Abstract Research concerning "cancer energetics" has become a popular area of investigation. This topic comprises two distinct fields: energetics at (1) the cellular level and (2) the whole organism level. Both of these have relevance to Cancer Risk and Cancer Prevention.

The field of cellular energetics includes studies of specific energy sources (glucose, fatty acids, etc.) utilized by various normal and neoplastic cell types, the various metabolic pathways used (glycolysis vs oxidative phosphorylation, etc.), and related issues. One of the key issues in this field (reviewed in [1]) relates to the Warburg hypothesis, which concerns the preferential use of glycolysis rather than oxidative phosphorylation by cancer cells. Recent studies have supported some of Warburg's classic observations in this area. At first glance, the preferential use of glycolysis by cancer cells seems paradoxical, because glycolysis yields substantially less energy per glucose molecule consumed than does oxidative phosphorylation. However, on closer examination, the explanation may relate to the fact that neoplastic cells require large supplies not only of energy, but also of the substrate molecules required for membrane synthesis and so on. Glycolysis yields these substrates as by-products, while oxidative phosphorylation does not. While glycolysis yields substantially less energy per glucose molecule consumed than oxidative phosphorylation, part of the neoplastic phenotype involves very efficient glucose transport into the cell (which is the basis for tumor imaging with labeled glucose in positron emission tomography scanning). Thus, while the energy yield per glucose molecule through glycolysis is relatively low, energy demands can be met as the supply of glucose is assured by the high levels of glucose transport, and the building blocks for macromolecular synthesis are also provided.

Whole organism energetics concerns the impact of the balance between caloric intake and energy consumption on carcinogenesis and cancer behavior. Large-scale population studies (for example [2]) have established that excess body weight is associated with increased risk of subsequent cancer mortality. Further work has shown that this is not simply attributable to a relationship between body size and cancer risk. Rather, it involves for many cancers a combined increase in risk with a worsening of prognosis, such that the effect of obesity on cancer-specific

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mortality is for many cancer types greater than the effect on risk. Given the magnitude of the global "obesity epidemic," this topic deserves our attention. In affluent countries, the proportion of the population considered overweight to a degree sufficient to influence cancer behavior has been rapidly increasing. In certain areas, more than a third of the population would now be estimated to have increased their risk of cancer mortality based on body mass index. This threatens to attenuate recent progress in cancer control. While fewer data are available concerning the specific influence of childhood obesity on subsequent cancer risk, this is another area of great concern.

What are the mechanisms by which obesity (energy intake in excess of energy expenditure) may influence neoplasia? Does excess food intake influence cellular energetics? Surprisingly little is known about the relationship between "whole organism" nutrition and cellular bioenergetics. Evolutionary pressure has resulted in mechanisms that preserve circulating levels of fuels such as glucose, even in the setting of starvation, almost until the time of death. There is only limited evidence that alterations in blood levels of glucose, lipids, or other blood constituents that are a consequence of excess energy intake have a direct effect on cellular energy metabolism, but this possibility requires further study. On the other hand, there is considerable evidence that it is the changes in the endocrine environment which arise as a consequence of excess energy intake that influence carcinogenesis and cancer progression. These changes include increased tissue and circulating levels of insulin, inflammatory cytokines, and alterations in adipokines such as leptin or adiponectin.

We have recently been extending earlier work concerning the relationship of insulin-like growth factors to cancer risk [3] by examining the role of insulin itself as a candidate mediator of the effect of obesity on cancer mortality. It is well known that obesity is associated with increased insulin resistance in classic "target tissues" for insulin action such as fat, muscle, and liver, which leads to elevation in circulating insulin levels. Recent results show that insulin receptors are perhaps unexpectedly commonly expressed on many neoplastic cell types [4]. Thus, insulin may directly stimulate cancer growth in obese, hyperinsulinemic subjects.

A review of older literature reveals that this is not a new concept. For example, more than 30 years ago, it was demonstrated that the growth of carcinogen-induced mammary cancer in rats was greatly curtailed, and in some cases tumors actually regressed, when insulin levels were lowered by administration of alloxan, which is a pancreatic beta cell poison that results in insulin deficiency [5]. This insulin deficiency in fact modeled type I (insulin-deficient) diabetes and was associated with hyperglycemia. The authors attributed the effect on the mammary gland tumor to the insulin deficiency. However, by current standards, this work is interesting but incomplete, and requires confirmation with endpoints including changes in signal transduction.

Our more recent collaborative work with Dr. Venkateswaran and colleagues [6] has yielded data consistent with the older data. In this study, our goal was to model variation of insulin level within a clinically relevant range, rather than to extremes, and determine if this would influence the behavior of a prostate cancer xenograft model. We used a high-fat, high-sucrose diet to induce a moderate elevation in insulin levels, and observed that this resulted in a significant acceleration of tumor growth. While the experiment did not demonstrate in a formal fashion a causal link between the rise in insulin level and the more aggressive proliferation, we did observe the presence of insulin receptors in the tumors, and documented increased activation of the signaling pathway downstream of the insulin receptor in the tumors of the animals on the diet that led to hyperinsulinemia.

Recent data from population studies provide further evidence for an association of high insulin levels with more aggressive behavior of breast,

prostate, and other cancers in subjects who are overweight. While this association may be causal, it must be recognized that other factors that potentially may influence tumor behavior, such as leptin, do vary with insulin levels—thus insulin may be acting as a surrogate for another mediator rather than being directly involved mechanistically. However, the simplest model to account for the association would postulate that insulin itself is indeed the mediator. In the case of breast cancer, we [7] and others [8] have observed an increased risk of disease relapse among women with higher levels of insulin or c-peptide, an insulin surrogate. In the case of prostate cancer, data from the Physicians' Health Study has shown a relationship between higher levels of c-peptide and the risk of fatal prostate cancer [9]. Similar studies are underway for colorectal and other cancers.

In terms of relevance to clinical cancer prevention, the relationship between body mass index and overall cancer mortality [2] implies that efforts to avoid excess energy consumption relative to utilization would be useful. In fact, it is unclear if avoiding obesity would act at the very earliest stages of carcinogenesis, or if (like many other cancer prevention strategies) it would actually act to prevent early cancer progression events.

At present, while there are many datasets that demonstrate a relationship between obesity and cancer mortality, there is a paucity of long-term intervention studies to demonstrate conclusively that interventions that improve energy balance, such as dieting and increasing exercise, reduce cancer risk. However, this would seem to be likely.

If further studies provide additional evidence that insulin is an important mediator of the effect of obesity on risk, the potential role of metformin in cancer prevention will deserve study. Metformin is widely used in type II diabetes, where it is known to act to reduce hyperglycemia by reducing hepatic glucose output [10]. This has a secondary effect of lowering insulin levels.

Metformin has other actions that may be relevant. There is in vitro evidence that it acts directly on cancer cells as an AMP kinase (AMPK)-dependent growth inhibitor, which could provide a further benefit [11–12]. This mechanism involves activation of the LKB1–AMPK pathway, which is a signaling system that normally serves to reduce cellular energy-consuming activities when there is cellular energy depletion. This involves, in part, inhibition of m-tor-dependent protein translation and inhibition of proliferation, which may complement the benefits of reduction of circulating insulin level. On the other hand, recent evidence suggests that some neoplastic cells may react to this "perceived cellular energy deficiency" by increasing secretion of vascular endothelial growth factor (VEGF), in an attempt to increase vascular supply, and this can have undesired effects [13]. It remains to be determined if this action of metformin will outweigh its potential utility, as metformin has beneficial effects in other in vivo models [14, 15].

Early population studies detected unexpectedly low cancer incidence and mortality among diabetics on metformin [16, 17], so this topic deserves further research. It remains possible that—particularly among metabolically defined subsets of individuals at increased risk for cancer, namely those who are obese and hyperinsulinemic, or those who have the so-called "normal weight, metabolically obese" phenotype [18]—metformin or other insulin-lowering approaches (including lifestyle modification) will be particularly important as risk-reduction strategies.

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