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Tuning in Tumor Metabolism: The Cost of Being a Cancer Cell

V Krishnan Ramanujan*

Metabolic Photonics Laboratory, Departments of Surgery and Biomedical Sciences, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA 90048, USA

The Problem

The genetic origin of cancers has been now accepted as a central principle of oncogenesis and the continued discovery of oncogenes and tumor suppressor genes is expanding the labyrinths of complexity in cancer biology [1-3]. Molecular pathway analyses of the critical oncogenes and their aberrant genetic modificationshave given a wealth of information on the deregulation of these pathways in cancer and how this knowledge can be exploited for designing drugs for cancer treatment. It is still not clear how these individual pathways interact between each other to yield a global cancer geno/phenotype. Common wisdom in the field dictates that it is not prudent to focus only on a few gene targets or a few molecular pathways to obtain a comprehensive understanding of cancer. This realization has led to the advent of large scale, systems approach to cancer such as genome-wide association study (GWAS) without providing useful clues on the underlying molecular mechanisms. Despite all these advancements, a comprehensive understanding of cancer(s) is still a dream. Genetic heterogeneity that is commonly observed in human cancers is a robust example of why gene target-based drugs never attain 100% efficacy even within a cohort of patients with apparently similar tumor type. The problem at hand is therefore not of finding more "new" gene targets but of finding the missing piece in integrating our current repertoire of cancer-specific molecular pathways. We hypothesize that focusing on tumor metabolism could potentially rope-in diverse tumor genetics pathways thereby providing a common metabolic denominator for understanding deregulation of energy metabolism in cancer.

Energy Metabolism in a Cancer Cell

Despite the tremendous progress for the past few decades (discovery of oncogenes, tumor suppressors, cancer signaling pathways), cancer related mortality and morbidity are still high as we are uncovering the labyrinths of complexity of cancer cell transformation. An intriguing puzzle is how tumor genetics and tumor metabolism collectively determine the cancer phenotype and the clinical manifestations. A number of alterations in cellular metabolism accompany cancer cell transformation [4-7]. These could range from altered glucose metabolism to coordinated changes in cell cycle deregulation and multiple facets of energy metabolism. Mutations in oncogenes and/or tumor suppressor genes and other carcinogenic events could transform a normal cell to a cancer cell. The question is : "*What does it take to sustain and to propagate this cancer cell in the host environment ?*". From a single cell perspective, mitochondria are the major bioenergetic organelles in eukaryotic cells that perform two critical functions namely, the ATP production and the programmed cell death (apoptosis). A sensitive balance between these "life" and "death" functions of the mitochondria is vital to cellular survival and eventually, to the physiological health. Mitochondrial DNA mutations have been implicated in organismal aging, neurological disorders such as Alzheimer's disease, Parkinson disease as well as in cancer [3,8-10]. A poorly understood biochemical hallmark of cancer is the "*metabolic switch*" first observed by Warburg [11,12] – which pertains to the condition where the tumor cells preferentially depend on the glycolytic pathway and avoid an apparently more efficient mitochondrial pathway even in the presence of oxygen (aerobic glycolysis) [5,11-21]. Despite this apparently counter-intuitive bioenergetics signature of cancer cells, there is emerging set of evidences that point out to significant implications of this feature in biosynthesis of macromolecules (amino acids, fatty acids etc.,) that are required for cancer cell sustenance and proliferation. Warburg phenotype could therefore be a just a unique metabolic state stemming from the trade-off between glycolytic upregulation (at the cost of avoiding a more efficient mitochondrial bioenergetics pathway) and the need to divert the glycolytic byproducts to biosynthetic routes [22]. This feature is already in clinical use where radioactive glucose analog (2FdG) is used to achieve contrast (owing to increased tumor uptake) in positron emission tomography. Despite the clinical utility and the realization of its ubiquitous nature, a clear mechanistic understanding of the metabolic switch is still lacking. In particular, there is no clarity on what are the molecular players involved in triggering/sustaining metabolic switch in cancer cells although the recent studies on pyruvate kinase M2 (PKM2) seem to offer a good starting point [23]. Recent reports even question the original Warburg hypothesis in the light of new evidence that the apparent "glycolytic" upregulation may not be exclusive to cancer cells only [24,25]. It is not clear if cancer cells indeed have "dysfunctional" mitochondria (original hypothesis) or if the cancer cells tend to "evade" mitochondrial function owing to tighter regulatory steps in mitochondrial oxidative phosphorylation (OxPhos) than in glycolytic pathway. Another ramification of Warburg hypothesis is the "chicken and egg" paradox between altered mitochondrial dysfunction and cancer cell transformation – thereby confounding the problem of causality of Warburg phenotype observed in cancer cells. Regardless of such a dilemma, we believe it is possible to adopt a pragmatic view where we appreciate that there is a *reciprocal relationship between mitochondrial defects and cell transformation*. With this perspective, we could potentially exploit this reciprocity by developing imaging assays for probing the "tumor-induced mitochondrial alterations" so as to enable us to accomplish the goals of early detection of in vivo tumors as well as to discover mitochondrial biomarkers that could further enable us in evaluating tumor aggressiveness and patient prognosis. This strategy is particularly attractive because this is applicable to all tumor types irrespective of their genetic background – owing to the fundamental nature of mitochondrial energy metabolism. We would like to reiterate that Warburg phenotype is distinctly different from

***Corresponding author:** V Krishnan Ramanujan, PhD, Assistant Professor of Surgery & Biomedical Sciences, Metabolic Photonics Laboratory, Cedars-Sinai Medical Center, 8700 Beverly Blvd., D6067, Los Angeles, CA 90048, USA, Tel: (+1) 310-423-7666; E-mail: Ramanujanv@csmc.edu

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hypoxic metabolic state where glycolytic up-regulation stems from the unavailability of oxygen in the case of solid tumors [26,27]. This particular situation opens up a new window of opportunity for early metabolic intervention of tumors before hypoxia and angiogenesis set in. This also opens up an experimental challenge of detecting tumors earlier than what is currently being accomplished. What we need therefore is an appreciation for identifying tumor-specific metabolic targets and a coordinated effort for developing high through-put/high content technological tools for early detection of tumors and chemoprevention.

Preclinical Technologies for Probing Tumor Metabolism

Preclinical phase of most of the human cancers is relatively long and is the most difficult to detect by the current technologies. An ideal early detection technology must reliably detect the smallest cancer cluster(s) (~ a few tens to hundreds of cancer cells) anywhere within the target tissue. Most of the currently used clinical screening techniques such as mammography, magnetic resonance imaging, positron emission tomography and ultrasound imaging all have their own unique advantages and drawbacks but all fail to meet the above criterion (Figure 1). In breast cancer for example, the most used clinical screening tool is mammography which detects cancer-associated calcifications. Owing to the high false positive rate and relatively poor specificity, this technique still has not reached its perfection [28,29]. A few other techniques based on exploiting the differential tissue scattering properties (e.g., Raman spectroscopy) and those based on optical diffuse reflectance have shown promising results in preclinical animal models in research laboratories but have never found their way into the clinical arena. One of the major bottlenecks in current methods could be the fact that these techniques attempt to detect "tumor specific signatures" either based on endogenous differences in tumor growth and the background host tissue or on passive contrast agents that may or may not be successful in tumor-specific localization. A potential solution to this problem could be achieved by the following two distinct steps. First, we need to identify key metabolic targets that uniquely distinguish tumor metabolism from the host metabolism. We need to develop tools not just to visualize these metabolic targets passively, but also to *actively* monitor the differential tumor metabolism in vivo. Resolving the spatiotemporal activity of metabolic targets (e.g., enzymatic activity) in real-time can be a powerful approach to actively probe tumor metabolism. Towards this direction, methods to probe Warburg [11,12] metabolism in tumors could increase our ability to detect smallest possible lesions thereby enhancing the efficacy of early intervention. Translating our current knowledge from genomics to the realm of metabolomics in preclinical animals models will greatly enable this strategy for validating critical metabolic targets that can be utilized in the clinical setting. Second, we need to adopt a pragmatic approach of combining more than one technique in the same screening setting to maximize the information content from the metabolic imaging sessions. Optical imaging provides high molecular specificity whereas tomography and magnetic resonance methods provide better depth information than the optical imaging techniques [6,30-35]. However, by a strategic combination of these two different techniques can yield a synergistic edge to metabolic imaging of tumor-specific signatures.

Bench-to-Bed Transition

Only a small fraction of the entire body of cancer research conducted all around the world every year really achieves its translational potential and reaches the clinical utility. The aforementioned bottlenecks may not be the only set of limiting factors. It is imperative that we obtain a comprehensive understanding of the common metabolic denominator of the various classes of tumors with different genetic/receptor background. As mentioned above, multimodal metabolic imaging of tumors could potentially yield useful repertoire of metabolic targets that can further our understanding of the origins of tumor heterogeneity,

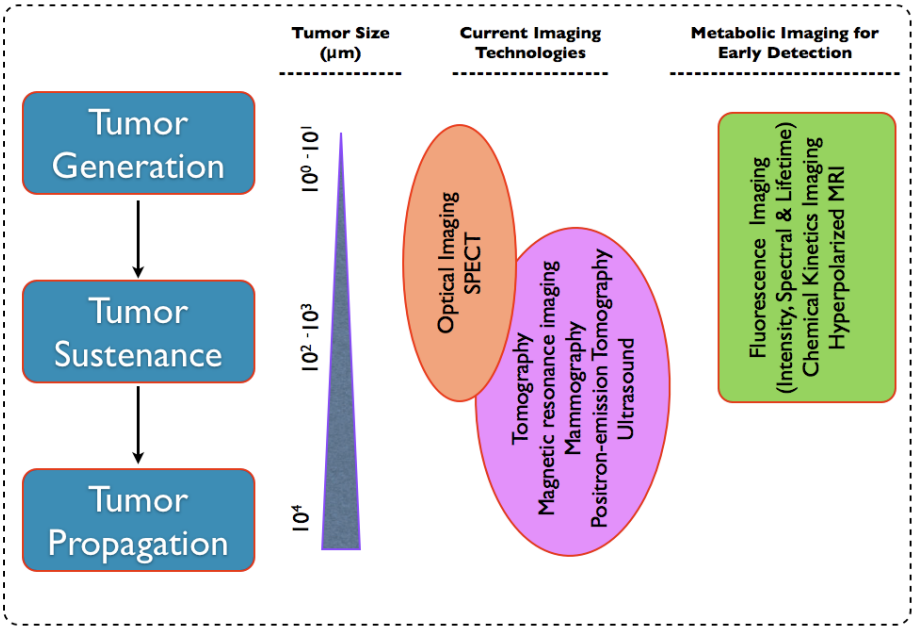

Figure 1: Schematic representation of the key steps of tumorigenesis (generation, sustenance and propagation) and the typical tumor size limits associated with each of these steps. Current clinical screening tools are limited to detecting tumor sizes of the order of a few millimeters which can be significantly improved by the proposed multimodal metabolic imaging of tumors.

drug resistance etc., Attempts also need to be made to bridge the gap between the research success in preclinical animal models and the clinical success in human patients. At the end of the day, we are all in pursuit of not just an intellectual acumen but of solving real-life problems of human cancers.

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