Metabolic Syndrome and Cancer: From Bedside to Bench and Back

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Abstract

As older patients present with an average of three comorbidities beside their cancer, geriatric oncology can provide unique clues to translational research in aging and cancer. We illustrate this approach with the example of the metabolic syndrome and cancer. Epidemiologic and clinical cohorts highlighted an association between the metabolic syndrome and a higher risk and worse prognosis of various cancers. In a bedside-to-bench transition, this led to an interest in analyzing the potential mechanisms underlying this association. At least ten potential mechanisms could be implicated, with the challenge of understanding which are the dominant ones in human patients. Bench-to-bedside studies are beginning to shed some light on that aspect, and some therapeutic trials are beginning to exploit the lessons learned.

Translational research is a bidirectional endeavor and often merges knowledge from several disciplines. An excellent illustrative example is the interaction between metabolic syndrome and cancer. Such a topic is highly relevant to geriatrics, as the prevalence of metabolic syndrome increases with age to reach about 40% of the population aged 60 and older [1]. It also illustrates an increasingly recognized phenomenon: the impact of comorbidity on cancer risk and prognosis. Here again, this example illustrates the principle that a patient’s diseases cannot be considered in isolation and need to be addressed in an integrated manner.

Research about metabolic syndrome and cancer started from the observation that patients with diabetes had a higher risk of cancer [2, 3] and a worse prognosis [4–9] once diagnosed. The observation was extended to the metabolic syndrome. Associations were found for example with the risk of brain [10], breast (in postmenopausal women) [11], cervical [12], colorectal [13–16], liver [17, 18], lung, pancreatic [19, 20], and prostate cancer [21], and the prognosis of breast [22], colorectal [23, 24], and prostate cancer [25, 26]. Although these associations were first described in
Table 1. Potential mechanisms by which metabolic syndrome interacts with the behavior of cancer

Insulin-like growth factor-1 pathway activation
Hyperinsulinemia/insulin resistance
Hyperglycemia, advanced glycation end-products and their receptor (RAGE)
Atypical PKC dysregulation
Leptin and adiponectin
Vascular damage and VEGF increases
Inflammation
Impaired immunity
Peroxisome proliferator-activated receptor modulation

middle-aged patients, they also apply to elderly patients [27]. However, epidemiologic studies provide mixed results as to which components of the metabolic syndrome matter most (insulin resistance, hypertension, hypercholesterolemia/hyperlipidemia, or obesity) [10, 12–15, 19–21, 24, 28]. Therefore, going from bedside to bench might provide some clues as to the potential mechanisms involved (table 1).

From Bedside to Bench

Several mechanisms can be postulated for the association of metabolic syndrome and cancer. They may affect the tumor, the host, or both.

(1) The most explored pathway is the insulin-like growth factor-1 (IGF-1) pathway. This pathway consists of IGF-1, IGF-2, several binding proteins, and the IGF-1 receptor. This receptor in turn activates the PI3K-Akt pathway and its subsequent consequences in cell growth and apoptosis. This pathway is of interest in insulin resistance syndromes because of the interactions with the insulin pathway. Insulin has some cross-activating effect on the IGF-1 receptor. The insulin-receptor and the IGF-1 receptor can also form heterodimers. This receptor is overexpressed in more than 90% of colon cancer cells [29, 30]. Its level of expression is associated with tumor grade and stage and it induces resistance to apoptosis in colon cancer cells through the Akt/Bcl-xL pathway, as demonstrated by some Moffitt work [29, 31]. Its blockade inhibits growth and angiogenesis in colon cancer [32]. Elevated plasma insulin levels activate insulin, and possibly IGF-1, receptors, and insulin itself might stimulate the IGF-1R [33]. The activity of plasma IGF-1 is modulated by its binding to IGF-binding proteins. Total IGF-1 levels and IGFBP levels decrease with age [34, 35]. However, free IGF-1 levels were found increased in subjects above the age of 70 [35]. Elderly patients may also have a small rise in the number of IGF type 1 receptors per cell [36]. IGF-1 decreases with higher BMI [34]. IGF-1 and IGFBP-1 appear to be both decreased in metabolic syndrome patients (no data on the resulting impact on free IGF-1) [37]. Diabetic patients also have decreased IGF-1 levels, correlated with poor
glycemic control and a worse outcome of cardiovascular disease [38]. No data on free IGF-1 in metabolic syndrome or diabetes are to our knowledge available, but some indirect evidence suggests it might be elevated [39]. These results point toward a somewhat complex but potentially important implication of the IGF-1/IGF-1R pathway in cancer patients with metabolic syndrome.

(2) Hyperinsulinemia and insulin resistance. Hyperinsulinemia might by itself activate cell multiplication. This finding is consistent with the increasing body of literature suggesting that hyperinsulinemia seems to be the critical factor in the association of metabolic syndrome and colon cancer. Increased risk of colon cancer or excess of colon cancer deaths were found in patients with recently diagnosed diabetes or impaired glucose tolerance [40]. C-peptide concentrations, which are a measure of insulin secretion, were found to be a stronger predictor of colorectal cancer risk than was the metabolic syndrome [41]. Postprandial insulin [42] and nonfasting C-peptide [41, 43], a measure of hyperinsulinemia rather than insulin resistance, are stronger predictors of colon cancer risk than is the fasting insulin concentration [42, 44]. Finally, in one study, chronic insulin therapy was associated with a significantly increased risk of colorectal cancer among patients with type 2 diabetes [45]. In addition to the epidemiologic evidence, mechanistic studies have also suggested direct mitogenic and proliferative effects of insulin on tumors [46]. Insulin has two receptors: IR-A and IR-B. The first one mediates the mitogenic effects and the second one the metabolic effects of insulin. IR-A can be aberrantly expressed in tumor cells, and has a high affinity for IGF-2 as well [47]. These receptors can dimerize with the IGF-1 receptor. It is also interesting to note that peritumoral vessels express a high level of insulin receptors [48]. Another way hyperinsulinemia might stimulate cancer growth is through the NF-κB pathway, as IKK-β appears to be a key mediator in insulin resistance. High-dose salicylates, which inhibit IKK-β, can reverse hyperglycemia, hyperinsulinemia and dyslipidemia in obese rodents in a COX-independent fashion [49].

(3) Hyperglycemia and advanced glycation end-products (AGEs). Sustained hyperglycemia by itself might favor cancer growth. Most tumors are glucose-avid, as demonstrated by the diagnostic effectiveness of PET scanning. This may be true for example if protein kinase C (PKC)-ζ is not turned down in tumors from metabolic syndrome patients (see below). Oral antidiabetics such as phenformin, buformin, and diabenol have been shown to inhibit colon carcinogenesis and shift phenotype to more differentiated tumors in rats [50]. Their postulated mechanism of action is a calorie restriction-like action, decreasing hyperinsulinemia, hyperglycemia, and oxidative stress. This effect may be mediated by the restoration of PKC-ζ function in the muscle. Another potential mechanism of action by hyperglycemia is AGEs. These increase with age and diabetes [51] and induce similar ‘aging’ changes. AGEs are produced by nonenzymatic glycation of proteins with reducing sugars and subsequent metal-catalyzed oxidations. Oxidation of glycated proteins or interaction of AGEs with cell surface receptors produces superoxide radicals, contributing to oxidative stress and cell damage. As mentioned above,
in colon cancer the receptor for AGE expression is linked with metastatic disease. Several methods exist to dose AGES, each of which has limitations. In at least one study, HbA1c had the closest relationship with clinical complications of diabetes, when compared with Nε-carboxymethyllysine and pentosidine, as AGE products were mainly influenced by the quality of diabetes control [52]. The receptor for advanced glycation end-products (RAGE) is a member of the immunoglobulin superfamily. It binds multiple ligands, such as AGES, β-amyloid, and, of interest to cancer progression, amphoterin [53]. This binding triggers a sustained period of cellular activation. The receptor exists at low levels in normal tissues except for lung tissue and becomes upregulated where its ligands accumulate. RAGE is implicated in a broad spectrum of diabetic complications. In the animal, blocking RAGE activation by using soluble RAGE appears to prevent or decrease complications. Colon cancer cells express RAGE, and its ligation activates the ras pathway [54]. RAGE positivity was observed in 19, 81, and 100% of Dukes B, C, and D colorectal cancers in nondiabetic patients [55]. Amphoterin was expressed in most tumors regardless of stage. Animal experiments suggest that RAGE binding to amphoterin in the tumor bed enhances cell migration and invasion, while not markedly altering cell viability and angiogenesis, and that RAGE blockade creates less invasive phenotypes [53]. Binding of AGES to RAGE appears genotoxic via oxidative mechanisms [56]. Therefore, one can hypothesize that RAGE upregulation and binding could be a potential mechanism by which metabolic syndrome worsens the prognosis of colon cancer, and could be targeted with inhibitors such as sRAGE or RAGE Fab'. RAGE is also overexpressed in other cancers, such as pancreatic and prostate cancers. Notable exceptions are lung and esophageal cancer, in which a higher stage is associated with a downregulation of RAGE.

(4) Animals and humans with metabolic syndrome have a markedly decreased activation of the atypical PKC-ζ in their muscle, but not in their liver. PKC-ζ is implicated in glucose uptake, apoptosis, and is also an activator of JUN-B, and therefore is connected to the VEGF signaling pathway. With failure of muscle glucose uptake, resultant hyperinsulinemia increases activity of liver PKC-ζ, which controls lipid synthesis. Thus, lipid production by liver is increased, thereby causing VLDL-associated hypertriglyceridemia and reciprocal decreases in HDL lipids. On the other hand, PKB/Akt activity in the liver is diminished as the metabolic syndrome worsens and this loss of PKB/Akt activation leads to increases in hepatic glucose output, and therefore contributes to hyperglycemia and the appearance of overt diabetes.

The level of PKC-ζ and its responsiveness to insulin, IGF-1 and other growth factors in cancer cells of patients with metabolic syndrome is unknown. Whether insulin/IGF-1 action is impaired or enhanced in cancer cells is uncertain. As anti-apoptotic factors that further increase glucose uptake and VEGF production, PKC-ζ and PKB may both be particularly important in tumor progression and metastatic activity. Interestingly, treatment with oral antidiabetics such as rosiglitazone and metformin increases muscle AMPK activity and this restores PKC-ζ activity in skeletal
muscle. These muscle insulin sensitizers diminish hyperinsulinemia and this may decrease insulin-dependent actions in cancer cells [57–59]. On the other hand, atypical PKC-ζ might also impair tumorigenesis by repressing IL-6 production [60]. The closely related atypical PKC-ι/λ has also been described as an oncogene, but the impact of metabolic syndrome on its level in humans is unknown [61, 62].

(5) Leptin and adiponectin. Obese patients have increased levels of leptin and decreased levels of adiponectin compared to normal weight subjects [47]. Adiponectin is also reduced in diabetic individuals [63]. Leptin mediates the feeling of satiety, improves insulin resistance and hyperglycemia. Obese people appear to demonstrate leptin resistance [64]. Adiponectin regulates energy homeostasis, glucose and lipid metabolism, and has anti-inflammatory and anti-angiogenic properties. Breast cancer patients with metabolic syndrome have higher levels of leptin in their mammary tissue and higher levels of leptin receptors on their tumors than obese patients without metabolic syndrome [65].

(6) Vascular damage and VEGF. As noted above, the levels of VEGF may be increased in metabolic syndrome patients [66–68]. VEGF is a key promoter and sustainer of the tumoral neovascularization. Its inhibition by bevacizumab prolongs the survival of metastatic colon cancer patients [69].

(7) Insulin-mediated vascular proliferation. Peritumoral vessels overexpress the insulin receptor [48, 70]. In vitro and in vivo experiments demonstrated that insulin can stimulate angiogenesis [70, 71]. These effects occur independently of VEGF/VEGFR signaling, but are dependent upon the insulin receptor itself. Downstream signaling pathways involve PI3K, AKT, sterol regulatory element-binding protein 1 (SREBP-1) and Rac1 [71]. Zhang et al. [72] showed that IR downregulated cancer cells induced xenograft tumors in mice had reduced growth, angiogenesis, lymphangiogenesis and metastasis compared with wild-type cells xenografts.

(8) Inflammation. Patients with metabolic syndrome are in a state of chronic low-level inflammation. Their IL-6 levels are elevated [73]. Their ability to produce the anti-inflammatory cytokine IL-10 appears impaired [74, 75]. Levels of IL-6 increase with age as well. To what extent this is an effect of age itself, or of the accumulation of clinical and subclinical morbidity is debated [76]. These high levels of IL-6 appear to be associated with insulin resistance and prognosis in colon cancer patients as well [77–79].

(9) Impaired immunity. Patients with metabolic syndrome have a decreased cellular immunity [80]. In this study, half of patients had thyroid dysfunction. In patients with normal thyroid function, there was a low relative number of CD3 cells, and hypergammaglobulinemia. There was a close correlation between the levels of free T₃ and CD3, CD4, and CD8 lymphocytes, and an inverse correlation of free T₄ with IgA and IgG levels. It should be noted that intratumoral immune modulation likely plays a large role in immunologic tumoral control. For example, increased amphoterin expression is associated with a depletion of tumor-infiltrating macrophages in colon cancer [81].
The peroxisome proliferator-activated receptors (PPAR). The three PPARs (α, β/δ, γ) are nuclear hormone receptors interacting with multiple cellular pathways. PPAR-γ is overexpressed in the muscle of obese and type 2 diabetic subjects and this is insulin-induced [82]. Activation of PPAR-γ by thiazolidinediones improves insulin sensitivity, has an antiproliferative effect on cancer cells in vitro, and an anti-inflammatory effect. In a cohort of diabetic veterans, thiazolidinediones users had a 33% reduction in risk of lung cancer. In another cohort study, the use of rosiglitazone or pioglitazone by diabetic patients was associated with a decrease in the risk of liver cancer, but not lung and bladder cancer. Rosiglitazone was associated with a decreased risk of colon cancer [83]. The risk of colon and prostate cancer was not statistically different [84]. Chronic activation of PPAR-α can induce hepatocellular carcinoma in rats [85]. PPAR-β/δ is a mediator of EGFR-induced carcinoma cell growth [86]. However, while chemical PPAR agonists have anti-tumoral properties, the link between endogenous overexpression/activation of the receptors and cancer risk in metabolic syndrome patients is unclear at this point.

In summary, metabolic syndrome might favor cancer development and progression via the IGF-1 receptor pathway, hyperinsulinemia itself, hyperglycemia and AGEs, atypical PKC dysregulation, leptin/adiponectin balance alterations, vascular damage and VEGF activation, Insulin-mediated angiogenesis, inflammation, impaired immunity, and/or PPAR modulation. These effects might be compounded in the elderly by synergistic aging-related changes such as higher free IGF-1 and IGF-R levels, increase in AGEs, and IL-6 levels. Such a list of potential factors leads to an important question that lends itself to a bench-to-bedside process that we address next.

From Bench to Bedside

Comparative Studies

Since patients with metabolic syndrome cumulate several risk factors, an important clinical question is: what is the dominant mechanism by which metabolic syndrome interferes with cancer? Identifying such a mechanism is important, since it will be the basis to design effective interventions aiming at the right target for maximum impact. For this we need to move back from laboratory models and return to the patients.

Several results point towards hyperinsulinemia itself being the key driver, although uncertainty remains about the dominant downstream mechanism of action. In a follow-up of the Cremona cohort study, insulin resistance was associated with cancer mortality, independently from diabetes, obesity/visceral obesity, and the metabolic syndrome [28]. In a study by Goodwin et al. [87], insulin-related factors and obesity-related variables had a different impact on the prognosis of breast cancer. Baseline hyperinsulinemia had most correlation with progression-free survival and overall survival during the first 5 years, whereas the effect of BMI and leptin levels had a