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Do Cancer Cells Care If Their Host Is Hungry?

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DOI 10.1016/j.cmet.2009.04.006

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 responsiveness 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 mm³.

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

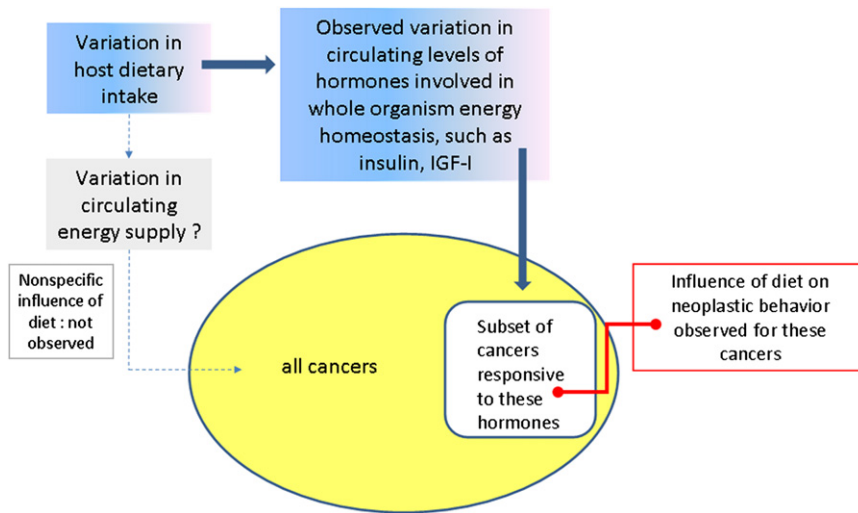


Figure 1. Cancer Endocrinology Meets Whole Organism Energy Homeostasis

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 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 constitutive, 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.

ACKNOWLEDGMENTS

Dr. Pollak's research is supported by the Canadian Cancer Society, the National Institutes of Health, and the Prostate Cancer Foundation.

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Live Longer sans the AT_{1A} Receptor

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DOI 10.1016/j.cmet.2009.04.002

Excessive activation of the AT_{1A} receptor (AT_{1A}R) by angiotensin II (Ang II) is implicated in the age-related development of hypertension, diabetes, and kidney disease. AT_{1A}R-deficient mice live longer and have lower levels of oxidative stress than wild-type mice (Benigni et al., 2009), suggesting a role for AT_{1A}R signaling in the aging process.

Persistent and poorly regulated hypertension is a major risk factor for many of the most prevalent age-related disorders that limit life span, including cardiovascular disease, stroke, kidney disease, and neurodegenerative diseases. Angiotensin II (Ang II), a peptide produced from renin via the proteolytic activity of angiotensin converting enzyme (ACE), is a key component of an endocrine/paracrine signaling system that increases vasoconstriction and blood pressure. Ang II functionally interacts with two forms of G protein-coupled receptor (GPCR), the AT₁ or AT₂ type receptors. The A subtype of the AT₁ receptor (AT_{1A}R) is located on the surface of vascular smooth muscle cells, and its activation by Ang II results in elevated levels of intracellular calcium, generation of reactive oxygen species (ROS), and contraction of the cells. Ang II therefore acts to increase vascular pressure, and accordingly ACE inhibitors and AT_{1A}R antagonists have proven to be highly effective for the treatment of hypertension (Werner et al., 2008). As maintaining cardiovascular health can have a major impact on longevity in humans, Benigni et al. (2009) recently examined the consequences of disruption of the AT_{1A}R gene on aging of the cardiovascular and renal organ systems in mice. Strikingly, both the average and maximum life spans of AT_{1A}R-deficient mice were increased by approximately 20%.

At a gross level the AT_{1A}R-deficient mice demonstrated no significant alteration in body weight, fasting blood glucose, heart weight/body weight ratio, or activity levels demonstrating an ability of the animal to partly mitigate the loss of AT_{1A}R with respect to overall energy metabolism. However, age-related pathologies in the cardiovascular system, including atherosclerotic lesions and cardiac fibrosis, were reduced in AT_{1A}R-deficient mice compared to wild-type control mice (Benigni et al., 2009). While the cellular structure and function of the kidneys and pancreas were unaffected by AT_{1A}R deficiency, age-related changes in the liver (degeneration of hepatocytes, vesicular steatosis, and exudation) were reduced in the AT_{1A}R-deficient mice. The aging process involves damage to cells by ROS, probably as the result of both increased free radical production and a reduced ability of cells to protect themselves against the ROS (Bokov et al., 2004). To determine whether the increased longevity of AT_{1A}R-deficient mice was associated with reduced levels of oxidative stress, levels of nitrotyrosine, a marker of oxidative attack on cellular proteins, were measured in the heart, artery, and kidney tissues from young and old wild-type mice and aged AT_{1A}R-deficient mice. In all three tissues, levels of oxidative protein damage were increased by aging

in wild-type mice, but not in the AT_{1A}R-deficient mice. Benigni et al. used only 20 AT_{1A}-deficient and 10 wild-type male mice of one mixed genetic background for their life span studies, an unusually small number of animals for such a study. It will therefore be important to repeat the experiments with larger numbers of mice of more than one genetic background; females should also be evaluated, as there may be sex differences in the effects of AT_{1A}R signaling on aging. In addition, a comprehensive assessment of how other blood-borne metabolic factors and hormones also change in response to the loss of Ang II signaling may also provide insights into the longevity mechanism.

The low-level oxidative damage in old AT_{1A}R-deficient mice may not be due to reduced production of ROS because numbers of mitochondria, a major source of free radicals, were increased in cells from the AT_{1A}R-deficient mice. Instead, the authors' data suggest that the lack of AT_{1A}R-mediated signaling results in increased production of proteins that protect cells against free radical attack. Indeed, the expression of two cytoprotective mitochondrial proteins, Namp1 and sirtuin 3, were increased in kidney cells of old AT_{1A}R-deficient mice compared to old wild-type mice (Benigni et al., 2009). Namp1 is a NAD⁺ biosynthetic enzyme that protects cells against genotoxic