabolic engineering [80–84]. Taken together, the FBA is a powerful metabolic network modeling method to explore cellular metabolism from a systems biology perspective.

4.2. Application of FBA in cancer modeling

In contrast to topological analysis, the FBA approach has been used in the development of human cancer metabolic models. In one study, the constraint-based modeling approach combined with machine learning methods have been explored for novel drug target prediction of existing anti-cancer drugs [85]. These modeling approaches have shown that the Warburg's effect comes along with optimally employing (glycolytic) enzymes for energy production when considering molecular crowding. This helps to generate building blocks for the biomass of the cancer cells. Taking solvent capacity constraints into consideration, the model correctly predicted a three phase oncogenic progression and high glutamine uptake in cancer [25].

Two other studies demonstrated the predictive power of cell line-specific models. Folger et al. [27] constructed a cancer model based on microarray data for non-small cell lung cancer metabolism. Model predicted genes which were essential for growth significantly. The results were in agreement with experimentally measured essential genes from an shRNA screen. This recognized that cell-line specific models could suggest novel targets.

A successive study established and confirmed a target related to hereditary leiomyomatosis and renal cell cancer (HLRCC). The HLRCC develops when the tumor suppressor gene fumarate hydratase (FH) is mutated. To model HLRCC, a murine renal cell line was derived, and then FH was disabled [86]. Metabolic models were built for the cell line before and after disabling FH. Simulations verified that a loss of FH is buffered by other pathways. Indeed, 24 model genes were synthetic lethal with FH, most of which donated to heme biosynthesis.

While the constraint-based cancer modeling field is still relatively young, the reconstructed models in recent studies has been shown the ability to predict therapeutic targets.

4.3. Constraint-based modeling tools

There are some useful software tools for performing constraint-based modeling of metabolic networks, including commercial, free, and online tools. We have provided here some of the most powerful packages (Table 2) which have been used widely in the recent decade:

(1) COBRA (COnstraint-Based Reconstruction and Analysis): is a MATLAB toolbox which is now widely used and is a powerful framework for flux balance-based analysis of metabolic networks. It could be applied for quantitative prediction of cellular behavior via a constraint-based approach. Precisely, this software makes it possible to predict behavior of optimal growth, robustness analyses, effects of gene deletions, sampling the series of probable cellular metabolic states, and network modules determination [87].
(2) VANTED: is another tool for the analysis and visualization of networks with related experimental data. Data could be uploaded into the software from large-scale biochemical experiments. Then it could be mapped on a network in three different ways; downloaded from the KEGG database, drawn with the tool itself, or imported by various standard formats [88].
(3) SurreyFBA: offers constraint-based simulations and network visualization. In addition to basic simulation, the tool also performs analysis of minimal substrate and product sets. It is a free, stand-alone software which could be useful for metabolic engineering [89].
(4) CellNetAnalyzer: is a MATLAB toolbox in a visual manner which performs a comprehensive structural analysis of signaling, regulatory, and metabolic networks. It provides a single package to achieve structural and qualitative analysis of mass-flow- and signal-flow-based cellular networks in a user-friendly environment. The specific strengths of CellNetAnalyzer are different methods for functional network analysis [90].
(5) RAVEN (Reconstruction, Analysis and Visualization of Metabolic Networks): is another software package which permits for semi-automated reconstruction of GEMs. It uses published models coupled with improvement approaches such as gap-filling and quality control features. It also includes methods for visualization simulation results, as well as a collection of methods for accomplishment simulations and analyzing the results [91].

5. Drug-target prediction and structural analysis

GEMs provide a useful tool for the study of diseases and the development of drugs. Several simulations and modeling methods have been developed to address the issues of drug-target prediction [92–96]. The structural features of metabolic networks contribute to the robustness and flexibility of the complex biosystems and may explain, in general, the fact that many drug candidates are ineffective (the drug effect is compensated by other pathways in the network) or show unexpected severe side effects [97–99]. Prompted by these findings, many scientists have proposed a system-oriented drug design strategy to replace the current "one gene, one drug, one target, one disease" approach [99–101]. Hence polypharmacology has been proposed as a concept for those drugs acting on multiple targets instead on one target [102].

It is also reasonable that multiple target modifications can more effectively convert the system from a disease state to a normal state than a single target modification. In fact, successful applications of multi-component therapies have been reported and multi-component drugs are already on the market [103,104]. Systems analysis will help us not only in the discovery of novel drug targets but also in developing new systems-based therapy strategies. Follow to this concept, the "network medicine" is a new subject that tries to link structural network properties to biological function and disease. Network medicine explores the molecular complexity of a special disease and relationships between distinct phenotypes which may lead to the identification of disease modules and pathways [105].

A better understanding of the implications of cellular interconnectedness for disease progression will lead to discovery of new disease genes and pathways. These advances may also reshape

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clinical practice, from discovery of more accurate biomarkers to a better disease classification leading to personalized therapies and treatment. Recently, there have been some studies on disease clustering approaches which aim to find different disease modules and predict new genes. Development of cell-line specific model enabled the identification of a potential new drug target for a specific tumor type, highlighting the potential of model-predicted cancer therapies which has been considered by two recent studies [27,57].

6. Outline

Aggressive cancers established evidence of a metabolic shift, including upregulation of the pentose phosphate pathway (PPP) and the glutamine transporter genes, downregulation of genes contributed in the TCA cycle, increased acetyl-CoA carboxylase protein, decreased AMPK and PTEN protein levels, and altered promoter methylation of miR-21 and GRB10 [106]. As far as we know, different strategies are available to target metabolic enzymes for cancer therapy including nucleic acid synthesis, amino acid metabolism/protein synthesis, lipid synthesis, glycolysis, TCA cycle/mitochondrial metabolism, fatty acid metabolism, and NAD metabolism [107]. In addition, the effects of the metabolic syndrome (such as obesity and Type 2 diabetes) on cancer development and progression show a close relation between metabolism and cancer [108].

Therefore, metabolic networks in human cancer are important area for systems modeling going forward since metabolic targets have also been considered in cancer chemotherapy [109–111]. However, cancers in particular are known to display various metabolic phenotypes in comparison with their progenitor cells, usually with an increased rate of overall metabolic activity to support their increased growth [112,113]. Some other hallmarks of cancer such as angiogenesis, evasion of apoptosis, metastasis, and avoidance of immune detection have been previously associated with human tumor metabolism [4,114].

As a result of complexity of cancer, computational models are being established to help both biological discovery and clinical medicine. The development of in silico models is facilitated by quickly progressing experimental and analytical tools which generate high-throughput biological data with lots of information. Besides, improvement of tissue-specific cancer metabolic models could promise new strategies for treatment. Structural (topological and constraint-based) approaches at genome-scale levels seem to be useful in developing diagnostic and prognostic molecular signatures, as well as in identifying new drug targets. For example, prediction of metabolic fluxes in renal-cell cancer has been performed using the topology of a network, and the stoichiometric and thermodynamic constraints in order to clarify and validate new drug targets [86].

Although structural perspective of cancer cellular metabolism could suggests new sights and opportunities for disease treatment, significant challenges remain including (1) data integration platforms, (2) discover details about mutations and enzyme regulation, and (3) expanding models to account for the other hallmarks of cancer.

Conflict of interest

No conflict of interest exists.

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