Do Cancer Cells Care If Their Host Is Hungry?

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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 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...
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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REFERENCES


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.
Excessive activation of the AT1AR by Ang II is implicated in the aging process. As maintaining cardiovascular health can limit life span, including cardiovascular diseases, stroke, kidney disease, and neurodegenerative diseases. Ang II functionally interacts with the AT1 or AT2 type receptors. AT1AR-deficient mice live longer and have lower blood pressure. Ang II increases vasoconstriction and blood oxidation enzyme (ACE), is a key component of an endocrine/paracrine signaling system that increases vasoconstriction and blood oxygen species (ROS), and contraction 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 vascular smooth muscle cells, and its activation by Ang II results in elevated levels of intracellular calcium, generation of reactive oxygen species (ROS), probably as the result of both intracellular calcium, generation of reactive oxygen species (ROS), probably as the result of both.

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Persistent and poorly regulated hypertension (Werner et al., 2008). To determine whether the increased life spans of AT1AR-deficient mice were due to abrogation of Ang II-dependent 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 control mice compared to wild-type control mice. While the cellular 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 control mice compared to wild-type control mice. While the cellular

Indeed, the expression of two cytoprotective sirtuins, sirtuin 3, were increased in kidney cells from the AT1AR-deficient mice. Instead, the authors' data suggest that the lack of AT1AR-mediated signaling results in age-related pathologies in the cardiovascular system, including atherosclerosis, cardiovascular fibrosis, steatosis, and exudation were reduced (degeneration of hepatocytes, vesicular structure and function of the kidneys and pancreas were unaffected by AT1AR deficiency, age-related changes in the liver deficiency). As maintaining cardiovascular health can limit life span, including cardiovascular diseases, stroke, kidney disease, and neurodegenerative diseases. Ang II functionally interacts with the AT1 or AT2 type receptors. AT1AR-deficient mice live longer and have lower blood pressure. Ang II increases vasoconstriction and blood oxygen species (ROS), and contraction of vascular smooth muscle cells, and its activation by Ang II results in elevated levels of intracellular calcium, generation of reactive oxygen species (ROS), probably as the result of both intracellular calcium, generation of reactive oxygen species (ROS), probably as the result of both.