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The metabolomic signature of hematologic malignancies

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ABSTRACT

The ongoing accumulation of knowledge raises hopes that understanding tumor metabolism will provide new ways for predicting, diagnosing, and even treating cancers. Some metabolic biomarkers are at present routinely utilized to diagnose cancer and metabolic alterations of tumors are being confirmed as therapeutic targets. The growing utilization of metabolomics in clinical research may rapidly turn it into one of the most potent instruments used to detect and fight tumor.

In fact, while the current state and trends of high throughput metabolomics profiling focus on the purpose of discovering biomarkers and hunting for metabolic mechanism, a prospective direction, namely reprogramming metabolomics, highlights the way to use metabolomics approach for the aim of treatment of disease by way of reconstruction of disturbed metabolic pathways.

In this review, we present an ample summary of the current clinical appliances of metabolomics in hematological malignancies.

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1. Introduction

Nutrient and oxygen supply of a cell influence the metabolic pathways engaged for the production of energy. In response to modifications cells either adapt or die. Several factors that were firstly characterized as cell death regulators are now recognized to physically or functionally interact with metabolic enzymes.

Therefore, many metabolic signals control the proclivity of cells to initiate self-destructive programs, in part by operating on nutrient sensors. This suggests the presence of "metabolic checkpoints" that determine cell fate in response to metabolic variations. However, it is known that the capacity of cancer cells to adjust their metabolism in response to challenging situations is a much more general event than previously supposed [1].

In fact, one method cancer cells gain advantage over non cancer cells is by adapting their metabolism to the production of lipids, nucleotides, and proteins necessary for cell proliferation. This supposition has led to the elaboration of metabolomics, a novel and potent tool founded on metabolic profiling techniques, that has been demonstrated to be really useful in the identification of early biomarkers correlated with cancer [2,3].

Metabolomics particularly focuses the activity of the small molecules (<10 kDa) generated by cells during their life cycles [4]. Metabolites are a direct readout of biochemical activity and offer an image of cellular state. Given the broad range of physical properties typical of the metabolome, evaluating the full set of metabolites present in biological matrices is a major challenge [5,6]. Different metabolic profiles have previously been described for several cancers [7–9].

Furthermore, in higher grade cancers, different metabolic states (energetic, anabolic, and phospholipid catabolic) were recognized and linked with the prognosis [9]. Tumor cells utilize a considerable amount of glucose and generate lactate for ATP production. ATP, required by proliferating cells, is originated from two main sources.

One is glycolysis, which metabolizes glucose to pyruvate, producing two molecules of ATP per molecule of glucose. The other is the tricarboxylic acid (TCA) cycle, which utilizes pyruvate and supplies electrons to the respiratory chain complexes in the mitochondria.

Most cancer cells shift their metabolism towards aerobic glycolysis by augmenting glycolysis and decreasing oxidative phosphorylation even under high-oxygen conditions [10–13]. This switch is known as the Warburg effect, which helps quickly replicating cells such as tumor cells by supporting the synthesis of essential cellular components, including the lipids and nucleotides required for fast cell duplication (Fig. 1).

Tumor tissues perform aerobic glycolysis through stimulation of oncogenes or reduction of cancer suppressor proteins. For example, the STAT protein family is a type of transcription factors that play a significant role in relaying signals from growth factors and cytokines.

STAT3 is implicated in oncogenesis by upregulating the transcription of numerous genes that influence cancer cell survival, resistance to apoptosis, angiogenesis and cell-cycle progression [14].

Recently, Demaria et al. determined a correlation of STAT3 with the Warburg effect, in a metabolomics analysis [15], which suggests that activated STAT3 acts as a major regulator of cell metabolism by stimulating both aerobic glycolysis and down-regulation of mitochondrial activity.

Akiyama et al. recognized latexin as a proteomic marker candidate for STAT3- targeting therapy using STAT3-specific shRNA gene transduction. In particular, latexin expression was upregulated in diverse STAT3-activated tumor cell lines [16].

However, mutations of other genes implicated in the TCA cycle, such as fumarate hydratase, succinate dehydrogenase, or isocitrate dehydrogenase (IDH) 1 or 2, are causally connected to familial cancer syndromes [17] or acute myelogenous leukemia (AML) [18].

The IDH enzyme has three different isoforms: IDH1 (peroxisomes and cytosol), IDH2 (mitochondria), IDH3 (mitochondria – TCA cycle), and usually catalyses the oxidative decarboxylation of isocitrate to alpha-ketoglutarate. So far IDH3 mutations in tumor have not been identified, whereas point mutations in the catalytic sites of both IDH1 and IDH2 are discovered in AML [19].

These mutations cause a pathological catalytic activity namely the decrease of ketoglutarate to 2HG. By the competitive inhibition of demethylases 2HG modifies the epigenome [20,21]. Clinical trials in glioma and AML are presently investigating several inhibitors of IDH1 (AG-120) or IDH2 (AG-221), or immunotherapy against IDH1 neoantigen [22–25].

Argininosuccinate synthetase 1 (ASS1) is an enzyme which is involved in arginine biosynthesis in mammals. Genetic or epigenetic silencing of ASS1 in solid cancers and AML makes them auxotrophic of this non-essential amino acid [26]. Mechanistically, absence of ASS1 activity helps proliferation as one of its substrates, aspartate, is free for use in nucleotide biosynthesis [27,28]. An important amount of the biosynthetic needs under aerobic situations can be met by glutamine [29], which is controlled by the activity of the MYC oncogene. The importance of non-essential amino acids like serine, proline and arginine has also been valued recently [30–34].

The relationship between metabolism and cell death regulation are intense and complex. Both necrosis and apoptosis may be inducted by metabolic perturbations, primarily due to the presence of refined detection systems that are wired to the cell death machinery through one or more signaling nodes. Thus, small metabolites as well as various enzymes implicated in metabolic pathways can change cell fate decisions.

On the other hand, numerous proteins originally described for their cell death-regulatory activity (e.g., p53, Bcl-2 family members) have a main metabolic function. Thus, any difference between metabolism and signaling has now decayed. In any case, mitochondria are central to the control of cell life and death, and are deeply involved in metabolism as they are responsible for energy production [35].

In tumor cells, the mitochondrion transforms its original role as just a "power house" to a new function as a biosynthetic hub, where more anabolic precursors are generated to sustain cell proliferation [10,36]. The mitochondrial checkpoint also controls the predisposition of cells to die as it controls the stimulation of caspase-1 by the NLR pyrin domain containing 3 (NLRP3) inflammasome [37].

Inflammasomes may work at the cell-autonomous level to eradicate cancer cells through apoptosis or, contrariwise, may increase the production of trophic factors for tumor cells.