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# Metabolic Switch: A Phenotype or a Phenomenon?

**Krishnan Ramanujan V***

*Departments of Surgery & Biomedical Sciences, Los Angeles, CA, USA*

## Statement of the Problem

A fundamental understanding of regulatory dynamics of energy metabolism is the key to unravel the complexity manifested in health that will provide valuable insights into how deregulation of energy metabolism may contribute to cancer and related human pathology. In the last few decades, the discovery of oncogenes and tumor suppressor genes has solidified the genetic paradigm of tumorigenesis. This has led to our current understanding of the multitudes of cancer specific signaling pathways that involve one or more mutations in the oncogenes and/or tumor suppressor genes [1-3]. Targeted therapies (e.g., tamoxifen, Herceptin for breast cancer) to specific cancer subtypes have their own success stories of manipulating certain gene signatures that are aberrant in cancer cells. Modifications in clinical practice of radiotherapy and chemotherapy have stemmed from a better understanding of molecular pathways from preclinical research. Does it mean that we have a near-complete control of primary and metastatic tumors in clinical patients? Perhaps not Can we claim that a comprehensive understanding of tumor genetic profiles in a global setting (e.g., GWAS, cancer genomics) or in a individual setting (e.g., personalized medicine) will yield to a complete eradication of cancer-related mortality and morbidity? Can tumor genetics research alone lead to a realistic goal of transforming cancer from a deadly disease to a more manageable health disorder as in diabetes or some cardiovascular diseases? Difficulty in answering these questions has led many research groups in search of the missing pieces and recent experimental evidences point out that tumor metabolism is an equally, if not more, important aspect as is tumor genetics [4-6]. Despite the genetic origins of cancers in the various human tissues, they are almost always accompanied by significant metabolic alterations. Alterations in PI3 kinase/AKT pathways, MAP kinase pathways and dysregulated lipid/glutamine metabolism are some of the common examples of metabolic aberrations that are associated with cancer progression and invasion. Another remarkable biochemical alteration that is commonly observed in a variety of cancers is the significant dependence on glycolytic pathway even in the presence of oxygen supply in cancer cells [1,5,7-12]. Conventional wisdom dictates that all human cells utilize the aerobic respiration in mitochondria since this route is more efficient than the anaerobic glycolysis. At the other extreme of oxygen deficit (e.g, hypoxia), the cells are forced to rely on glycolysis since mitochondrial function depends critically on the oxygen availability. The observation that many cancer cells display significantly elevated glycolytic dependence even in the presence of oxygen availability is intriguing and counter-intuitive. Such a switch from mitochondrial to glycolytic routes – "*metabolic switch*" - was originally hypothesized to be the consequence of mitochondrial dysfunction (Warburg hypothesis) [7,13]. However this hypothesis has not gained enough validity in the light of recent experimental data. In the following paragraphs, we will raise the key questions in the context of metabolic switch in cancer and discuss the potential opportunities for exploiting this metabolic phenotype for understanding fundamental cancer ramifications as well for designing novel therapeutic targets. We will close this discussion by asking if the observed metabolic switch is specific to cancers or a more generalized phenomenon in aberrant metabolism in other health disorders.

## Experimental Evidences for Metabolic Switch Phenotype in Cancers

As pointed out earlier, one of the strongest experimental observations in support of metabolic switch in cancer cells is the hyperactivated glycolysis in the presence of oxygen supply or aerobic glycolysis. In advanced tumors similar glycolytic upregulation occurs via oxygen-deficient hypoxic condition. In earlier studies there had been no systematic exploration of these two distinct metabolic states and we believe that further research in to this direction with appropriate preclinical model systems will shed valuable insight into the fundamental aspects of metabolic switch phenotype and into the tumor metabolism in general. It is not clear if the aerobic glycolysis state is as stable as the hypoxic glycolysis state since the latter has been shown to influence a variety of downstream and compensatory pathways that encompass growth-related genes and angiogenesis genes in favor of tumor growth and invasion. This opens up an interesting opportunity to explore the metabolic switch phenotype stemming from the aerobic glycolysis condition for potential windows through which tumor control can be achieved. On the other hand, experimental studies focusing on the mitochondrial dysfunction to explain metabolic switch phenotype have not been conclusive – at least not with the traditional cancer research tools. Initially it was thought that aerobic glycolysis directly contradicts the bioenergetics requirement since shutting down a more efficient mitochondrial pathway is counter-intuitive for rapid proliferation requirement of cancer cells. Recent studies and related review articles have clearly removed this misconception by directly linking the increased glycolysis with the biosynthetic routes for making lipids, nuclear acids etc., thereby supporting the cancer-associated proliferative demands [5,11,14,15]. With the advent of metabolomics/proteomic technology platforms and the availability of large clinical databases, it is conceivable that we will get a better handle on potential mitochondrial targets that can help understanding metabolic switch mechanisms and/or controlling metabolic switch phenotype in cancers. In our laboratory, we are currently pursuing this direction where we have started uncovering putative avenues for modulating mitochondrial complex I function in breast cancer models thereby directly targeting the metabolic switch characteristics for achieving optimal tumor control [10,16-19]. In particular, we aim to exploit this mitochondrial

***Corresponding author:** Krishnan Ramanujan V, Assistant Professor, Metabolic Photonics Laboratory, Departments of Surgery & Biomedical Sciences, Cedars-Sinai Medical Center, Davis Building Suite 6067, Los Angeles, CA 90048, USA, Tel: 1310-423-7666; E-mail: Ramanujanv@csmc.edu

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route in early detection of breast cancer lesions as well as in strategic metabolic intervention of advanced breast cancers in preclinical animal models and eventually in human cancers. More recently, an alternative model of metabolic switch has been put forward namely, the "reverse Warburg hypothesis" where it is postulated that in a tumor environment, the metabolic switch (and the associated alterations in glycolytic and mitochondrial pathways) phenotype is observed only in the stromal compartment rather than the epithelial compartment as originally thought [20]. Even though these studies have been carried out rigorously in established preclinical animal models systems and in human cancer cell lines, the clinical significance of this hypothesis in cancer detection and treatment is yet to be revealed. Regardless, all experimental evidences point out to clear signatures of metabolic switch characteristics in a variety of cancer models even though mechanistic underpinnings of these signatures are yet to be known. Even though we do not currently have a comprehensive molecular portrait of the metabolic switch phenotype in cancers, a few strong candidates are currently being explored in detail. One such target is the M2 isoform of a glycolytic enzyme pyruvate kinase which catalyzes the conversion of phosphorenol pyruvate to pyruvate in the terminal step of glycolytic cycle. Seminal studies on this enzyme were carried out by the group of Eigenbrodt [21-25] and more recently by other groups as well [26-28]. Appreciation for amino acid metabolism in addition to carbohydrate metabolism has rendered a more intricate and complex picture of the metabolic switch phenotype.

## Towards Clinical Utility: therapeutic and Biomarker Avenues

In step with the fundamental research on metabolic switch characteristics of cancer, a number of therapeutic opportunities were also attempted in the past by exploiting these altered glycolytic states. These studies involved global glycolytic inhibitors [2-deoxyglucose], pyruvate inhibitors [3-bormopyruvate] as well as apparent enhancers of mitochondrial metabolism [dichloroacetate] [29-31]. Despite the promise in preclinical models, human applications have not reached success with these drugs. In this direction, it is an open field for rational design of mitochondrial-specific drugs that will eventually mitigate the glycolytic hyperactivity thereby diminishing the concomitant tumor survival advantages. Our laboratory has been involved in targeting the redox/reactive oxygen species pathways pertinent to mitochondrial energy metabolism in breast cancer cells with a long-term goal of obtaining precise control on the metabolic switch phenotype in tumor reduction (Figure 1). In addition to early detection and metabolic intervention strategies, it will be prudent to identify the mitochondrial determinants of the metabolic switch phenotype in various cancer models. With the advent of highly sensitive mass spectrometry and proteomics approaches, we believe that we are at the exciting era of combining large-scale cancer cell screening and functional biomarker discovery platforms. More specifically, it will be valuable to develop specific strategies for targeting the metabolic windows of opportunity where it would be possible to control the onset of metabolic switch traits and even modulate these traits in aggressive cancers for favorable patient outcomes.

## Metabolic Switch beyond Cancer

In a more general sense, it is to be realized that metabolic switch phenotype is not specific to cancers since similar observations of hyperactivated glycolysis have been made in aging cells and in neurodegenerative disorders [32,33]. However, in these latter

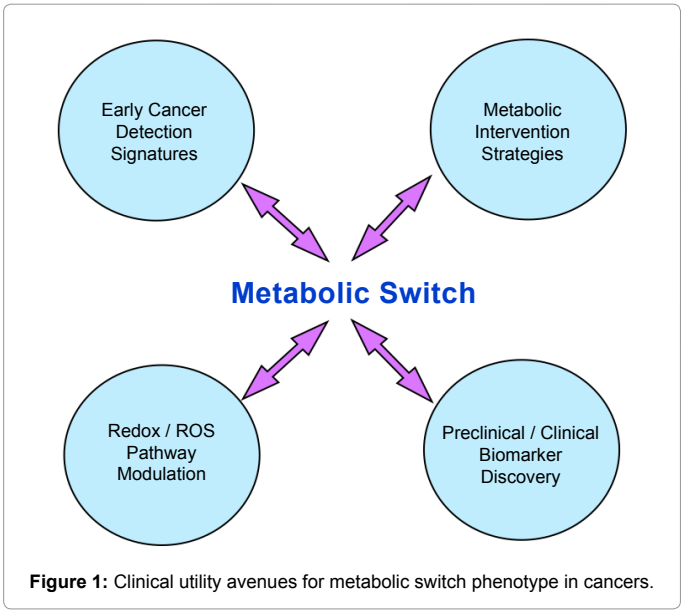


**Figure 1:** Clinical utility avenues for metabolic switch phenotype in cancers.

conditions, mitochondrial dysfunction has been found to be the dominant source of the observed metabolic switch phenotype which in turn, leads to cellular energy deficit and physiological decline unlike in cancers where the observed metabolic switch apparently yields a survival advantage. In a classical biological system, a specific genotype interacts with the environment to yield one or more phenotypes. However if there is a fundamental observation, as in metabolic switch, that has its definite existence beyond a single genotypic source, it is tempting to ask if the metabolic switch characteristics observed in various situations constitute a more robust metabolic phenomenon that is being shaped differently in the varied circumstances as in cancer, aging or neurodegeneration. Future research will need to focus on exploring these subtle ramifications of this enigmatic yet fundamental cellular phenotype so that it is possible to exert precise control on tumor metabolism in human cancers.

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