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Mechanistic Links between Obesity, Insulin, and Cancer

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Abstract

Obesity and type 2 diabetes (T2D) increase the prevalence and worsen the prognosis of more than a dozen tumor types; however, the mechanism for this association remains hotly debated. Here we discuss a potential role for insulin as the key hormonal mediator of tumor metabolism and growth in obesity-associated insulin resistance.

Introduction: Obesity and Cancer

Obesity rates have burgeoned over the past half-century, with more than 70% of American adults currently overweight or obese. Increasing evidence has emerged linking obesity to a heightened risk of numerous other health conditions, including cancer. The Centers for Disease Control (CDC) have now associated 13 distinct tumor types with overweight and obesity, including five of the ten most commonly diagnosed cancers (breast, colorectal, renal, thyroid, and endometrial) (Table 1). Adding further credence to a causative link between obesity and cancer risk, weight gain is associated with a 20–50% increase in the risk of diagnosis with an obesity-associated tumor type (esophageal, renal, colon, pancreatic, liver, gallbladder) [1]. It is less clear whether weight loss mitigates cancer risk in obese individuals: studies have suggested a beneficial – albeit modest – effect of weight loss to reduce obesity-associated cancer risk [1,2]; however, weight loss after cancer diagnosis actually portends poorer outcomes [2]. Taken together, these observations seemingly indicate that while obesity – or some perturbations that occur secondary to obesity – may contribute to the early events that initiate tumor growth or accelerate its progression, once the tumor reaches a critical size the risks of cancer cachexia, including a worsened ability to respond to curative therapies and a marked functional decline, outweigh the potential benefits of the insulin-lowering effect of weight loss.

In addition, T2D, caused in large part by obesity-associated ectopic lipid deposition in liver and skeletal muscle, which in turn impairs insulin-stimulated glucose transport in skeletal muscle, promotes decreased glycogen synthesis and increased gluconeogenesis in the liver, and therefore contributes to fasting and postprandial hyperglycemia and hyperinsulinemia [3], raises the risk of cancer in both men and women [4]. Interestingly, however, type 1 diabetes (T1D), caused by autoimmune destruction of the insulin-producing β -cells and not typically associated with obesity, was associated with a barely appreciable 7% increase in

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cancer risk in women and did not alter cancer risk in men [5]. The much greater impact of T2D in promoting cancer risk compared with T1D indicates that chronic hyperglycemia per se is likely to be insufficient to mediate the impact of obesity/T2D to promote tumor growth.

Purported Cancer-Promoting Factors Associated with Obesity

Of necessity, most studies exploring the link between obesity and cancer are associative, because numerous putative tumor-promoting factors are altered simultaneously as body weight increases. Worsening obesity tends to increase serum concentrations of glucose, insulin, insulin-like growth factor-1 (IGF-1), lipids, leptin, estrogen, resistin, and inflammatory cytokines and reduces IGF-binding protein and adiponectin levels, each of which has been suggested to contribute to cancer pathogenesis. In this forum, we focus on evidence regarding a potential mechanistic link between insulin and/or IGF-1 and obesity-associated tumor progression, while acknowledging that insulin/IGF-1 signaling is likely to be one of multiple factors, some of which may occur downstream of insulin action, that may hasten tumor growth pathogenesis in the setting of obesity.

Insulin, IGF-1, and Cancer

Circulating plasma insulin/IGF-1 concentrations have been shown to independently predict the risk of certain tumor types in humans [6] (Table 1). As IGF-1 can activate the insulin receptor, and vice versa, it is likely that the mechanisms by which each protein promotes tumor growth may over-lap to a large extent. The association between plasma insulin/IGF-1 concentrations and tumor appearance and progression is likely to be due to a direct effect of these hormones on malignant cells: the insulin receptor is commonly expressed in tumors, as are downstream mediators in the canonical insulin signaling cascade, although tumor insulin receptor expression and activation by insulin may not correlate with the obesity association of cancer types [7]. What is less well understood, however, is the mechanism by which insulin promotes tumor growth. Insulin receptor binding activates the insulin receptor substrate/phosphoinositide 3-kinase/Akt cascade, which ultimately promotes activation of the mammalian target of rapamycin complex (mTORC). mTORC signaling clearly plays a role in cancer cell proliferation via control of transcription, ribosome biogenesis, protein synthesis, angiogenesis, and autophagy and may participate in Warburg metabolism [8]; that is, a shift from oxidative to glycolytic metabolism allowing cancer cells to remain alive despite low perfusion/oxygenation, fueled by anaerobic metabolism of glucose to pyruvate, generating large quantities of lactate by reduction of lactate to regenerate NAD^+ , which is consumed during glycolysis. mTORC2 activity upregulates the expression of pyruvate kinase M isozyme-1 (PKM1), a constitutively active enzyme that converts phosphoenolpyruvate to pyruvate, thereby catalyzing – along with its conditionally activated counterpart, PKM2 – the final step in glycolysis. PKM1 was recently shown to promote tumor cell survival, highlighting an important permissive role for PKM1 regulation of glycolysis [9], which may occur at least in part downstream of insulin. Highlighting a key role for insulin in driving tumor cell division, the efficacy of phosphatidylinositol 3-kinase (PI3K) inhibitors is limited by the effect of these drugs to cause pronounced hyperinsulinemia, which may either over-come PI3K inhibition and/or activate PI3K-independent pathways to promote tumor growth [10].

While the growth-promoting functions of insulin through canonical mTOR/Akt/ribosomal protein S6 kinase signaling in tumor cells clearly contribute to tumor growth, the potential direct metabolic role of insulin in tumor cells is less clear. We have recently shown that insulin promotes glucose oxidation only in obesity-associated tumor types *in vitro*, while it enhances glucose oxidation independent of obesity association [7], and that both insulin-sensitizing and insulin-lowering agents slow colon tumor glucose uptake and reduce tumor glucose oxidation in an insulin-dependent manner in mice [11]. Combined with data demonstrating insulin upregulation of PKM2, promoting aerobic glycolysis [12], these findings suggest that insulin may play a dual metabolic role in tumor growth, promoting oxidative metabolism to enhance ATP synthesis for cell metabolism and nucleic acid synthesis, while also stimulating glycolysis to generate macromolecules used to assemble new cells.

Based on preclinical studies showing a dramatic effect of insulin to promote cell division *in vitro* and *in vivo*, human trials are ongoing to examine the impact of insulin-lowering interventions in humans with cancer; currently twelve National Cancer Institute-funded trials are ongoing to examine metformin's safety and – in some cases – efficacy to slow tumor growth in patients with various types of cancer, with several reports suggesting a beneficial effect of metformin to prevent or slow tumor growth, as reviewed recently [13]. However, metformin is not a true insulin sensitizer in that its major effects are to inhibit hepatic gluconeogenesis [14] and it will thus have a larger impact on reducing plasma glucose and insulin concentrations in the fasting state as compared to postprandial conditions. Conversely, exercise, which has been shown to improve cancer outcomes whether done before, during, or after cancer treatment [15], is expected to reduce postprandial glucose and insulin concentrations due to its insulin-sensitizing effect, but is likely to have little impact on endogenous glucose production in the fasting state. Thus, interventions that both improve insulin sensitivity and inhibit gluconeogenesis are likely to have a greater impact to slow obesity-associated tumor progression by reducing plasma insulin concentrations throughout the day. Future studies will be required to determine the impact of agents with a primary effect to lower circulating insulin by reducing both fasting and postprandial plasma glucose and insulin concentrations by promoting weight loss (e.g., GLP-1 analogs), by increasing renal glucose excretion (e.g., SGLT2 inhibitors), and/or by reducing ectopic lipid in insulin-responsive organs (e.g., liver-targeted mitochondrial uncoupling agents) on other obesity-associated determinants of tumor growth and progression. Trends in clinical trials exploring the relationships between obesity and cancer pathogenesis and prognosis have begun to reflect this concept: while metformin remains the most frequently studied intervention to reduce the impact of obesity on tumor growth, current clinical trials now include not only metformin but also glucose-wasting agents (SGLT2 inhibitors) and insulin-sensitizing interventions (thiazolidinediones, exercise, low-carbohydrate diets, and weight loss in overweight and obese individuals) (Table 2). By stratifying treatment responses by baseline clinical characteristics – such as hemoglobin A1c, fasting plasma insulin concentrations, or, ideally, glucose and insulin responsiveness determined in a glucose tolerance test – these studies may yield insights into which patients are most likely to respond to insulin-lowering adjuvants to cancer treatment. Thus, it may soon be feasible to apply precision medicine approaches to metabolic therapy in cancer patients, thereby enhancing the efficacy of standard cancer treatments.

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Table 1.**Impact of Insulin on Obesity-Associated Cancers^a**

Tumor type	Driven by insulin/IGF <i>in vitro</i>?	Associated with insulin/IGF in rodents?	Associated with insulin/IGF in humans?
Tumor types that the CDC has associated with obesity			
Postmenopausal breast	Yes	Yes	Yes
Colorectal	Yes	Yes	Yes
Endometrial/uterine	Yes	Yes	Yes
Esophageal adenocarcinoma			Yes
Gallbladder			
Gastric		Yes	Yes
Hepatocellular	Yes	Yes	Yes
Meningioma	Yes		
Multiple myeloma	Yes	Yes	
Ovarian	Yes	Yes	Yes
Pancreatic	Yes	Yes	Yes
Renal	Yes		
Thyroid			
Tumor types not currently associated with obesity by the CDC			
Prostate	Yes	Yes	
Osteosarcoma	Yes	Yes	

^a, 'Yes' indicates a positive association between insulin and cell division in at least four published *in vitro* studies, between insulin and tumor growth in at least three published *in vivo* rodent studies, or between insulin or c-peptide and cancer risk, stage at diagnosis, or death in at least two published human studies.

Table 2.

Trials Currently Recruiting or Not Yet Recruiting in the USA as of 17 November 2019 Examining the Impact of Insulin-Lowering Therapies On Cancer Risk, Prognostic Markers, or Outcomes

Tumor type	ClinicalTrials.gov identifier (NCT-)
(A) Incidence	
Metformin	
Breast cancer	01905046
SGLT2 inhibitors	
Bladder cancer	02695121
Breast cancer	02695121
Dietary interventions (all)	
Bladder cancer	00848289
Breast cancer	03448003, 02334085
Colon cancer	01647776, 03028831
Endometrial cancer	00587886
Esophageal cancer	01035398
Multiple cancer types	04125914
All cancers	03430141
Exercise	
Breast	03779867, 02494869, 03448003, 02334085
Multiple cancer types	04125914
Weight management	
Breast	02681120
Multiple cancer types	04125914
(B) Outcomes	
Metformin	
Breast cancer	01980823, 02874430, 03238495, 01042379, 03314688, 03760536
Colorectal cancer	03800602
Endometrial cancer	02035787
Head and neck cancer	02949700, 03618654
Leukemia/lymphoma	01750567
Lung cancer	03048500
Melanoma	03311308, 02143050
Multiple myeloma	03829020
Ovarian cancer	02437812
Pancreatic cancer	03889795
Prostate cancer	02176161, 02614859, 02946996
Renal cell carcinoma	02495103
Uterine cancer	02874430
Multiple cancer types	03889795, 03017833, 04114136, 02122185
Thiazolidinediones	
Multiple cancer types	04114136

Tumor type	ClinicalTrials.gov identifier (NCT-)
Diet	
Bladder cancer	03286699
Brain tumors	03328858, 03955068, 03278249, 03451799
Breast cancer	02744079, 03733119, 03535701, 01802346, 03045289, 03186937, 03314688, 03961685
Colon cancer	03286699
Gynecologic cancer	00719303
Head and neck cancer	03971656
Leukemia/lymphoma	02708108, 03016130, 03157323, 03823651
Lung cancer	03700437
Pancreatic cancer	03187028, 03256201
Prostate cancer	03679260, 03999151, 03329742, 03194516, 01802346, 02176902, 02454517, 03261271
Multiple cancer types	03574194
Exercise	
Bladder cancer	03286699
Breast cancer	04106609, 04013568, 03988595, 01943695, 03424915, 03961685
Colon cancer	03975491, 03286699, 00819208
Endometrial cancer	04025229
Gynecologic cancer	00719303
Lung cancer	03267368
Pancreatic cancer	03187028, 03256201
Prostate cancer	03070145, 03397030, 02613273, 03999151, 02435472, 02730338, 03987217
Multiple cancer types	03905356, 03996239, 03813615
Weight management	
Breast cancer	02750826
Endometrial cancer	03908996
Leukemia	02708108
Prostate cancer	03261271