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Authors

Wu, Yong

Liu, Yanjun

Dong, Yunzhou

et al.

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Diabetes–associated dysregulated cytokines and cancer

Yong Wu^{1,2,*}, Yanjun Liu³, Yunzhou Dong⁴, and Jay Vadgama^{1,2}

¹Division of Cancer Research and Training, Charles R. Drew University of Medicine and Science, Los Angeles, USA

²David Geffen School of Medicine, University of California, Los Angeles, USA

³Division of Endocrinology, Charles R. Drew University of Medicine & Sciences, UCLA School of Medicine, Los Angeles, USA

⁴Vascular Biology Program BCH3137, Boston Children's Hospital, Harvard Medical School, Boston, USA

Abstract

Epidemiological data demonstrate that patients with diabetes have an augmented risk of developing various types of cancers, accompanied by higher mortality. A number of mechanisms for this connection have been hypothesized, such as insulin resistance, hyperinsulinemia, hyperglycemia, and increased inflammatory processes. Apart from these potential mechanisms, several diabetes-associated dysregulated cytokines might be implicated in the link between diabetes and cancer. In fact, some inflammatory cytokines, e.g. TNF- α , IL-6 and leptin, have been revealed to play important roles in both initiation and progression of tumor. Here, we depict the role of these cytokines in key events of carcinogenesis and cancer development, including their capability to induce oxidative stress, inflammation, their participation in epithelial mesenchymal transition (EMT), angiogenesis, and metastasis. Finally, we will also highlight the existing knowledge in terms of the involvement of these cytokines in different cancer types and comment on potential significances for future clinical applications.

Keywords

diabetes mellitus; cancer; cytokine; angiogenesis; inflammation

Introduction

Diabetes mellitus (DM), the 12th leading cause of death worldwide [1], is a severe and chronic health problem worldwide that disturbs human body's ability to utilize the energy in food. It can be classified into three major types: type 1, type 2, and gestational diabetes. DM can cause serious acute and chronic complications that adversely impact the quality of life

Correspondence to: Yong Wu, Division of Cancer Research and Training, Charles R. Drew University of Medicine and Science, Los Angeles, CA 90059, USA, Tel: (323) 563-4885, Fax: (323) 563-4889; yongwu@cdrewu.edu, yongwu@ucla.edu.

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and survival of the majority of people with this disease. Cancer is the 2nd primary cause of death globally [1]. A growing number of studies demonstrate a positive link between DM and the risk of cancer and cancer-related mortality [2]. Currently, the number of people lives with diabetes worldwide is 250 million and this figure anticipated to reach 380 million in 20 years. Accordingly, one can assume that even a slight increase in the cancer risk associated with diabetes may have significant consequences at the population level.

The association between diabetes and cancer was first hypothesized more than 70 years ago and identified in the 1960s in population-based studies [3]. More recently, a number of studies [4] indicate that some type of cancers develop more frequently in patients with diabetes (primarily type 2 DM), whereas others such as prostate cancer happens less often in patients with diabetes. Diabetes imparts the highest relative risks (about 2-fold or higher) for liver, pancreas, and endometrium cancer, and lower risks (about 1.2–1.5-fold) for colon and rectum, breast, and bladder cancer [3]. Lung cancer does not seem to be associated with an augmented risk in diabetes, and the evidence for kidney cancer and non-Hodgkin lymphoma is indecisive. At present, few studies have investigated links between type 1 DM and cancer [3].

Despite their important clinical significance, the potential biologic links between these two diseases are poorly understood [3,5], which elicits a tremendous challenge for patient care. Some perplexing factors that have common or site-specific relevance make it hard to precisely evaluate cancer risk in patients with diabetes. These factors comprise diabetes duration, diverse therapeutic drugs, variable levels of metabolic control, and the potential existence of chronic complications. Currently, the mainstream view proposes that the relationship may be attributed to the direct effects of diabetes, i.e. hyperglycaemia [3,6] or alterations in fundamental metabolic conditions including insulin resistance and hyperinsulinaemia [3]. Hyperglycemia may contribute to increased cancer risk in diabetes via augmented oxidative stress and DNA damage [7,8]. Studies of the relationship between hyperglycemia and cancer risk have been conducted for a long time, nonetheless the underlying mechanisms remain unconvincing. Insulin is a growth factor with important metabolic and mitogenic actions, and its effect on cancer cells is advanced by multiple mechanisms acting at the receptor or post-receptor levels. Hence, hyperinsulinemia, exogenous insulin or insulin analogs [9-13] most probably favors cancer in patients with diabetes. However, Mink *et al.* [14] found no relationship between insulin levels and breast cancer (BC) incidence. Moreover, Kabat and colleagues demonstrated that baseline levels of insulin and the insulin resistance index do not correlate with an elevated risk of colorectal/ colon cancer [15]. In addition, elevated levels of insulin-like growth factor (IGF), steroid and peptide hormones, and inflammatory markers seem to play an important role in the association between these two heterogeneous and multifactorial diseases [2].

Recently, more and more attention has been given to the role of cytokine dysregulation in cancer initiation and progression. Cytokines are low-molecular-weight proteins synthesized by immune and stromal cells in response to several stimuli [16]. They mediate cell-to-cell communication and control differentiation, proliferation, immune cell activation, cell survival, cell migration, as well as cell death [16]. High blood glucose plays a pivotal role in the immune activation of diabetes, thus intensely enhances circulating cytokine levels via an

oxidative mechanism, and this effect is more prominent in patients with impaired glucose tolerance (IGT) [17]. Esposito *et al.* suggest that the IGT subjects have fasting plasma interleukin 6 (IL-6) and tumor necrosis factor (TNF-) levels much higher than control subjects [17]. A study evaluating the serum levels of cytokines, chemokines and adipokines simultaneously with BioPlex assay by Costantini *et al.* [18] reveals that IL-1 α , IL-2R, IL-12, IL-18, MIF, insulin, leptin, PAI-1, HGF, glucagon, resistin and adiponectin are elevated while ghrelin is declined in T2 DM patients versus healthy controls. TNF- α and IL-6 are possibly the best characterized pro-tumorigenic cytokines. They were originally suspected to be implicated in cancer due to activation of the oncogenic transcription factors NF- κ B, activator protein 1 (AP-1) and signal transducer and activator of transcription 3, also known as STAT3 in epithelial cells [19-22]. Afterwards, numerous other cytokines and stimuli were revealed to have pro-tumorigenic effects. In relation to diabetes-associated cancer initiation and progression, the current review discusses the involvement of dysregulated cytokines under the diabetic condition in carcinogenesis and cancer development, for future therapeutic purposes.

TNF- α and Interleukin-6 (IL-6)

Previous studies have revealed augmented circulating levels of inflammatory cytokines TNF- and IL-6 in patients with diabetes [23-27]. The plasma TNF- and IL-6 are probably produced by activated leukocytes and adipocytes and vascular endothelial cells. TNF- and IL-6 are typical pro-inflammatory cytokines with a pro-tumorigenic effect.

It is well known that unsolved inflammation can result in cancer. TNF- α is a pro-inflammatory cytokine involved in carcinogenesis [28]. Persistent exposure to low concentration of TNF- α can prompt a tumor phenotype [29]. TNF- α facilitates tumorigenesis and cancer development via activating nuclear factor- κ B [30] and increasing reactive oxygen species (ROS) and reactive nitrogen species (RNS) formation, which can trigger DNA damage [31]. TNF- α has more significant impact in the early stage of carcinogenesis, e.g. angiogenesis and invasion [19,30]. Kwong *et al.* incubated normal human ovarian epithelial cells with a sustained TNF- α dose and revealed emergence of a precancerous-like phenotype with structural and functional alterations, including overexpression of cancer markers, tissue disorganization and cell invasion [32]. In addition, persistent TNF- α exposure can promote tumor-forming sphere ability and expression of stem cell-transcription factors, thus inducing cancer stem cell phenotypes in oral squamous cell carcinoma [33].

Raised serum levels of IL-6 can be detected in patients with prostate cancer, colorectal adenomas, breast cancer, B-cell lymphoma, and myeloma [34,35]. IL-6 signaling is an imperative regulator of breast cancer stem cells, driving the malignant phenotype via differentiation and development of therapeutic resistance [36]. In addition, IL-6 strongly stimulates proliferation and growth of various cancer cell lines or primary tumors [37-39]. Notably, it has emerged as a biomarker for distinct inflammatory conditions and also a malignancy predictor, with sensitivity and specificity of approximately 60-70% and 58-90%, respectively [40,41]. Generally, tumor-bearing patients or animals with increased levels of IL-6 in serum or tissue have a poor prognosis [21,42-44]. Diminution of IL-6 signaling

pathway during tumor induction contributes to a reduction in tumor multiplicity and growth [45,46].

IL-6 binds to its receptor IL-6R α and co-receptor gp130 (glycoprotein 130), hence stimulating the JAK/STAT signaling pathway [47]. A number of studies have underlined the role of the IL-6/JAK/STAT pathway in tumor initiation and progression because STATs are transcription factors directly involved in tumorigenic processes [48,49]. Moreover, IL-6 may prompt tumorigenesis by hypermethylating tumor suppressor genes and hypomethylating long interspersed nuclear element-1 (LINE-1) in oral squamous cancer cell lines [50]. In addition, IL-6 converts noncancer cells into cancer stem cells, promoting tumor invasion and expansion. Particularly, Kim *et al.* suggest that noncancer stem cells can secrete IL-6, which activate the IL-6R/JAK/STAT3 pathway, leading to increase in Oct4 gene expression [51].

According to aforementioned studies, IL-6 can be used as a therapeutic target for cancer treatment. Several antibodies against IL-6/IL-6R are presently evaluated in phase I/II clinical trials aimed to develop of therapeutic substitutions. An anti-IL-6 monoclonal antibody, Siltuximab (CNTO 328), has presented hopeful outcomes for ovarian cancer, prostate cancer, non-small cell lung cancer (NSCLC) and multiple myeloma [52-56]. Tocilizumab, a humanized recombinant monoclonal IL-6 receptor (IL-6R) antibody has been analyzed in NSCLC cells by Kim *et al.* Western analyses demonstrated stimulation of the NF κ B pathway by tocilizumab. Their data suggest that tocilizumab has a potent anticancer effectiveness through apoptosis induction, proposing that this anti-IL-6R antibody may be employed as a novel targeting molecule for NSCLC treatment [57].

Leptin

Leptin is an imperative pro-inflammatory cytokine mainly produced by white adipose tissue and implicated in pathophysiological mechanisms associated with diabetes and its complications [58]. Leptin levels are elevated in overweight or obese people [59]. A study examining the link between plasma leptin levels and diabetes mellitus demonstrate that higher plasma leptin concentrations are associated with diabetes mellitus but not independently associated with diabetes mellitus after adjustment for body mass index (BMI) [60]. Leptin can adjust energy homeostasis through modulating food intake and energy expenditure via its effect on the hypothalamus; alternatively, it also induces cell growth, migration, and invasion [61]. Thus, leptin may play an important etiologic role in triggering malignant transformation or tumor development. For instance, preclinical evidence has revealed that leptin stimulates esophageal, colorectal, prostate and breast cancer cell proliferation [62-66] and is responsible for the association between diabetes and prostate cancer [67]. The leptin-receptor might predict poor prognosis in patient with advanced gastric cancer (AGC) [68]. In addition, a pooled analysis from three cohorts by Stolzenberg-Solomon et al. supports an relationship between enhancing leptin levels and pancreatic cancer [69]. The role of leptin in promoting cancer development has also been substantiated by in vivo studies. Actually, leptin-deficient and -resistant mice (ob/ob and db/db mice) do not develop transgene-triggered mammary cancers [70,71].

The mechanisms underlying leptin-related cancer development have been extensively studied. Leptin enhances the synthesis and release of cytokines by macrophages and proangiogenic factors, including fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF), and matrix metalloproteases 2 and 9 (MMP-2/9) [72], which can prompt neoangiogenesis or further promote cancer cells [73]. Leptin has also been shown to significantly augment endothelial cell (EC) growth via a BCL2-dependent mechanism [74-77]. Leptin can elevate estrogen synthesis via activation of aromatase, thus promoting cancer growth in breast and endometrial cancer [78]. Recently, Chang *et al.* demonstrate that leptin stimulates STAT3 and G9a histone methyltransferase to silence miR-200c, a genetic program of epithelial homeostasis in breast cancer stem-like cells (CSC) that induces malignant development [79]. In addition, leptin is able to activate STAT3 in colitis-associated colon cancer (CAC) cells [80-84]. A recent study suggests that leptin can induce EMT in BC cells and this involves IL-8 activation via the PI3K/Akt signaling pathway [85].

Plasminogen activator inhibitor-1 (PAI-1)

Extracellular proteases regulate various physiological and pathological processes, e.g. organ development, inflammation, tissue injury/repair, and cancer [86,87]. The urokinase plasminogen activator (uPA)-plasmin is one of the most explored protease systems [88-90]. The serine protease uPA is activated when binding to its receptor uPAR on the cell surface [91]. The proteolytic activity of uPA is explicitly regulated by plasminogen activator inhibitor-1 (PAI-1), a glycoprotein of roughly 50 kDa, which upon combining with uPA facilitates the swift endocytosis of the trimolecular uPA/PAI-1/uPAR complex [92,93]. PAI-1 is synthesized by vasculature-surrounding cells such as endothelial cells and platelets. Its circulating active form is comparatively unstable. Nevertheless, PAI-1 is stabilized by vitronectin (VN) in blood circulation and extracellular matrix. This abundant glycoprotein is involved in thromboembolic diseases, atherosclerosis, fibrosis, cell migration, cell invasion, cell proliferation, cancer, and tissue remodeling [94]. PAI-1 expression can be regulated by multiple factors, such as TGF- β 1 [95], inflammatory factors [96], lipids [97-100], glucose and insulin [101-103], p53 and the cell cycle [104-106], phorbol ester [107,108], hypoxia [109,110] and cell adhesion [111-114].

In the last two decades, increasing evidence suggests that an elevated level of PAI-1 protein in human primary tumors represents one of the most helpful biochemical markers of an unfavorable prognosis in a number of human cancer types. This observation has given the motivation to substantial research on the role of PAI-1 in cancer growth, invasion, and metastasis [115]. Recently, Buta *et al.* propose that tumor size and PAI-1 can be used in combination as prognostic and predictive phenotypes in node-negative, postmenopausal BC patients bearing histological grade II tumors with ER/PR expression [116]. Positive stroma PAI-1 protein expression in the human epidermal growth factor receptor 2 (HER2)-negative patients is related to lower risk of death, hence it might identify a subgroup of HER2-negative advanced BC patients who may benefit from trastuzumab treatment [117] and can be securely spared the toxicity and expenses of adjuvant chemotherapy [118]. Both PAI-1 and uPA stimulate cancer development and metastasis. Increased uPA and PAI-1 in BC tissue are independent and effective predictors of unfavorable outcome of BC patients, including patients with lymph node-negative disease. Apart from being prognostic

biomarkers, overexpression of uPA and PAI-1 is capable of predicting benefit from adjuvant chemotherapy in early BC patients [118]. In addition, Suh *et al.* demonstrated that upregulation of PAI-1 is associated with aggressive lymph node metastasis in AGC [119].

The first evidence illuminating the link of PAI-1 to more aggressive cancers came from the observation that PAI-1 possesses a proangiogenic property via its anti-protease and vitronectin-binding functions facilitating the detachment of endothelial cells from vitronectin and their movement to fibronectin rich tissues [120,121]. Nonetheless, this angiogenesis activity is dose-dependent with a stimulatory activity at physiologic levels [120,122] and a suppressive activity at pharmacologic levels [123]. PAI-1 hinders spontaneous apoptosis in tumor cells via various mechanisms. It suppresses Fas/Fas-L-mediated apoptosis in a number of human cancer cells via regulating pericellular plasmin activity [124,125]. Moreover, extracellular PAI-1 affects intrinsic (mitochondria-dependent) apoptosis through inhibiting the initiator caspase-9 in cancer cells [126]. Intracellular PAI-1 supports cell survival and protects cancer cells from chemotherapy-triggered apoptosis via suppressing caspase-3 [127].

Since PAI-1 expression is increased in a number of cancer types, it has been anticipated to be a possible target for cancer treatment. However, the role of PAI-1 in tumorigenesis still remains controversial. PAI-1 at physiological level might promote angiogenesis and cancer growth [123,128-132]. Angiogenesis and cancer do not develop under PAI-1-deficient condition [129,133]. Nevertheless, substantial studies suggest that PAI-1 at pharmacological levels hinders cancer growth and angiogenesis [123,128,130,131,134-137]. The suppression of PAI-1 by Tiplaxtinin (PAI-039), a specific inhibitor of PAI-1, or siRNA can inhibit tumor-initiating cells within head and neck cancer cell lines via downregulating the sex-determining region Y-box 2 (Sox2) [138]. Some studies reveal that antibodies against PAI-1 may inhibit human cancer cell metastasis in mouse xenograft models [139-141]. Furthermore, the researchers have screened a number of small molecule PAI-1 inhibitors [142-144], trying to develop some novel cancer therapeutic agents.

Resistin

Resistin, a signaling molecule secreted by adipocytes and monocytes, belongs to cysteine-rich protein family named “resistin-like molecules” [145,146]. It is up-regulated in obesity and participates in the pathogenesis of insulin resistance [146,147], type 2 diabetes [148-150] and metabolic syndrome (MS) [151]. Accumulating evidence shows that resistin plays an imperative controlling role in inflammatory disease [152,153]. Resistin expression at mRNA level is significantly augmented by pro-inflammatory cytokines [154,155]. Clinically, resistin concentrations are related to inflammatory markers obviously independent of BMI and can be used as a predictive factor for coronary atherosclerosis [152,156,157].

Sun et al. [158] and Dalamaga *et al.* [159] demonstrate that patients with breast cancer (BC) have strikingly enhanced resistin levels when compared with control subjects and patients with benign breast lesions (BBL). Additionally, the biological gradient of BC risk by plasma resistin concentrations still exists following adjustment for measurers of adiposity. The dose-

dependent relationship between resistin levels and BC risk is remarkably prominent in female with superfluous exposure to estrogens. Thus, resistin might have an adiposity-independent role in BC pathogenesis. High resistin levels in BC tissue are related to a more malignant pathological status and unfavorable patient survival [160]. Thus, resistin might be potentially employed as a prognosis predictor for BC, a marker for hormone treatment stratification, as well as a possible therapeutic target. Moreover, resistin has been discovered to associate with other cancer types such as prostatic, colorectal, gastroesophageal and endometrial cancer [161-168]. In cancer patients, resistin is dramatically related to tumor markers, cancer stage, tumor size, grade and lymph node invasion [159,169].

Resistin's effects on cancer progression involve multiple mechanisms. Deshmukh *et al.* substantiate that resistin stimulates growth and aggressiveness of BC cells, and these effects are mediated by STAT3 activation [170]. In addition, resistin advances chondrosarcoma metastasis and expression of MMP-2 via activating the AMP-activated protein kinase (AMPK)/p38 mitogen-activated protein kinase (MAPK) pathway and downregulating miR-519d expression. Hence, resistin might represent a latent new therapeutic target in chondrosarcoma metastasis [171]. Hsieh YY *et al.* demonstrate that resistin promotes stromal cell-derived factor-1 (SDF-1) expression by Toll-like receptor 4 (TLR4) and stimulation of p38 MAPK/NF κ B pathway in gastric cancer cells, which could explain a novel role of resistin in the association between obesity and gastric cancer [172].

In addition to aforementioned diabetes-associated dysregulated cytokines, other diabetes-related cytokines involved in cancer initiation and progression include C-X-C chemokine ligand 16 (CXCL16) [173-183], IL-1 [184-187], IL-10 [188-192], IL-12 [193-195], IL-18 [196-198], macrophage migration inhibitory factor (MIF) [199-202], and hepatocyte growth factor (HGF) [203-207].

Concluding comments

Diabetes, especially T2DM, and diabetes risk factors might be related to cancer. Robust and conceivable evidence propose associations between diabetes and cancer; nonetheless, the underlying mechanisms are poorly understood and there is little applicable clinical management of patients presenting with these diseases concomitantly. Accordingly, a multidisciplinary method is required to reveal the mechanisms underlying the links between diabetes and cancer, eventually improve clinical outcomes.

Currently, increasing attention has been given to the role of cytokine in cancer initiation and progression. Diabetes-associated cytokine dysregulation may be an important pathogenesis responsible for diabetes-related cancer. The important role of cytokines has been described, as a diagnostic or prognostic marker for tumor. For instance, the measurement of the serum concentrations of cytokines, e.g. resistin, IL-6 and IL-10, may have guiding significance for tumorigenic process or prognosis [40,208]. While various cytokines prompt carcinogenesis, their pro-tumoral roles rely on the equilibrium of distinct inflammatory mediators and the stage of cancer development. Therefore, investigating the roles of these mediators in various cancers or stages of development is indispensable for designing novel personalized managements by means of these latent therapeutic targets.

Although advancement has been made in the comprehension of the mechanisms of diabetes-associated dysregulated cytokines in tumorigenesis and cancer development, establishing a correlation between cytokines regulation and disease progression, as well as response to treatment still remains a challenge.

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Abbreviations

AGC	Advanced Gastric Cancer
AMPK	AMP-Activated Protein Kinase
AP-1	Activator Protein 1
BBL	Benign Breast Lesions
BC	Breast Cancer
BMI	Body Mass Index
CAC	Colitis-Associated Colon Cancer
CXCL16	C-X-C Chemokine Ligand 16
DM	Diabetes mellitus
EC	Endothelial Cell
EMT	Epithelial Mesenchymal Transition
FGF2	Fibroblast Growth Factor 2
HER2	Human Epidermal Growth Factor Receptor 2
HGF	Hepatocyte Growth Factor
IGF	Insulin-Like Growth Factor
IGT	Impaired Glucose Tolerance
IL-6	Interleukin 6
LINE-1	Long Interspersed Nuclear Element-1

MAPK	p38 Mitogen-Activated Protein Kinase
MIF	Macrophage Migration Inhibitory Factor
MMP	Matrix Metalloproteases
MS	Metabolic Syndrome
NSCLC	Non-Small Cell Lung Cancer
PAI-1	Plasminogen Activator Inhibitor-1
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SDF-1	Stromal Cell-Derived Factor-1
STAT3	Signal Transducer and Activator of Transcription 3
TLR4	Toll-like Receptor 4
TNF	Tumor Necrosis Factor
uPA	Urokinase Plasminogen Activator
VEGF	Vascular Endothelial Growth Factor
VN	Vitronectin