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Integrated Imaging of Cancer metabolism

Robert A Gatenby and **Robert J Gillies**

In 1901 Wilhelm Roentgen received the first Nobel Prize in physics for his discovery of a "new kind of ray." In 1931, eight years after Roentgen's death, Otto Warburg received the Nobel Prize for physiology or medicine in part for his discovery of altered glucose metabolism in cancers. There is no evidence that they ever met although, interestingly, some correspondence exists between Roentgen and Warburg's father, Emile, who was a noted physicist. In the early 21st century the seemingly unrelated work of these two disparate intellectuals has coalesced into a vast clinical and research enterprise in which imaging of cell metabolism is providing new and critical insights into human cancer.

Cellular metabolism serves two primary functions: to provide energy for cellular processes and to provide essential anabolic precursors. The three major substrates serving these purposes are sugars (glucose), amino acids (glutamine) and fatty acids (ketones). For energy production, normal tissues in well-oxygenated environments typically rely on highly efficient forms of aerobic metabolism to generate ATP. Depending on the tissue, the major substrates providing this energy are fatty acids and glucose, To be oxidatively metabolized, the substrates have to be transported into mitochondria to supply reducing equivlanets to oxidative phosphorylation. While fatty acids and ketones can be directly imported into mitochondria, glucose derived carbons enter mitochondria as pyruvate. Under aerobic conditions, pyruvate is metabolized in mitochondria to produce about 36 moles of ATP per mole of glucose. However, under anaerobic conditions, lack of O_2 as the final acceptor in the electron transport chain prevents aerobic metabolism from progressing. As a result, under hypoxic conditions, pyruvate is reduced to lactate to re-generate oxidized nicotinamide adenine dinucleotide, NAD^+ from reduced NADH, and thus produces only 2 moles of ATP per mole of glucose. Because of the significantly increased efficiency of aerobic metabolism of glucose, glycolysis is typically upregulated only under in the presence of hypoxia, which was first described by Louis Pasteur in 1857 (prior to Nobel's gift) and is known as the Pasteur Effect.

Unlike normal tissues, cancers commonly constitutively upregulate glycolysis that persists even under normoxic conditions - first described by Otto Warburg in 1926 and is known the "Warburg Effect" [16]. In the past several years, much progress has occurred in understanding the genetic pathways that yield this phenotypic property(1) reference our J Nuc Med article - below). Control of the glycolytic pathway is multifactoral, but critical upstream effectors include the c-myc and ras families of oncoproteins, the p53 tumor suppressor and the hypoxia sensitive transcription factor, HIF-1α. Although there is still much to learn, much is known about the molecular mechanisms that generate the Warburg effect. In contrast, less is know about why these metabolic changes occur. Since cancers arise through a prolonged sequence of mutations and clonal expansions – a process often described as somatic evolution - aerobic glycolysis must confer a selective proliferation advantage that is significant. A number of possible benefits have been suggested. The glycolytic metabolic pathway, although inefficient, has the benefit of speed allowing more turnover of glucose which may benefit rapid synthesis of macromolecules necessary for proliferation. We have proposed that the acid produced by upregulated glycolysis benefits the tumor cells by promoting invasion and shielding them from the toxic effects of the immune system (2). Others have proposed that glycolysis is upregulated in order to provide

anabolic precursors (3), which was the original theory of Warburg, yet still lacks empirical support.

For decades, Warburg's seminal observations were generally viewed as an interesting laboratory finding of little clinical relevance. However, this changed when Warburg's work was linked Roentgen's new kind of rays through FdG PET imaging. Although slow to build, the subsequent tsunami of data that has led to stunning realization – the Warburg effect is present in the vast majority of clinical cancers and is exacerbated in those that are the most malignant. Millions of PET scans have demonstrated that primary and metastatic cancers almost invariably take up far more glucose than surrounding normal tissue. Initial applications of FdG PET imaging focused on separating benign from malignant lesions such as lung nodules. Later, FdG PET was shown to be generally more accurate CT or MRI in staging many cancer types. Most recently, various metrics to quantify glucose uptake have been used as biomarkers for prognosis or response to therapy. Regardless its clinical utility, the abundance of these findings has elevated altered glucose metabolism to be a "Hallmark" of cancer and has fundamentally changed our understanding of cancer biology and the importance role that altered metabolism plays in the process of carcinogenesis and progression.

Although fundamentally important, altered glucose metabolism is only the tip of the iceberg. Cellular glucose uptake reflects complex underlying dynamics that includes the mutations, epigenetic alterations, changes in protein localization, intra- and extra-cellular enzyme kinetics, and regional micro-environmental conditions such as hypoxia and acidosis. These conditions, which vary significantly between tumors and even with different regions of the same tumor, represent fundamental properties of the tumor that govern its clinical progression and response to therapy. Glucose is only one of a panel of substrates whose metabolism is altered in cancers. It has gained pre-eminance because of its consistent alteration and the availability of an imageable analog, FDG. A challenge and opportunity is to use the range of available imaging data to identify additional metabolic perturbations at the tissue and sub-tissue level in individual tumors. If we can deconvolve the occurrence and mechanisms that govern metabolic alterations with clinical imaging, extraordinary insight into these critical tumor dynamics is possible.

The current work by Kung represents an important advance in this area by providing evidence that glutamine metabolism can be non-invasively interrogated using hyperpolarized 13-C magnetic resonance spectroscopy. Hyperpolarization of stable MR-active isotopes involves microwave induced transfer of electron spin magnetization to nuclei at low temperatures. This is not a new phenomenon, having first been described by Albert Overhauser in 1953. More recent studies by Golman have developed techniques to make hyperpolarization of biologically actives substrates practical (4). The first applications of this technology have used 13-C labeled pyruvate, which plays a pivotal role in glucose metabolism and the Warburg Effect. A number of other MR-visible substrates have subsequently been polarized and used in vivo, but are generally limited to carbons with long (~1 min) spin-lattice relaxation times, T1. As one of the predominant relaxation mechanisms is spin-spin dipolar coupling, spin ½ carbons with directly coupled spin ½ hydrogens are know to relax rapidly. Substituting hydrogens with spin 1 deuterons is known to reduce dipolar relaxation and the target 13-C can exhibit substantially longer T1 values, making them appropriate for in vivo hyperpolarized application. The advance of Kung is not only in the synthesis of the deuterated 13-C, but also an initial application of the central and important metabolite. In vivo glutamine donates its nitrogen to the metabolic pool via glutaminase, to produce glutamate, which is an important substrate for mitochondrial metabolism. Glutamine metabolism is often accelerated in cancers and cancer cells, and can be a primary source for nitrogen, energy production and fatty acid synthesis (5).

In the future, finding clinical imaging strategies that characterize the critical multiscalar properties governing tumor metabolism will be complicated, but not hopelessly so. The key will be application of imaging modalities and advanced image analysis technologies to extract imaging data that characterize a subset of critical tumor properties. As a case in point, FdG PET provides detailed information on regional variations in glucose uptake, yet these regional data are rarely used to extract informative data and insight. What are the tumor properties that lead to these uptake values? Is regional hypoxia, for example, driving the Pasteur Effect or is the Warburg Effect increasing uptake even when oxygen is present? These questions may be addressable if metabolic images are combined with complementary imaging technologies to identify regional variations in other tumor parameters. Do regions of tumor with high blood flow and high glucose uptake represent fundamentally different cancer populations than regions of high blood flow and low glucose metabolism? Are regions high in FDG uptake coincident with, or exclusive of, regions with elevated glutamine metabolism? What are the roles of hypoxia and perfusion on these variations?

There is one additional critical advantage to imaging characterization of tumor biology – it can be repeated. Tumors are complex adaptive systems and any perturbation of that system by therapy will elicit a highly non-linear response that may well vary in different tumor regions. Thus, repeat imaging can serve as a monitor for response to therapy and, perhaps more importantly, for evidence of emergence of resistance to therapy.

The future of cancer imaging, in other words, lies not in any one modality. Rather it lies in the creative application of multiple modalities together. This will require much more than just superimposition of images. It will require application of sophisticated image analysis techniques to extract maximal amounts of information from the images. Precise spatial co-registration of this information is necessary to generate regional maps of multiple parameters such as glucose uptake, MRI diffusion, contrast enhancement, spectroscopy. Through such multidimensional characterization of tumor regions both at baseline and following therapy, a precise characterization of underlying tumor biology in individual patients will be possible. This can guide therapy selection and response to treatment including emergence of resistant clones and their adaptive strategies.

There are, of course, many open questions in understanding tumor energy metabolism. One that is enormously important is the “completeness” of glucose utilization in energy production. That is, in measuring glucose uptake are we

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