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Anticancer drug discovery through genome-scale metabolic modeling

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Abstract

Altered metabolism has long been recognized as a defining property of cancer physiology, but is experiencing renewed interest as the importance of such alterations are becoming fully realized. Once regarded merely as a side effect of a damaging mutation or a general increase in proliferation rate, metabolic network rewiring is now viewed as an intentional process to optimize tumor growth and maintenance, and can even drive cancer transformation. This has motivated the search for anticancer targets among enzymes in the metabolic network of cancer cells. Genome-scale metabolic models (GEMs) provide the necessary framework to systematically interrogate this network, and many recent studies have successfully employed GEMs to predict anticancer drug targets in the metabolic networks of various cancer types.

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Introduction

Cancer remains a leading cause of death worldwide—approximately one-third of individuals will develop some form of the disease within their lifetime [1]. Although there have been substantial advancements in the detection, diagnosis, and treatment of many cancer types, the highly complex and heterogeneous nature of the disease continues to impede further progress. There are many contributors to the initiation and progression of cancer, and are generally grouped into distinct categories termed the "hallmarks" of cancer [2]. In addition to characteristics such as resisting cell death and evading growth suppressors, a recent addition to the hallmarks was the reprogramming of energy metabolism [2,3].

Perturbed metabolic activity in cancer cells is not a new concept. Indeed, one of the most notable metabolic alterations in cancer cells, the Warburg effect, was identified in the 1920s [4,5]. However, a metabolism-centric approach to understanding and treating cancer has experienced a revived interest in recent years, due to advancements in high-throughput biological profiling techniques (e.g., transcriptomics, proteomics, metabolomics), which now enable a systematic and mechanistic mapping of cancer-specific remodeling of metabolism. Furthermore, the strong link between metabolic behavior and cancer outcomes, as well as the identification of many cancer-driving "oncometabolites", has highlighted the metabolic network as a promising source of novel anticancer drug targets [6,7].

The complexity of the metabolic network, which is further obscured by the substantial heterogeneity of cancer, prevents tracing specific properties or outcomes back to an individual metabolic feature or subsystem. In order to investigate such a broad and interconnected system, a computational approach is required [8]. One such class of approaches employs the use of genome-scale metabolic models (GEMs), which are mathematical representations of the network of reactions comprising the metabolic functionality of the cell [9]. A number of recent approaches have demonstrated that GEMs can with success be used to gain a more mechanistic understanding of tumor physiology, as well as to identify novel anticancer drug targets in the cancer metabolic network.

We review here the recent use of GEMs in the investigation of cancer metabolism, focusing specifically on their application for predicting targets or therapies for cancer treatment. We further discuss the limitations of current GEM-based approaches, as well as perspectives on future developments that seek to improve their accuracy and versatility. The recognition of the critical role metabolism plays in cancer, in addition to the demonstrated success of employing GEMs for anticancer target discovery, highlights an upward trend in the importance of GEMs to the ongoing battle against cancer.

Metabolism as a target of anti-cancer therapies

The importance of metabolism in the context of cancer was highlighted nearly a century ago in the work of Otto Warburg, where his discovery of increased glucose consumption by cancer cells compared with normal tissue is still exploited in modern clinical applications, such as tumor imaging with ^{18}F-deoxyglucose positron emission tomography (FDG-PET) [5,10]. This altered metabolic behavior, termed the "Warburg effect", includes a fermentation-like shift in glucose usage away from the TCA cycle and oxidative phosphorylation toward lactate production, despite the presence of sufficient oxygen to operate the seemingly more optimal aerobic respiratory pathway [4]. Extensive work since the discovery of this behavior has shed new light on the underlying cause, suggesting an intentional rewiring of metabolism to support the increased demands of precursor metabolites, in particular those that are part of glycolysis, for the synthesis of building blocks and further to macromolecules, rather than the initially proposed byproduct of "injured" mitochondria [3,11]. However, a definitive mechanism is still unclear, and the emerging picture is one of increasing complexity—not only is the Warburg effect absent in some cancers, there are a growing diversity of metabolic patterns exhibited among different cancer types, and even among cells comprising the same tumor [12].

Rewiring metabolism can confer a number of benefits to tumors ranging from rapid proliferation to improved oxidative stress tolerance, but often come with penalties such as increased nutrient demand or enhanced sensitivity to other forms of stress [13]. These new vulnerabilities and any other metabolic features that differentiate cancer from normal healthy cells constitute an attractive pool of metabolic targets for anti-cancer therapy development [6,14].

Although proliferating cancer cells still utilize oxidative phosphorylation for a significant fraction of their ATP production, their metabolic network is generally reprogrammed to optimize production or import of metabolites required for rapid cell proliferation, such as NADPH and glutamine [3]. Glutamine serves as an excellent source of reduced nitrogen to generate purine and pyrimidine bases for nucleotide biosynthesis, as well as for the production of nonessential amino acids [13]. Some cancers even exhibit "glutamine addiction," where high uptake rates of the amino acid are required to support additional functions such as NADPH production for macromolecular biosynthesis and redox balancing, generation of oxaloacetate to replenish TCA cycle intermediates (anaplerosis), and driving exchange reactions to import additional extracellular amino acids [15,16]. This glutamine requirement has been targeted in approaches such as using glutamine analogs to inhibit its utilization or enzymatic depletion of glutamine levels in the blood; however, many of these treatments exhibit high host toxicity, and thus require further development [15].

Another non-essential amino acid that many cancers import or synthesize at an increased rate is serine, which is used to produce phospholipids and other amino acids, in addition to providing one-carbon units for folate metabolism [17]. The increased serine demand in tumors represents a promising metabolic target, and development of inhibitors for the serine biosynthetic pathway are currently ongoing [18]. The folate cycle is often upregulated in certain cancers [13,19], and generates precursors for purine biosynthesis and methylation, and can contribute to nearly half of the total cellular NADPH supply [20]. As such, folate metabolism represents yet another attractive target for anticancer therapy development. Interestingly, one of the first-developed chemotherapy treatments (methotrexate) functioned by interfering with folic acid utilization [21], and is still in use today [14,17].

Targeting the unique metabolic behavior of tumor cells has been demonstrated to be an effective anticancer approach, but the frequent host toxicity of many treatment strategies highlights the difficulty of working in such a narrow therapeutic window. Future efforts to target cancer metabolism therefore require approaches that account for the tightly connected and interactive nature of the metabolic network, to minimize potential collateral damage. One such promising approach employs the use of GEMs to help analyze and predict potential anticancer therapeutics in the metabolic network.

Construction and application of genome-scale metabolic models

GEMs are a mathematical representation of the network of reactions comprising all known metabolic functions of the biological system under study [22]. The stoichiometry of all the reactions are collected in a matrix, which specifies the involvements and molar ratios of reactants and products participating in each reaction. Another feature of GEMs is that for each reaction the corresponding enzyme(s) and its associated gene(s) are specified, and the models hereby also provide gene—protein—reaction—metabolite associations [23]. The relationship between each of these GEM components enables translation between gene, protein, reaction, and metabolite information, thus facilitating the use and integration of many different types of high-throughput omics data [24].

GEMs have been constructed for a wide spectrum of species and biological systems, including those of plants, bacteria, and fungi, and have been applied for purposes ranging from metabolic engineering of yeast