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Mini-review

Incretins and thiazolidinediones in glucose homeostasis and cancer: Role of common polymorphisms

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ABSTRACT

With growing epidemiologic and molecular evidence linking the pathogenesis of diabetes mellitus and oncogenesis, the role of anti-diabetic drugs as antineoplastic agents becomes a subject of intense investigation. Several trials are underway assessing the effect of adding metformin to the existing chemotherapy regimen in the treatment of cancers. This review has a focus on other commonly used drugs classified into two broad groups, incretins and thiazolidinediones. The aim of this review is to discuss the common genetic polymorphisms implicated in the pathogenesis of type 2 diabetes mellitus (type 2 DM) and how they are linked to molecular pathways involved in carcinogenesis.

1. Introduction

According to the 2009 Behavioral Risk Factor Surveillance System conducted by the Centers for Disease Control (CDC), approximately 72.5 million US adults are obese. Recent estimates of the annual medical costs associated with obesity are as high as \$147 billion [1]. Paralleling the increasing obesity rates is another related debilitating chronic disorder, diabetes mellitus. In another CDC study, the prevalence of diabetes mellitus among the US adult population was projected to increase from 14% in 2010 to 21% by 2050 [2]. We currently have established evidence (Cancer Prevention Study II, National Enhanced Cancer Surveillance System) supporting the association between obesity, diabetes mellitus, and cancer. In the United States, one in every four deaths is attributed to cancer, and the National Institutes of Health estimated the overall costs of cancer in 2010 at \$263.8 billion [3].

Diabetes, obesity, and cancer are three diseases that are chiefly recognized by their phenotypes: persistent hyperglycemia, body mass index (BMI), and presence of a neoplastic process, respectively. It was only in 1997 that the World Health Organization recognized diabetes as a global health problem [4]. Subsequently, various programs have been initiated to detect diabetes and treat its symptoms.

Initial epidemiological studies of diabetes provided concrete evidence of its interrelationship with obesity [5]. Diabetes and obesity, which were a problem of the developed world, now seem to be a global problem, as evidenced by data from developing countries, where obesity not only contributes to insulin resistance but also has been associated with other health conditions, such as chronic gut inflammation [6] and in utero malnourishment leading to fetal programming [7]; epigenetic influences; and dietary factors [8].

Population studies have demonstrated a relationship between several obesity-related diseases and cancer. In the data published by the American Cancer Society, obesity was associated with breast cancer in postmenopausal women; colon, endometrial, kidney, esophageal (adenocarcinoma), pancreatic, gallbladder, and thyroid cancers; gynecological malignancies; myeloma; Hodgkin's lymphoma; and aggressive forms of prostate cancer [3]. Whereas obesity is consistently associated with an elevated risk of multiple malignancies [9], diabetes has a more complex risk relationship, showing an increased risk of visceral malignancies and a decreased risk for prostate cancer [10].

Although traditional epidemiological studies have continued to decipher the unitary phenotype associated with these disorders, the field of genomics recently provided us with tools to pinpoint the responsible genetic loci. Recent work in genomics has established an intriguing relationship between diabetes, obesity, and cancer [11].

The aim of this review was to discuss the common genetic polymorphisms implicated in the pathogenesis of type 2 diabetes mellitus (type 2 DM) and how they are linked to molecular pathways

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involved in carcinogenesis, with emphasis on transcription factor 7-like 2 (TCF7L2) and its modulation by incretin-based therapy and peroxisome-proliferator activator receptor gamma (PPARγ), modulated by thiazolidinediones (TZDs).

2. Mechanism of action of incretins (glucagon-like peptide 1 agonists) and thiazolidinediones in diabetes mellitus

2.1. Incretins (glucagon-like peptide-1 agonists and dipeptidyl-peptidase-4 inhibitors or gliptins)

It is now well understood that defective actions of the gastrointestinal incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) play critical roles in the pathogenesis of type 2 DM.

GLP-1 and GIP have an amino acid sequence homology and are secreted from intestinal L cells in the distal ileum and colon and intestinal K cells in the duodenum and jejunum, respectively [12]. DPP4 is the enzyme expressed on most cell types and is responsible for the rapid degradation of GLP-1 and GIP. It acts as a substrate for the class of anti-diabetic drugs termed “gliptins.” This enteroinsular axis can be regulated by certain polymorphisms, as discussed later in this review.

GLP-1 acts through its G protein-coupled receptor (GLP-1R), and most of the downstream effects are mediated through the second messenger cyclic adenosine monophosphate (cAMP). cAMP acts through its effector downstream molecules protein kinase A (PKA) and cAMP-regulated guanine nucleotide exchange factors (GNEFs). The actions can be divided into those on beta cells, alpha cells, insulin synthesis, differentiation, and proliferation [13].

In beta cells, GLP-1 and GIP stimulate glucose-dependent insulin secretion, acting through GLP-1R, which is expressed in these cells. This action of GLP-1R on the potassium channel (K_{ATP}) is mediated by PKA and GNEF. Loss of action of GLP-1 and GIP in sulfonylurea receptor (SUR) knockout mice (SUR−/−) suggests the important role of the former in the secretagogue action of incretins [14]. GLP-1 also causes increased insulin synthesis through increased transcription of Pdx-1 [13]. GLP-1Rs are also located on the alpha cells, and GLP-1 causes direct suppression of glucagon secretion [13].

All the above-mentioned mechanisms are glucose dependent and primarily affect glucose homeostasis. GLPI agonists also cause an increase in beta cell mass by direct cellular expansion (Pdx1) and also by inhibiting apoptosis (reduced caspase 3). It is interesting that this effect is also observed in normoglycemic environments and may have a bearing on the increased incidence of cancers linked with incretin therapies [15,16]. Reduced apoptosis and increased beta cell mass was also demonstrated using exendin 4 (long-acting GLP-1) on db/db mice. Akt1 and p44 MAP kinase were overexpressed, and caspase 3 was suppressed, suggesting that proliferation and antiapoptotic pathways were constitutively active [16].

2.2. Thiazolidinediones (glitazones)

PPARγ is the member of the nuclear receptor superfamily that is most abundant in the beta cells of the pancreas. It is the prime target for the group of drugs called TZDs; acting as PPARγ agonists, they exert their insulin-sensitizing action via increased PPARγ expression in the adipose tissue, thus increasing adipocytes and subcutaneous adipose tissue mass [1]. Increased PPARγ expression in the adipose tissue results in increased fatty acid uptake and storage by increasing the transcription of fatty acid transport protein-1 and acyl-coenzyme A synthetase [17]. In the vascular endothelium, PPARγ activation results in suppression of matrix metalloproteinase-9 (MMP-9) and monocyte chemoattractant protein-1, which are important mediators of vessel wall inflammation [17]. Decreased circulating free fatty acid levels protects beta cells, the liver, and the skeletal muscle from their toxic effects, thus improving insulin sensitivity.

In addition, PPARγ is essential in the modulation of cellular differentiation and proliferation [18]. PPARγ and its interaction with glycogen synthase kinase-3β (GSK3β) and CAAT/enhancer-binding proteins act to modulate adipocyte differentiation via production of adiponectin [18]. Furthermore, PPARγ agonists inhibit cell proliferation by increasing proteasomal degradation of cyclin D1 and downregulating the Wnt/β-catenin pathway, thus decreasing the binding of transcription factors and subsequently leading to growth inhibition [18].

2.3. Metformin

It is also important to discuss metformin, as it is the first-line treatment modality for type 2 DM and a proven anticancer drug. Several clinical studies have reported reduced incidence of neoplastic diseases in type 2 DM patients treated with metformin, as compared with diet or other antidiabetic agents. The mechanism of action of metformin is the activation of AMP-activated protein kinase (AMPK), a key player in the regulation of energy homeostasis.

AMPK has been described as a metabolic master switch [19] affecting carbohydrate and lipid metabolism. This heterotrimer affects hormone-sensitive lipase in fatty tissue and promotes insulin secretion in the presence of hypoglycemia and glucose uptake in muscles. Owing to its effects on 4 key tissues, that is, pancreatic islet, liver, skeletal muscle, and adipocyte tissues, AMPK is postulated to be responsible for insulin resistance, a characteristic feature of type 2 DM.

Moreover, by activating AMPK, metformin inhibits the mammalian target of rapamycin complex 1, resulting in decreased cancer cell proliferation. Metformin also induces activation of LKB1 (serine/threonine kinase 11), a tumor suppressor gene, which in turn activates AMPK. LKB1 is a primary upstream regulator of AMP-activated protein kinase. LKB1 has been linked to Peutz–Jeghers syndrome and visceral malignancies [20], indicating the importance of metformin as a promising anticancer drug. Hence, several clinical trials are currently underway, using metformin as monotherapy and adjunctive therapy for cancers [21]. However, whether other non-insulin-based antidiabetic regimens can reproduce the effects of metformin remains to be determined.

3. Key players and genetic polymorphisms

3.1. Insulin, insulin-like growth factors and cell proliferation: the insulin-like growth factor axis

The insulin-like growth factor (IGF) axis consists of ligands (insulin, IGF-1, and IGF-2) and receptors (IGF-1R and IGF-2R; Fig. 1). In addition, a group of circulating proteins determines the bioavailability of IGF-1 and IGF-2 [21]. These proteins are termed “IGF-binding proteins” (IGFBPs). There are currently at least 6 known IGFBPs, which are labeled as IGFBP1-6.

It is interesting that IGFBPs have been shown to function independent of IGF-mediated mechanisms and inhibit the canonical Wingless-INT (Wnt)/β catenin pathway [22]. The canonical Wnt pathway regulates the amount of β catenin entering the nucleus, therefore affecting genetic expression.

There is sufficient data to suggest that IGF-1 and IGFBPs are associated with certain cancers. Data from 17 prospective studies based on 12 countries showed that circulating IGF-1 is positively