Do Cancer Cells Care If Their Host Is Hungry?

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A recent report by Kalaany and Sabatini concerning mechanisms underlying the inhibitory effect of dietary restriction on the growth of certain tumors adds to the evidence that insulin and IGF-I are hormones with relevance to oncology.

Recent progress in the field of "cancer energetics" involves descriptions of the influence of oncogenes and tumor suppressor genes on the metabolic pathways used by cancer cells to generate ATP (Jones and Thompson, 2009). However, an important gap in knowledge in this field involves an issue beyond the cellular level—the influence of whole organism energy balance on cancer biology. The strong inhibitory effect of host dietary restriction on the growth of certain experimental tumors is a classic observation that predates even Warburg's work concerning cancer energetics, yet studies concerning the mechanisms underlying this phenomenon are sparse.

A recent paper (Kalaany and Sabatini, 2009) provides important data which add to prior evidence that the inhibitory effect of dietary restriction on tumor growth is attributable to the effect of the diet on insulin and insulin-like growth factors (Figure 1). They confirm that restriction of food intake lowers both insulin and IGF-I levels and show that the degree of in vitro mitogenic responsivity of various cell lines to insulin or IGF-I can be used to predict which corresponding xenografts will be growth inhibited in vivo by dietary restriction. Furthermore, they demonstrate that PI3 kinase-activating mutation or loss of function of PTEN is sufficient to confer resistance to the growth inhibitory effects of dietary restriction.

A simple model to account for these observations is that some cancers are responsive to insulin and/or IGFs, and that these neoplasms thrive when levels of these mitogens are sufficient to contribute to activation of the PI3K pathway. Many studies are consistent with this hypothesis. The implicated receptors are expressed by many human cancers (e.g., Law et al., 2008), and epidemiologic data (reviewed in Pollak, 2008) provide evidence that high circulating levels of the implicated ligands are associated with adverse cancer prognosis and/or increased cancer risk. Examples of consistent experimental data include findings that tumor growth is reduced in mice with mutations that lower IGF-I levels (Majeed et al., 2005), and that the growth inhibitory effect of caloric restriction on a bladder cancer model can be abolished by infusing IGF-I (Dunn et al., 1997).

However, the simplest model may not be complete. The dietary restriction employed by Kalaany and Sabatini would be expected to result in alterations in additional hormones (such as leptin, adiponectin, FGF21, and/or glucagon), and an influence of these on neoplasms has not been excluded. Additional work to compare in vitro the influences of physiologic concentrations of these hormones to those of insulin and IGF-I would be of interest. Measurements at later time points of in vivo changes in AKT pathway activation within cancers as a function of host diet would also be relevant, as some data reported concern tumors less than 20 mm^3.

Apart from the effects of dietary restriction on the hormonal environment of cancers, does it reduce energy supply to the tumor? Kalaany and Sabatini do not report changes in glucose, amino acids, or fatty acids associated with the degree of caloric restriction employed. Such measurements would be of interest, but it is likely that the host breaks down muscle and fat at sufficient rates to maintain circulating energy supply to normal tissues, and to cancers. Therefore, host dietary restriction may inhibit growth of certain cancers through changes in hormone concentrations rather than by causing energy depletion at the cellular level.

What about the role of the energy sensor AMP-activated kinase in tumor growth inhibition by dietary restriction? In single-cell organisms and in studies of cancer cells in vitro, reduced supply of energy sources leads to activation of AMPK, which
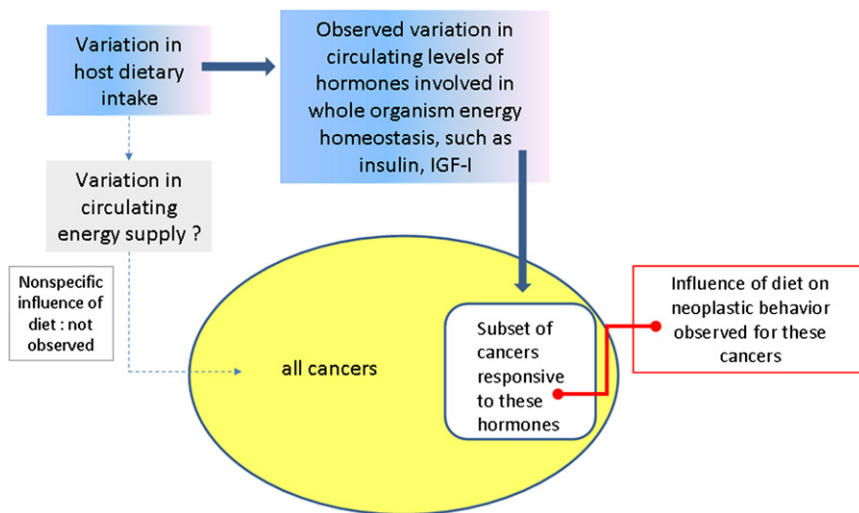
Figure 1. Cancer Endocrinology Meets Whole Organism Energy Homeostasis
Recent data from the Sabatini lab add to prior evidence suggesting that dietary restriction limits growth of certain cancers through its effects on insulin and IGF-I, rather through reduced energy supply to cancer cells. This is contributes to the rationale for investigations of novel cancer therapies that target insulin and IGF-I signaling.

inhibits energy-consuming processes including proliferation in order to maximize chance of survival. There is evidence that AMPK within cancers can also be activated by host dietary restriction (Jiang et al., 2008), but again this may be a consequence more of hormonal activation of AMPK than of a lack of energy supply to cancer cells.

Is there clinical relevance to the results of Kalaany and Sabatini? The concept that one can deprive a cancer of energy by starving the host seems far-fetched, because as long as there is muscle or fat to break down, the host will do all it can to maintain blood glucose (to the tumor's advantage). However, if one accepts the view that much of the effect of caloric restriction is attributable to hormonal changes such as reduced insulin rather than to reduction in energy supply to cancers, there are indeed medical implications.

Insulin and IGF-I signaling in cancer cells, now strongly implicated by the Sabatini lab in the inhibitory effects of host dietary restriction on cancer growth, had already been identified as a potential target for novel therapies (reviewed in Pollak, 2008). Dozens of drug candidates including anti-receptor antibodies, anti-ligand antibodies, and tyrosine kinase inhibitors with varying degrees of specificity for members of the insulin receptor family have been shown to have antineoplastic activity in preclinical models, and are being evaluated in ongoing clinical trials (Pollak, 2008). The data reported by Kalaany and Sabatini provide additional rationale for these studies, as well for agents that act downstream. One inconsistency deserves attention: there is limited evidence that agents that target insulin/IGF-I signaling have activity even in cancers with PTEN mutations (Burtrum et al., 2007), a result that contrasts with the data of Kalaany and Sabatini. This requires further study— it may be that in certain contexts, loss of function of PTEN results in hypersensitivity to IGF or insulin receptor activation rather than to constituitive, ligand-independent pathway activation.

The results of Kalaany and Sabatini add to the rationale for studies of the opposite phenomenon: the stimulatory effect on certain tumors of excess host energy intake. This has public health implications, given the obesity epidemic and the impact of obesity on cancer mortality (Calle et al., 2003). The same signaling system may be involved: there is experimental evidence that diet-induced hyperinsulinism may activate insulin receptor signaling within cancers (Venkateswaran et al., 2007), raising the possibility that neoplasms of patients who are obese and/or hyperinsulinemic may remain insulin sensitive, even if their classic insulin target tissues are insulin resistant. In this context, AMPK activators such as metformin deserve study because of their insulin-lowering activity—indeed, retrospective population studies (reviewed in Pollak, 2008) have associated metformin use with reduced cancer mortality, and in a murine experimental model, metformin abolished the tumor growth acceleration associated with high-energy diet (Algire et al., 2008). AMPK activators have a separate rationale based on direct action on cancer cells, which is associated with an antiproliferative effect (Zakikhani et al., 2008).

The experiments of Kalaany and Sabatini involved established cancers: extensions to carcinogenesis models and the prevention context will be of interest, as pharmacologic or lifestyle measures to avoid excess insulin or IGF stimulation of at-risk tissues may also slow the process of stepwise cellular transformation.

Historically, the field of "cancer endocrinology" involved studies of dependency of subsets of breast and prostate cancer on gonadal steroids, and this led to the development of widely used and effective cancer treatments. The data reported by Kalaany and Sabatini add to prior evidence suggesting that the paradigm of hormonal dependence of neoplastic growth may be extended to insulin and IGFs.

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