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Mini-review

Diabetes and cancer, common threads and missing links

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ABSTRACT

Diabetes mellitus is a serious and growing health problem worldwide and is associated with severe acute and chronic complications. Accruing epidemiological and clinical evidence have suggested that an increased cancer incidence is associated with diabetes as well as certain diabetes risk factors and diabetes medications. Several pathophysiological mechanisms for this relationship have been postulated, including insulin resistance and hyperinsulinemia, enhanced inflammation, aberrant metabolic state, endoplasmic reticulum stress, and deregulation of autophagy. In addition to these potential mechanisms, a number of common risk factors, including obesity, may be behind the association between diabetes and cancer. Furthermore, different anti-diabetic medications may modify cancer risk and mortality in patients with diabetes. This Review discusses evidence to support the relationship between diabetes and cancer development as well as the underlying mechanisms. We also discuss the relationship of current diabetes treatments and cancer risk or prognosis. Understanding the mechanisms that connect type 2 diabetes or diabetes treatments to cancer are crucial for establishing the fundamental strategies concerning about primary prevention, early detection and effective therapy against these diseases.

Introduction

Diabetes is a common chronic disease with tremendous impact on health worldwide. Statistical data from the World Health Organization (WHO) reports that about 347 million people worldwide have diabetes and it is predicted to become the 7th leading cause of death in the world by the year 2030. Epidemiologic study suggests that people with diabetes are at significantly higher risk for many forms of cancer and greater cancer mortality, predominantly type 2 diabetes mellitus (T2DM) [1]. In 2010, the American Cancer Society and the American Diabetes Association released a consensus report that recommended regular cancer screening for diabetics and careful consideration in selecting diabetes medication for patients at very high risk for cancer or recurrent cancer [2].

Different cancer types, as well as T2DM could share a number of major risk factors. Some risk factors are nonmodifiable, such as age and sex. There is no doubt that the incidence and mortality of cancer and diabetes are increasing with age, although the two diseases have trends of attacking young adults. Sex is another risk factor; overall cancer occurs more frequently in men. Similarly, men show slightly higher risk of diabetes than women. Cancer and diabetes also share many modifiable risk factors, including obesity, diet, physical activity, tobacco smoking and alcohol drinking. Except for the common risk factors, meta-analyses have revealed T2DM to be an independent risk factor for the development of several different types of cancer [3,4]. The fact that we should pay more attention is that some medications used to treat hyperglycemia are associated with either increased or decreased risk of cancer. Although, the mechanisms that underlie the associations between T2DM and cancer risk remain far from understood, the insulin-insulin like growth factor (IGF) axis, inflammation, autophagy, endoplasmic reticulum stress (ER stress) and other mechanisms have been proposed to be important in this process. In this review, we describe the epidemiological evidence supporting the relationship between cancer and T2DM, and discuss the biologic links and mechanisms associated with T2DM, the metabolic syndrome, and obesity that may promote cancer initiation, growth, and metastases.

Epidemiological evidence for the connection of T2DM to cancer

Metabolic syndrome is a clustering of at least three of five of the following disorders: abdominal obesity, high blood pressure, elevated fasting plasma glucose, high triglycerides, and low high-density lipoprotein (HDL) levels. Metabolic syndrome is associated with a greater risk of developing diabetes with insulin resistance as the cornerstone. Researchers have paid much attention to the relationship between diabetes and cancer. A multi-national program named as "The Metabolic Syndrome and Cancer (Me-Can) Project" was initiated in 2006 to investigate factors of the metabolic syndrome on the association with cancer risk. Me-Can Project and other investigators reported that a number of cancers, including liver,

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pancreas, endometrium, colorectal, gastric, breast and bladder are associated with higher metabolic syndrome score, although gender difference can be observed in some types of cancer [5–10].

Among these cancers, the greatest increase in risk has been found in hepatocellular carcinoma (HCC). T2DM is associated with an increased incidence of HCC, the relative risks (RR) is 2.01, with the 95% confidence intervals (CI) as 1.61–2.51, in comparison with individuals without T2DM [11]. The increased incidence of HCC is independent of geographic location, alcohol consumption, history of cirrhosis, or infections with hepatitis B virus (HBV) or hepatitis C virus (HCV). The relationships between pancreatic cancer and diabetes are more complex as the two diseases may be of reciprocal causation. Diabetes is a risk factor for pancreatic cancer (RR = 1.97, 95% CI = 1.78–2.18) [12]. Meanwhile, evidence suggest that recently-developed diabetes may be a consequence of pancreatic cancer due to impaired phosphatidylinositol 3-kinase (PI3-K) signaling or islet dysfunction [13]. Moreover, other pathological changes caused by pancreatic cancer may also contribute to the new-onset diabetes. Pancreatic tumor mass of ductal adenocarcinoma most commonly arises from the head of the pancreas, which are the sections where the bile duct joins with the pancreatic duct. Hence, the bile duct obstruction is often happened in pancreatic cancer patients. A recently published work investigated the relationship between blood glucose homeostasis and partial pancreatectomy. The authors revealed that surgically reversible blood glucose dysregulation diagnosed concomitantly with a (peri-) pancreatic tumor appears secondary to compromised liver function due to tumor compression of the common bile duct and the subsequent increase in insulin resistance, which is called as “cholestasis-induced diabetes” [14]. Bile acid is involved in the regulation of hepatic glucose metabolism by the nuclear receptor farnesoid X receptor (FXR) and induce glucagon-like peptide-1 (GLP-1) secretion by the G-protein-coupled membrane receptor TGR5-mediated pathways [15]. In addition, new-onset diabetes in pancreatic cancer patients is likely to be a paraneoplastic phenomenon caused by tumor-secreted adrenomedullin. Levels of adrenomedullin were higher in patients with pancreatic cancer who developed diabetes compared those who did not [16]. Mechanically, pancreatic cancer causes paraneoplastic β-cell dysfunction by shedding adrenomedullin^{+}/CA19-9^{+} exosomes into circulation that inhibit insulin secretion through ER stress and failure of the unfolded protein response (UPR) [17].

The RR of cancer at other sites ranging from 1.27 (95% CI 1.16–1.39) for breast cancer [18] to 2.22 (95% CI 1.8–2.74) for endometrial cancer [19]. In these cancers, diabetes may be an independent risk factor. A prospective study of six European cohorts revealed that abnormal glucose metabolism is associated with an increased risk of cancer and cancer death overall and at several cancer sites independent of body mass idex (BMI). RR (95% CI) per 1 mmol/L increment of glucose for overall incident cancer is 1.05 (1.01–1.10) in men and 1.11 (1.05–1.16) in women, and corresponding RRs for cancer death are 1.15 (1.07–1.22) and 1.21 (1.11–1.33), respectively [5]. Notably, T2MD is significantly inversely associated with risk of developing prostate cancer [20]. However, obese men with prostate cancer have higher cancer mortality rates than those of patients with normal body weight [21].

During the last several years, epidemiologic evidence linking anti-diabetic drugs with cancer risk has been considered. Anti-diabetic therapies may either target for lowering of glucose by insulin sensitizers (e.g. metformin and thiazolidinediones) or stimulate the pancreas to secret much more insulin (e.g. sulfonylurea drugs). In addition, once T2DM patients become insulin dependent, they are treated with different analogs of insulin. Recently, a meta-analysis demonstrated that the use of metformin or thiazolidinediones is associated with a lower risk of overall cancer incidence (RR = 0.86, 95% CI 0.83–0.90; RR = 0.93, 95% CI 0.91–0.96 respectively). In contrast, insulin, sulfonylureas and alpha glucosidase inhibitor use is associated with an increased risk of overall cancer incidence (RR = 1.21, 95% CI 1.08–1.36; RR = 1.20, 95% CI 1.13–1.27; RR = 1.10, 95% CI 1.05–1.15, respectively) [22]. Such a fact not only reminds the clinicians to choose the anti-diabetic medications deliberately, but also facilitates the exploration of biological links and mechanisms to decipher the linking between the two diseases.

Biological mechanisms linking diabetes and cancer

Several mechanisms have been proposed to explain links between diabetes and increased cancer risk (Fig. 1), including deregulation of insulin and IGF signaling, obesity and inflammation, metabolic symbiosis; moreover, ER stress and autophagy have also emerged as important cellular mechanisms linking diabetes to cancer.

Insulin-IGF axis

Insulin resistance is common in individuals with obesity or T2DM, in which insulin action is impaired in peripheral target tissues and then circulating insulin levels are frequently increased. Hyperinsulinemia also results in reduced levels of IGF binding protein-1 (IGFBP-1) and IGFBP-2 (which normally bind to and inhibit the action of IGF-1), thus increasing the levels of free and bioactive IGF-1. Both insulin and IGF-1 activate the receptor tyrosine kinase pathway, insulin receptor (IR) and IGF-1 receptor (IGF-1R) respectively, which are expressed at higher levels in malignant cells. Activation of these receptors results in activation of insulin response substrate-1 (IRS-1) and downstream mitogen-activated protein kinase (MAPK) pathway, phosphoinositol-3 kinase/Akt (PI3K-Akt) pathway, as well the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. The results of activating these pathways are promoting protein synthesis, increasing cellular proliferation, protection from apoptotic stimuli and participating in the initiation and maintenance of cancer stem cells [23]. There is a high degree of homology between IGF1R and IR, they can form hybrid receptors. IGF1 and IGF2 have high affinity for the hybrid receptors compared with insulin and increased levels of hybrid receptors have been observed in many cancer tissues [24]. Experimental evidence suggested that decreasing circulating insulin levels in mice or down-regulating the IR in cancer cells and xenografts reduced tumor growth, angiogenesis, lymphangiogenesis, and metastasis [25,26]. Moreover, increased circulating insulin can induce a reduction of the sex hormone-binding globulin, leading to increases in bioavailable sex hormones [27]. Elevated endogenous sex steroid levels are associated with a higher risk of postmenopausal breast and endometrial cancers. Because the pivotal roles of IGFs in tumorigenesis and growth, more than 10 of IGF/IGF-1 inhibitors (monoclonal antibodies against IGF-1R or its ligands, and IGF-1R tyrosine kinase inhibitors) have entered clinical trials but demonstrating unsatisfactory results [28], suggesting that other critical mechanisms exist and participate in the mediation of cancer-promoting roles of insulin/IGF signaling.

Obesity and the inflammation

Diabetes and obesity are closely linked; approximately 80%–90% of patients diagnosed with T2DM are also obese. Diabetes and obesity display mutual promotion effects. Insulin resistance creates increased levels of insulin and glucose in the blood stream, which is a major underlying cause of excess weight and obesity, whereas inflammation factors releasing by the infiltrated macrophages in pancreatic tissue destroy insulin-producing β cells and facilitate the progression of T2DM [29]. Obesity performs the cancer promotion effect through many aspects. First, obesity promotes the establishment of tumor microenvironment. The survival of cancer