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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.

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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