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Review

Dysregulated metabolism contributes to oncogenesis

Matthew D. Hirschey[a,b,c,*], Ralph J. DeBerardinis[d,1], Anna Mae E. Diehl[a,1], Janice E. Drew[e,1], Christian Frezza[f,1], Michelle F. Green[b,1], Lee W. Jones[g,1], Young H. Ko[h,1], Anne Le[i,1], Michael A. Lea[j,1], Jason W. Locasale[c,k,l,1], Valter D. Longo[m,1], Costas A. Lyssiotis[n,1], Eoin McDonnell[b,1], Mahya Mehrmohamadi[l,1], Gregory Michelotti[a,1], Vinayak Muralidhar[o,p,1], Michael P. Murphy[q,1], Peter L. Pedersen[r,1], Brad Poore[i,1], Lizzia Raffaghello[s,1], Jeffrey C. Rathmell[b,c,1], Sharanya Sivanand[t,1], Matthew G. Vander Heiden[o,p,u,1], Kathryn E. Wellen[t,1], Target Validation Team[2]

[a] Department of Medicine, Duke University Medical Center, Durham, NC 27710, USA
[b] Duke Molecular Physiology Institute, Duke University Medical Center, Durham, NC 27701, USA
[c] Department of Pharmacology & Cancer Biology, Duke University Medical Center, Durham, NC 27710, USA
[d] Children's Medical Center Research Institute, University of Texas – Southwestern Medical Center, Dallas, TX 75390, USA
[e] Rowett Institute of Nutrition and Health, University of Aberdeen, Aberdeen, Scotland, United Kingdom
[f] MRC Cancer Unit, University of Cambridge, Hutchison/MRC Research Centre, Cambridge, United Kingdom
[g] Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA
[h] University of Maryland BioPark, KoDiscovery, Baltimore, MD 20201, USA
[i] The Sol Goldman Pancreatic Cancer Research Center, Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21231, USA
[j] New Jersey Medical School, Rutgers University, Newark, NJ 07103, USA
[k] Division of Nutritional Sciences, Cornell University, Ithaca, NY 14850, USA
[l] Field of Genetics, Genomics, and Development, Cornell University, Ithaca, NY 14850, USA
[m] Andrus Gerontology Center, Division of Biogerontology, University of Southern California, Los Angeles, CA 90089, USA
[n] Department of Molecular and Integrative Physiology and Department of Internal Medicine, University of Michigan, Ann Arbor 48109, USA
[o] Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA 02139, USA
[p] Harvard-MIT Division of Health Sciences and Technology, Harvard Medical School, Boston, MA 02115, USA
[q] MRC Mitochondrial Biology Unit, Wellcome Trust-MRC Building, Cambridge, United Kingdom
[r] Department of Biological Chemistry and Department of Oncology, Johns Hopkins University, Baltimore, MD 21205, USA
[s] Laboratory of Oncology, Istituto Giannina Gaslini, Genoa, Italy
[t] Department of Cancer Biology, Abramson Family Cancer Research Institute, University of Pennsylvania, Philadelphia, PA 19104, USA
[u] Dana-Farber Cancer Institute, Boston, MA 02115, USA

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ABSTRACT

Cancer is a disease characterized by unrestrained cellular proliferation. In order to sustain growth, cancer cells undergo a complex metabolic rearrangement characterized by changes in metabolic pathways involved in energy production and biosynthetic processes. The relevance of the metabolic transformation of cancer cells has been recently included in the updated version of the review "Hallmarks of Cancer", where dysregulation of cellular metabolism was included as an emerging hallmark. While several lines of evidence suggest that metabolic rewiring is orchestrated by the concerted action of oncogenes and tumor suppressor genes, in some circumstances altered metabolism can play a primary role in oncogenesis. Recently, mutations of cytosolic and mitochondrial enzymes involved in key metabolic pathways have been associated with hereditary and sporadic forms of cancer. Together, these results demonstrate that aberrant metabolism, once seen just as an epiphenomenon of oncogenic reprogramming, plays a key role in oncogenesis with the power to control both genetic and epigenetic events in cells. In this review, we

* Corresponding author at: Duke Molecular Physiology Institute, 300 N. Duke Street, Durham, NC 27701, USA.
E-mail address: matthew.hirschey@duke.edu (M.D. Hirschey).
[1] Equal contribution; authors listed alphabetically.
[2] The complete list of contributing authors on the target validation team are listed alphabetically in the acknowledgements.

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discuss the relationship between metabolism and cancer, as part of a larger effort to identify a broad-spectrum of therapeutic approaches. We focus on major alterations in nutrient metabolism and the emerging link between metabolism and epigenetics. Finally, we discuss potential strategies to manipulate metabolism in cancer and tradeoffs that should be considered. More research on the suite of metabolic alterations in cancer holds the potential to discover novel approaches to treat it.

1. Introduction

A non-profit organization called Getting to Know Cancer launched an initiative entitled "The Halifax Project" in 2011, which was charged with identifying synergistic molecular targets and/or small molecules for each of the areas that are widely considered to be hallmarks of cancer [1]. The rationale for this approach is based on the idea that cancers harbor significant genetic heterogeneity [2], which is often not addressed with monotherapeutic approaches. While efforts have been made to combine therapies to overcome resistance, rising drug costs, significant levels of toxicity, and a lack of overall success have stymied efforts to effectively treat cancer with multi-drug combinations [3].

Thus, the first aim of the Halifax Project was to produce a series of reviews, including this review on cancer metabolism, to broadly assess current knowledge on the biology of cancer. The overall goal of the Halifax Project is to identify biological targets and prospective lead compounds that could potentially be used to reach each prioritized area, and synergistically target multiple hallmarks of cancer. By building this rationale into the approach a priori, the problem of heterogeneity might be overcome. In theory, multiple low toxicity approaches could be experimentally combined, which then might lead to synergism within a given hallmark, such as cancer metabolism. Future studies will build upon these findings and test these hypotheses, as well as integrate these concepts into the approaches recommended in other hallmark areas in this special issue.

In this review, we first discuss the relationships between metabolism and cancer. We focus on major alterations in nutrient metabolism, as well as the emerging links between metabolism and epigenetics. Next, we discuss potential therapeutic strategies that could be used to manipulate metabolism in cancer cells or to manipulate host metabolism thereby influencing cancer metabolism. Finally, we describe tradeoffs that should be considered when leveraging these approaches. Together, this information will be the basis of significant future research to fully realize the potential of targeting metabolism in cancer.

2. Classic metabolic derangements

The first realization that metabolism is altered in cancer can trace its roots to the work of Otto Warburg. During the 1920s, Warburg found that unlike most normal tissues, cancer tissues fermented glucose to lactate at high rates regardless of the presence of oxygen [4,5]. This was in contrast to the results that Pasteur had obtained previously studying fermentation in yeast, whereby O_2 was found to inhibit fermentation [6,7]. To study the metabolism of cancer in vivo, Warburg used Jensen sarcoma cells to form tumors within the abdomens of rats. By comparing arterial glucose and lactate concentrations to venous glucose and lactate concentrations, Warburg was able to infer the glucose uptake and lactate excretion by the tumor. Whereas normal tissues took up 2–18% of arterial glucose, tumors consumed 47–70%. Lactate was not significantly changed in blood after perfusion of normal tissues, but by Warburg's calculations, tumors converted 66% of their consumed glucose into lactate. Thus, Warburg surmised that tumors take up much more glucose than normal tissues and convert a much larger percentage of it to lactate [4].

Warburg's work on respiration and fermentation in cancer cells ultimately led him to propose that "the respiration of all cancer cells is damaged" [8]. In fact, he reasoned that known carcinogens, such as arsenic and hydrogen sulfide, likely worked by inhibiting respiration. He suggested that the primary oncogenic insult was an inability of cells to oxidize glucose carbons, and that X-rays were carcinogenic mainly due to their effect on mitochondria [8], which by this time had been shown to be the respiratory center of cells.

The exact molecular mechanisms leading to altered metabolism in cancer and the Warburg effect remain a major unsolved question; for a review, see [9]. Subsequent studies have shown that while changes in mitochondrial respiration are sometimes seen in cancer cells, these alterations are not likely the driving lesion for most cancer cells. For example, Warburg's follow-up work suggested that oxidative respiration was important in malignant tumors, and reported that placing rats in 5% O_2 for 40 h resulted in the death of most cancer cells, suggesting that oxygen was needed for viability of those cancer cells [4]. Similarly, the work of his contemporaries showed that oxygen consumption is intact in many cancers, thereby decoupling the Warburg effect from defective oxygen consumption [10,11]. However, oxygen consumption cannot be a direct measurement of intact respiration, because mitochondrial coupling/uncoupling influences the efficiency of oxygen consumed to ATP produced. Nevertheless, many cancer cells display increased glucose uptake and elevated lactate production, irrespective of oxygen availability – also called "aerobic glycolysis" or the Warburg effect [12], and this observation remains a hallmark of altered metabolism in cancer cells.

3. Emerging metabolic derangements

While the mechanisms leading to the Warburg effect are under intense investigation, the general consensus of the field is that dysregulated metabolism and altered mitochondrial structure–function [13] is consistently found in several cancer cell types. These changes may occur before, as a result of, or in combination with, the genetic changes driving cancer, including oncogene expression or tumor suppressor loss; for recent comprehensive reviews on these concepts, see [14,15]. For example, one well-studied link between oncogenesis and glucose metabolism is the phosphoinositide 3-kinase (PI3K) signaling pathway. Activating mutations in PI3K or overexpression of the AKT oncogenes, which lie downstream of PI3K, can induce high rates of aerobic glycolysis in non-transformed cells. This occurs in part by increasing expression and localization of the high-affinity glucose transporter, GLUT1, on the plasma membrane [16,17]. In addition, activation of the PI3K pathway can accelerate flux through glycolysis by increasing the activity of hexokinase-2, phosphfructokinase-1 (PFK1), or phosphofructokinase-2 (PFK-2) [18–20]. The tumor suppressor p53, which has a well described role in DNA damage sensing, cell cycle control, and control of apoptosis, is also able to oppose the Warburg effect by stimulating respiration and reducing glycolytic flux [21–23]. Thus, loss of p53 in cancer cells