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Hyperglycemia as a mechanism of pancreatic cancer metastasis

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TABLE OF CONTENTS

1. ABSTRACT

As a vital step in the progression of cancer, metastasis poses the largest problem in cancer treatment and is the main cause of death of cancer patients. In pancreatic cancer, almost 80% of patients have locally deteriorated or metastatic disease and thus are not appropriate for resection at the time of diagnosis. Due to the high rate of incidence and mortality, it is crucial to study the molecular mechanisms of metastasis to clarify therapeutic targets to hinder the spread of cancer. Diabetes mellitus has long been considered a potential risk factor for pancreatic cancer. In this review, we comprehensively describe the role of hyperglycemia in governing critical steps of the metastatic process. In particular, we focus on the hyperglycemia-dependent aspects of the Epithelial-Mesenchymal Transition (EMT) and vascular dysfunction. Furthermore, we discuss how hyperglycemia-related production of reactive oxygen species (ROS) may play an important role in these two processes. A deep understanding of metastasis mechanisms will identify novel targets for therapeutic intervention.

2. INTRODUCTION

Distant metastasis, considered as the fatal step in solid cancer progression, is responsible for nearly 90% of cancer-related deaths (1). It is commonly believed that the poor prognosis of pancreatic ductal carcinoma dues to both the inherently aggressive biology of the disease and its late diagnosis in most cases (2). The process of tumor metastasis consists of four pivotal steps (3): first, cancer cells lose cell–cell adhesion, gain mobility and escape from the primary tumor site. Next, cancer cells penetrate the tumor stroma and enter the blood circulation or the lymphatic system via intravasation. Most cells undergo apoptosis due to anoikis conditions (4), however, if cancer cells survive in circulation, they can reach more suitable sites and extravagate from the circulation into the surrounding tissues. Finally, in metastatic colonization, cancer cells form macrometastases in the new host environment.

Several health and environmental factors have been associated with pancreatic carcinogenesis, including

diabetes mellitus (DM). In cancer patients with type-2 diabetes or hyperglycemia, the proportion of tumor recurrence, metastasis or fatal outcome is higher than in patients without metabolic disease (5).

In recent years, epithelial-mesenchymal transition (EMT) has received significant attention in cancer metastasis. Cancer cells undergoing EMT is able to obtain invasive properties and get into the surrounding tissue, leading to the creation of a suitable micro-environment for cancer proliferation and metastasis (6). Here, we highlight the significance of EMT in cancer development and our emerging understanding of its regulation in tumor metastasis. We also present our hypothesis that hyperglycemia is able to enhance pancreatic cancer metastasis by both EMT induction and vascular destruction via oxidative stress.

3. DIABETES AND PANCREATIC CANCER

DM is a very common metabolic disorder of hyperglycemia that eventually affects all systems in the body. There are two types of DM, type-1 and type-2. In adults, type-2 DM accounts for 90%–95% of all diagnosed cases of DM (7). Many studies have demonstrated that DM, especially type-2 DM, is positively associated with an enhanced risk of certain cancers, including pancreatic cancer (8-9). In 2005, a meta-analysis of 17 case–control and 19 cohort studies published between 1966 and 2005 showed that the combined age-adjusted and sex-adjusted odds ratio (OR) for pancreatic cancer associated with diabetes was 1.82 (95% CI, 1.66–1.89) (10). In 2007, another meta-analysis of 6 case–control studies and 3 cohort studies confrmed that a two-fold higher risk of pancreatic cancer was observed in type-1 and young-onset DM patients compared with individuals without DM (95% CI, 1.37–3.01) (11). It is reported that new-onset diabetes (i.e., less than 24 months in duration) has not only been considered as a high-risk group for pancreatic cancer but also a symbol of early, asymptomatic cancer, as patients with new-onset diabetes have a higher probability than the general population that diagnosed with pancreatic cancer afterwards (older patients with new-onset diabetes have an almost eight-times higher risk than the general population) (12). In a recent case–control study, Ben *et al.* (13) demonstrated that a moderate increased risk of pancreatic cancer was discovered among cases with long-standing diabetes (i.e., no less than 24 months in duration), with an AOR of 2.11 (1.51–2.94). Meanwhile, in the cases with new-onset DM, the AOR is 4.43 (3.44–5.72) compared those without DM in Chinese Han people. Diabetes and hyperglycemia have been demonstrated to be independent predictors of mortality from cancer of the pancreas (14-15).

In the recent decades, investigations have revealed that anti-diabetic drugs are able to prevent and treat cancers. Peroxisome proliferator-activated receptor (PPAR)-gamma ligands, as anti-diabetic drugs applied in current clinic, appear to display anti-tumor activities on pancreatic cancer progression (16). As the agonist of PPAR-gamma, thiazolidinediones (TZDs) have been used as anti-diabetic drugs for the treatment of type-2 DM. Accumulating evidence has shown that TZDs can lead to anti-cancer effect in several human cancer cell types through the induction of growth inhibition, apoptosis and inhibition of cell invasion (17-21). Metformin, a drug in the biguanide class of oral hypoglycemic agents, is another widely used anti-diabetic drug in the world (7). It has been demonstrated that metformin usage is associated with reduced cancer risk. The properties of metformin are mediated by activating AMP-activated protein kinase (AMPK), because activated AMPK can not only lower blood glucose levels but also suppress tumor formation and inhibit cell growth (22-23). As a result, PPAR-gamma agonists and metformin may be useful as adjuvant therapies with conventional chemotherapeutics.

It has been proven that hyperglycemia can not only promote proliferation of pancreatic cancer cells (24) but also increase the invasion including perineural invasion in the patients with pancreatic cancer that lead to a poor prognosis (25). Recently, we proved that high glucose (HG) can increase the production of ROS in the pancreatic cancer cell lines BxPC-3 and Panc-1, which further leads to cell motility and invasiveness (26). Hyperglycemia-mediated cancer cell EMT and vascular destruction via oxidative stress may be two vital mechanisms that facilitate cancer metastasis.

4. EPITHELIAL TO MESENCHYMAL TRANSITION (EMT)

The concept of EMT was originally introduced by studies performed on chick embryos more than 40 years ago and was well established in 1982 (27-29). EMT contains three essential processes: first, alterations of cell-cell and cell-extracellular matrix (ECM) interactions occur to make the epithelial cells released from the surrounding tissue. Then the cytoskeleton is reorganized so that the cells can get the ability to move through ECM. In addition, a new transcriptional program is induced to acquire morphological and functional characteristics of mesenchymal-like cells (30-31).

Epithelial structure is maintained by cell-cell interactions which consist of tight junctions, cadherin-based adherens junctions and gap junctions that allow direct chemical interactions between neighboring cells and desmosomes. The cell-cell and cell-ECM contacts are also defined as tissue polarity (32). Epithelial cells are usually polarized in a regulated apical–basolateral pattern. On the contrary, due to the lack of stable cell junctions as well as typical apical–basolateral polarization, many mesenchymal cells usually exhibit high motility (31,33).

Discussions were put forward at a 2007 meeting on EMT in Poland and at a subsequent conference in March 2008 at Cold Spring Harbor Laboratories in order to classify EMTs into three subtypes based on the biological and biomarker context (34). Type 1 EMT occurs during normal physiological processes including implantation, embryogenesis and organ development. Specific expression of transcriptome contributes to phenotypic variants of the cells in our body and further facilitates functional diversity.

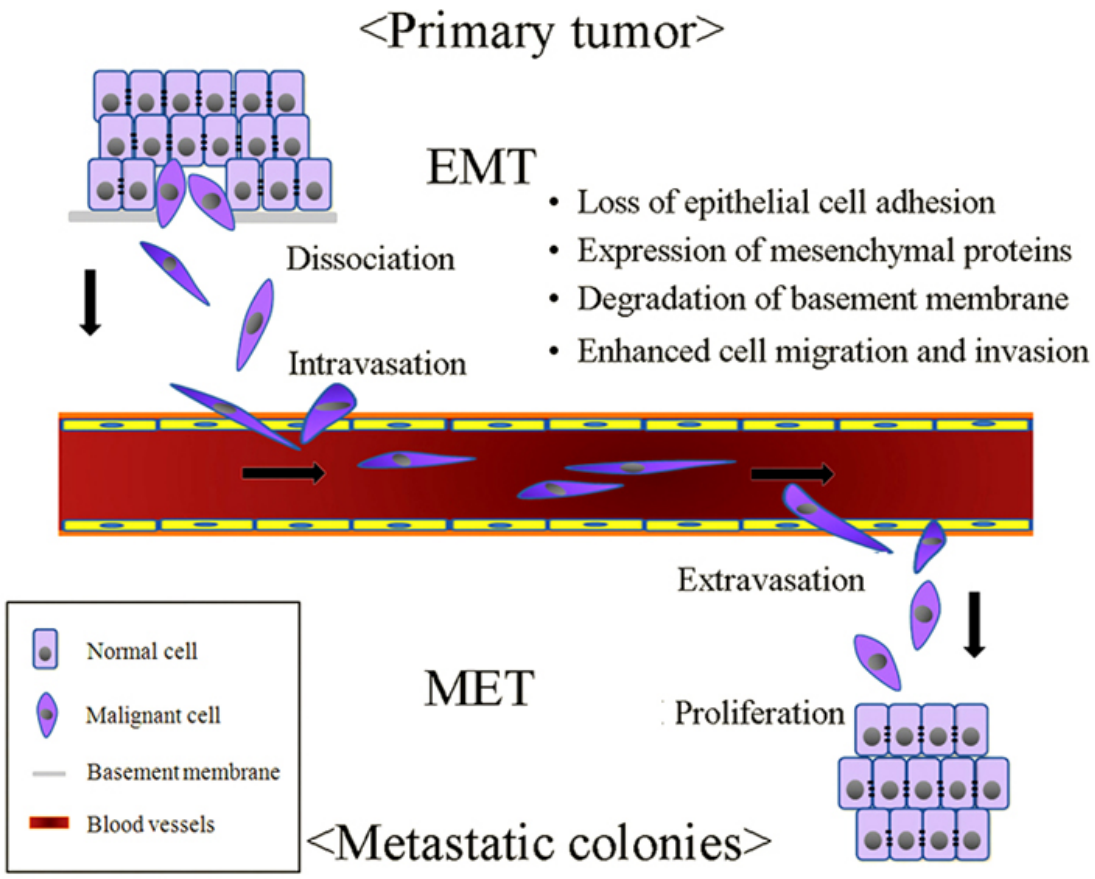

Figure 1. Mechanisms of metastasis. The epithelial–mesenchymal transition (EMT) and mesenchymal–epithelial transition (MET) are involved in cancer metastasis. EMT includes 4 important steps: 1) loss of epithelial cell adhesion, 2) expression of mesenchymal proteins and acquisition of a mesenchymal-like state, 3) degradation of basement membranes and 4) enhanced cell migration and invasion that facilitate tumor cell invasion into stroma and entrance to the circulation. At suitable metastatic sites, cancer cells form the new metastatic foci through MET.

EMT plays an important role in cellular diversity during growth and development (33). Type 2 EMT, associated with wound healing, tissue regeneration and organ fibrosis (31,35) is involved in the generation of fibroblasts concurrent with wound repair to reconstitute tissue integrity. Deregulated form of EMT, also known as type 3 EMT in cancer progression has been detected in both experimental animal models and clinical studies (33,35-37). It is reported that type 3 EMT occurs in genetically and epigenetically modified cancer cells, usually at the invasive front of a tumor mass. Although the three classes of EMTs represent distinct biological processes, they share a common set of genetic and biochemical elements that in turn lead to diverse phenotypic programs (34,38).

5. EMT AND CANCER PROGRESSION

Over the last few years, increasing evidence has shown that EMT plays an essential role in tumor progression (Figure 1). It is believed that aquiring the migratory characteristics of a mesenchymal-like state enhance the invasive capabilities of cancer cells (39). It has been demonstrated that an EMT switch is associated with an unfavourable prognosis in many different types of tumors, such as in pancreas ductal adenocarcinoma (40), gastric cancer cells (41), hepatocellular carcinoma (42-43), esophageal squamous cell carcinoma (44), bladder cancer (45), and lung cancer (46).

A typical symbol of EMT is the loss of the cell-cell adhesion molecule E-cadherin expression and gain of mesenchymal markers (vimentin, fibronectin, alpha-smooth muscle actin and others) (47). As a 120 kDa transmembrane glycoprotein, E-cadherin is involved in calcium-dependent cell–cell adhesion and is bound via catenins proteins to the actin cytoskeleton. While the function of E-cadherin is to maintain the normal intercellular adhesion, loss of its expression has been recognized as a prerequisite for tumor cell metastasis and correlates with tumor grade and stage (48-50).

Several transcription factors including Snail/Slug family (51-53), Twist (54-55), ZEB family (ZEB1, ZEB2) (56-58) and E12/ E47 (59) have been proven to be involved in the transcriptional suppression of E-cadherin and the progression of EMT. Snail is a transcription factor that is

thought to be frequently involved in EMT in various cancers. Snail-induced EMT promotes cancer metastasis utilizing not only the enhanced invasive ability but also induction of multiple immuno-related mechanisms including immunosuppressive cytokines, regulatory T cells, impaired dendritic cells, and cytotoxic T lymphocyte resistance. It has been demonstrated that Snail blockade inhibits both cancer invasion and the multiple immunosuppression at the same time, resulting in efficient inhibition of cancer metastasis (60). Additionally, among the increasing numbers of miRNAs associated with cancer progression, members of the miR-200 family have been specifically shown to play a key role in regulating EMT, because miR-200 family influences the level of ZEB and induces upregulation of E-cadherin in cancer cells which in turn inhibits cell motility (61). Some studies implicate Snail in the initial migratory phenotype of primary tumors, and thus Snail is considered an early marker of EMT. By contrast, Slug, ZEB family members and Twist may be responsible for maintaining migratory cell behavior, malignancy and other oncogenic characters (1).

There are several key molecules and signaling pathways that induce EMT. They consist of the transforming growth factor beta (TGF-beta) superfamily, Receptor Tyrosine Kinases, autocrine factors, and the Notch-, Hedgehog-, Wnt- and NF-kappaB-dependent pathways (62). Of these, TGF-beta was the first EMT inducer described in normal mammary epithelial cells. As a major and best-featured inducer of the EMT phenotype in a variety of biological and pathophysiological condition, it was shown to act by signaling through its receptor serine/threonine kinase complex (63).

Furthermore, the acquisition of EMT characteristic has been involved in drug resistance and could result in recurrence and metastasis after standard drug treatment (64). While silencing of EMT-related genes can partially regain drug sensitivity in resistant cells (65).

It is an interesting observation that cells that have undergone EMT form tumors at secondary sites that resemble the primary tumor, with loss of the mesenchymal phenotype. Returning to a well differentiated epithelial phenotype at the secondary sites where tumor format is also recognized as mesenchymal–epithelial transition (MET). This EMT-MET mechanistic model could play an important part in explaining metastasis of cancer cells: EMT induces the phenotype change from epithelial cells to mesenchymal cells, and then leads to the cancer cells escape from their unfavorable primary sites, while MET reverses these changes and promotes colonization in suitable sites (66-67).

6. EMT AND HG

DM is rapidly becoming a major public health issue (68). In the latest decades, accumulating data and studies have started to appear to examine the relationship between EMT and HG, focusing on diabetic renal injury (69-70) and peritoneal dialysis (71) are well focused. Tubular EMT is known as a highly regulated process that consists of four key steps: 1) loss of epithelial cell adhesion, 2) mesenchymal phenotype gene expression and actin reorganization, 3) basement membrane disruption and 4) enhanced cell migration and invasion (72).

EMT occurs and contributes to the early development and progression of diabetic renal interstitial fibrosis (73). In diabetes, a phenotypic transformation into matrix-producing fibroblasts takes place in renal proximal tubular epithelial cells. In the clinical setting, transitioned epithelial cells are also associated with renal fibrosis and dysfunction (74). Studies showed that the p38 mitogen-activated protein kinase (MAPK) signaling pathway is involved in HG-induced EMT in cultured renal tubular epithelial cells (75). It has been demonstrated that TGF-beta, the most potent inducer of EMT, is elevated in HG-exposed cells (76). In addition, TGF-beta isoforms as well as their receptors are upregulated in both experimental and human diabetic nephropathy (77). Moreover, there is increasing evidence demonstrating that hypoxia (78), also plays a role in the development of renal fibrosis, including via induction of EMT. As a member of the Per-ARNT-Sim family of basic helix-loop-helix transcription factors, hypoxia inducible factor-1alpha (HIF-1alpha) participates in mediating cellular adaptation to hypoxia, which includes promoting fibrogenesis via EMT during hypoxia and such involvement has been shown in both cancer cells (79) and renal epithelial cells (80). Snail has been demonstrated to be upregulated by hypoxia and HG, and in combination the effect is additive (81). Besides, pretreatment with Troglitazone, which is used to treat Type-2 diabetes, inhibits the HG-induced EMT process and protects cells from consequential membrane transport dysfunction through PI3K/Akt, GSK-3beta, Snail, and beta-catenin in primary cultured renal proximal tubular cells (82)

EMT has been discovered in human peritoneal mesothelial cells (HPMC) and it may play an important role in the development and progression of peritoneal fibrosis that leads to peritoneal membrane disfunction (71,83). High concentrations of glucose also induce EMT of HPMC *in vitro*, as determined by decreased expression of E-cadherin as well as increased expression of alpha-SMA, fibronectin, type I collagen and increased cell migration (84). Bone morphogenetic protein-7 (BMP-7) is a 35 kDa homodimeric protein of the TGF superfamily. It is an endogenous anti-fibrotic factor that prevents tissue fibrosis (85-86). Both BMP-7 peptide and transduction with an adenoviral vector of BMP-7 protect HPMCs from EMT. Furthermore, adenoviral-mediated expression of BMP-7 decreased peritoneal EMT and ameliorated peritoneal thickening in an animal model of peritoneal dialysis (84).

As the most widely used anti-diabetic drug in the world, there is increasing evidence showing that metformin also has great potential efficacy in treating cancer (87-88). Non-cytotoxic concentrations of metformin efficiently inhibit a stem cell phenotype by transcriptionally repressing EMT, a stem cell characteristic. Metformin treatment regulates the phenotype of CD44 (pos)CD24 (neg/low) breast cancer stem cells through decreasing expression of key EMT factors including both the transcription factors

ZEB, Twist, Slug and the cytokine TGF-beta (89). Cufi *et al.* (90) recently found the following: 1) metformin treatment enhances expression of the E-cadherin in MCF-7 breast cancer cells; 2) metformin treatment prevents TGF-beta induced loss of MCF-7 membranous E-cadherin; 3) metformin exposure reduces TGF-beta-induced Madin-Darby canine kidney (MDCK) cells morphological alternation to mesenchymal phenotype cells; 4) metformin exposure decreases TGF-beta-promoted cell scattering; 5) treatment with metformin prevents cytoplasmic accumulation of the mesenchymal marker vimentin in TGF-beta-treated MDCK cells significantly. Taken together, these facts suggest that metformin may be useful for treating cancer patients to prevent EMT.

Reactive oxygen species (ROS) play a major role in EMT induced by HG. Antioxidants, N-acetylcystein (NAC) and catalase significantly reverse HG-induced EMT both in HPMC (71) and renal PTCs (82). Interestingly, metformin treatment can restore the antioxidant status, and enzymatic activity in type 2 diabetic patients (91). Although no study yet has shown directly whether HG itself is responsible for cancer EMT, HG is able to promote the production of ROS that could further induce EMT (31). Thus, it is reasonable to hypothesize that HG may trigger EMT in cancer cells. This theory warrants future study.

7. HYPERGLYCEMIA AND OXIDATIVE STRESS

Oxidative stress, also referred to as a ROS-antioxidant imbalance, occurs when the ROS level exceeds the antioxidant capacity (92). ROS include a number of chemically reactive molecules derived from oxygen, such as superoxide anion, hydrogen peroxide, hydroxyl radical, nitric oxide and others. The main physiological functions of ROS are to defend against infection and regulate the activity of transcription factors (93). However, oxidative stress is also involved in the processes of cell death, mutation, chromosomal aberration, and even carcinogenesis (94). In recent years, more and more researchers have proven that hyperglycemia is a direct trigger of oxidative stress (95-97).

A pivotal mechanism leading to oxidative stress in hyperglycemia is the increased formation of ROS by the mitochondrial electron-transport chain (98). Brownlee (99) suggested that increased mitochondrial formation of ROS can be attributed to increased glycolytic production of pyruvate and NADH that further leads to an increase of the mitochondrial proton gradient with excess production of superoxide anion. There are six major pathways that contribute to production of ROS involving glucose: glyceraldehyde autoxidation, PKC activation, glycation, sorbitol metabolism, the hexosamine pathway and oxidative phosphorylation (100). Furthermore, increased ROS production via hyperglycemia is always accompanied by the dynamic change of mitochondrial morphology and by increased fission or decreased fusion to fragment mitochondria. Chronic HG exposure is responsible for a progressive conversion in gene expression, including a decrease in mitochondrial biogenesis. This further interferes oxidative metabolism and increases ROS production, establishing a vicious metabolic cycle that will lead to irreversible organ damage in diabetes (101-102). The main antioxidant enzymes include superoxide dismutase (SOD), catalase and glutathione peroxidase. Antioxidant nutrients (vitamine C and E) and glutathione are the most important non-enzymatic antioxidants (103). Hyperglycemia can attenuate antioxidant enzyme activity and in turn create a state of oxidative stress (104-105). In addition, the thioredoxin system can also regulate cellular redox balance. Thioredoxin reduces ROS through a reversible process in which thioredoxin is oxidized at two cysteine residues (Cys-32 and Cys-35). Afterward, thioredoxin is reduced by thioredoxin reductase and NAPDH (106). As the endogenous inhibitor of thioredoxin, thioredoxin-interacting protein has been proven to be up-regulated significantly under hyperglycemia condition in several different kinds of cells such as aortic smooth muscle cells, fibroblasts, islet cells, mesangial cells, breast cancer cells, HeLa cells, prostate carcinoma cells and others (107-113). Moreover, Glucose-6-phosphate dehydrogenase (G6PD) is one of the major intracellular reductant. HG also inhibits G6PD activity and leads to the production of ROS (114).

8. OXIDATIVE STRESS, CANCER METASTASIS AND EMT

One main feature of a successful cancer is its ability to aquire invasive and migratory ability that further promotes cancer cells to escape from primary site to a more favorable site (115-116). Metastasis of tumor cells is a complicated process that involves not only tumor cells but other cells that produce very high-level ROS, including macrophages, dendritic cells and lymphocytes (117-119). Metastasizing tumor cells that enter the systemic circulation are always suffering increased oxidative stress, by which most of them are severely damaged or even killed (120). However, when ROS levels are not high enough to kill cancer cells, it may be a stimulator of tumor progression by promoting cell proliferation, migration and invasion (121). It has been reported that spontaneous generation of ROS in tumor tissue is positively correlated with clinical stage in small cell lung cancer and squamous cell carcinoma patients (122). Kozuki *et al.* (123-124) showed that ROS potentiate the invasive motility of the rat ascites hepatoma cell line AH 109A in a co-culture system with rat mesentery-derived mesothelial cells. Additionally, investigations have shown that the levels of antioxidant enzymes in many kinds of tumors including human pancreatic carcinoma (125) are low. Moreover, treatment with catalase derivatives significantly reduces the number of metastatic colonies on the surface of the liver, which indicates that the removal of hydrogen peroxide is effective in suppression tumor hepatic metastasis (126). Anti-metastatic effects were also observed using SOD derivatives in a spontaneous pulmonary metastasis model (127). We have previously demonstrated that hyperglycemia can increase the invasiveness and migration of the human pancreatic cancer cell lines BxPC-3 and Panc-1 via the production of ROS (26).

In recent years, an increasing number or researchers have focused on the role of ROS in EMT-related cancer metastasis. The study of Mori *et al.* (128)

first established a direct link between extracellular generation of ROS and EMT. In their study, normal mouse mammary gland epithelial cells (NMuMG cells) were exposed to a low dose of hydrogen peroxide for periods of 2 to 4 days. A phenotypic conversion of mouse NMuMG mammary epithelial cells from an epithelial to a fibroblast-like phenotype was observed, which was associated with the dissolution of cell-cell contacts, redistribution of E-cadherin in the cytoplasm, and up-regulation of a set of integrin family members and matrix metalloproteinases (MMPs). Chronic hydrogen peroxide treatment also resulted in persistent activation of ERK1/2, p38 MAPK and the small GTPase Rac1; moreover, the treatment was sufficient to induce increased invasiveness of NMuMG cells in a reconstituted model system.

Recently, ROS and changes in redox homeostasis have been implicated in the activation of EMT in several cancer models. TGF-beta signaling is involved in a large majority of cellular processes including EMT. It has been reported that TGF-beta1 can increase dichlorofluorescein-sensitive cellular ROS, ERK1/2 and p38 MAPK, increase alpha-SMA expression and fibronectin secretion and decrease E-cadherin expression. Antioxidants effectively inhibit TGF-beta1 induced cellular ROS, ERK, p38 MAPK and EMT. Hydrogen peroxide can reproduce nearly all of the effects of TGF-beta1 (129). A new study showed that the synthetic glucocorticoid dexamethasone can inhibit transforming TGF-beta1-induced EMT through suppression of ROS generation (130). MMPs have been considered important factors in triggering EMT in recent years. Rac1 isoforms are usually believed to be involved in the regulation of ROS generation by the NADPH oxidase complex. Radisky *et al.* (131) proved that MMP-3 is able to induce the expression of an alternatively spliced form of Rac1, which causes an increase in cellular ROS and in turn leads to increased expression of the transcription factor Snail and EMT. The antioxidant agent N-acetylcysteine (NAC) effectively inhibited MMP-3-induced EMT. Hypoxia is a common feature of many cancers that contributes to tumor progression and compromises tumor cell death by radiotherapy and chemotherapy (132). Recently, Cannito *et al.* (133) suggested that hypoxic conditions can trigger an EMT program in many different kinds of human cancer cells, including in the pancreatic cancer cell line Panc-1. Cancer cells respond to hypoxia by a series of changes such as fibroblastoid phenotype, Snail nuclear translocation and changes in E-cadherin. The increased generation of ROS by mitochondria of hypoxic cells has been correlated with early and transient inhibition of glycogen synthase kinase-3beta and nuclear translocation of Snail. These findings suggest that early redox mechanisms can activate the switch for hypoxia-dependent acquisition of EMT characteristics. Taken together, these observations suggest that ROS play an important role in EMT progression.

9. DIABETES AND VASCULAR DESTRUCTION

It has been widely known that diabetes vasculopathy includes microvascular as well as macrovascular diseases, the former of which is the main cause of the cardiovascular and cerebral vascular incidents, while the latter is the essential pathological basis of many crucial chronic complications such as diabetic nephropathy, diabetic retinopathy and diabetic peripheral lesion (134). Extensive research during the past several decades has revealed the mechanism by which continued hyperglycemia or diabetes can lead to vascular dysfunction, which in turn could bring about serious consequences including cancer, and cardiovascular, neurological, and pulmonary diseases. Hyperglycemia promotes vascular complications through various mechanisms and formation of advanced glycation end products and increased oxidative stress have been proposed to contribute to both macrovascular and microvascular diseases. Many of the earliest pathologic responses to hyperglycemia are manifest in the vascular cells that become aware of elevated blood glucose levels directly. In the macrovasculature, these contain endothelial cells and vascular smooth muscle cells. In the microvasculature, these contain endothelial cells, pericytes (in retinopathy), and podocytes (in renal disease) (135).

Endothelial cell dysfunction plays an important role in the development of diabetic microvascular as well as macrovascular diseases (136-137) and it is considered to be an early marker of such vascular complications in DM patients (138-139). A number of mechanisms, including increased cytokine, ROS production and the glucose-specific effects (140-142) contribute to the changes in endothelial cell growth that occur in response to hyperglycemia condition. Evidence shows that endothelial cells exposure to HG triggers apoptosis (143-144), suggesting that endothelial cell apoptosis may be one of the important mechanisms of endothelial dysfunction in diabetes. Previous studies have demonstrated that significant alterations appear in cell growth and cell death while exposed to HG. Particularly, HG reduces human endothelial cell proliferation with a concomitant increase in apoptosis (145-146). With endothelial cell dysfunction, diabetes further impairs vascular endothelium cell structure, leading to endangium damage and increased thrombin and endothelin in the vasculature. Ultimately, this will result in permanent microvascular contraction and blood vessel luminal stenosis (147).

Hyperglycemia is known to increase endothelial cell permeability. There is increasing evidence demonstrating that endothelial cells and the basement membrane as well as endothelial cell production of basement membrane proteins can be altered in the presence of HG (148). Endothelial cells and the basement membrane operate as an integrated co-regulatory unit. Cells produce basement membrane proteins, which further lead to subsequent cell-signaling regulation (149). Morss *et al.* (148,150) showed that exposure to HG enhances basement membrane permeability to a biologically active factor, and linked hyperglycemic changes in endothelial cell function, especially apoptosis and permeability, to an alteration in basement membrane cytokine storage. Increased permeability *in vivo* is known to be related to arterial albumin, fibrinogen, and low density lipoprotein cholesterol deposition. Glucose-induced permeability alters basement membrane and vascular wall FGF-2 content

(151). The basement membrane size and composition in both the micro- and macrovasculature is changed in diabetes (152).

Hyperglycemia, as a primary cause of vascular complications in diabetes, shows the similar pathological characteristics as diabetes microvascular disease. Early in the disease, some alterations including swollen vascular endothelial cells, deficient smooth muscle cells and increased vasopermeability occur. In the later stage, exacerbated changes appear such as blood vessel basement membrane thickening, vascular paramorphia and dysfunction, as well as abnormal growth of new vessels and poor function, leading to endothelial dysfunction and reduced new blood vessel growth (153-155). Exposure to HG induces angiogenesis in a pathological manner (156). Most solid tumors develop a pathophysiologic microenvironment that is characterized by an irregular microvascular network and blood flow patterns (115,157). The well-balanced microenvironment where angiopoiesis takes place has been broken down under most pathological state including hypoxia and hyperglycemia and subsequently results in a series of changes in vasculature. Despite the variety of metabolic and stress effects and extracellular signals induced by HG, the endothelial cell growth response is largely consistent across vascular beds (158). The MAPK have been shown to play a key role in mediating cell growth and responses to stress mentioned above (159).

As shown previously, there are increasing studies suggesting that ROS and the resulting oxidative stress may play a pivotal role in HG-induced apoptosis (160). Recent findings demonstrated that endothelial cell apoptosis induced by high-glucose is mediated by ROS (141) and antioxidants (161). High-glucose-induced apoptosis can be attenuated by inhibiting ROS generation in human endothelial cells (143,161). Hyperglycemia has been known to induce oxidative stress, inhibits cell proliferation and induces vascular endothelial cells apoptosis (143,145,162). ROS production is increased in patients with diabetes, which could contribute to the generation and development of vascular complications (155,163). Moreover, oxidative stress has been shown to play a key role in endothelial cell death in diabetic retinopathy (164). It has been demonstrated that antioxidants and the inhibition of nitric oxide production decrease diabetes- and HG-induced retinal endothelial cells apoptosis (165). Additionally, a caspase-independent mechanism is found in HG-induced apoptosis in retinal neural cells (166). Under diabetic conditions, the ROS generated from the glucose metabolism will interfere with PI3K/Akt protein kinase B in the insulin signaling pathway, decreasing NO production. Meanwhile, more NO is consumed when it reacts to ROS, damaging the vascular endothelium dependent relaxation (167). Additionally, an abundance of ROS restrains IRS1 and S2 signal transduction and reduces Akt (protein kinase B) production, which will further induce smooth muscle contraction. HG can directly/indirectly influence smooth muscle cells structure and function (168). In conclusion, oxidative stress acts as a bridge to link hyperglycemia and vascular destruction.

10. CONCLUSIONS AND FUTURE PERSPECTIVES

Metastasis, as an important feature of malignant tumors, is a “hidden” event inside the body that is difficult to discover. It is believed to consist of four steps: invasion, intravasation, extravasation, and metastatic colonization. In recent years, two broad mechanisms for metastasis have received significant attention: epithelial-to-mesenchymal transition (EMT) and angiogenisis. Diabetes mellitus, a risk factor for pancreatic cancer, has an intimate relationship with both EMT and angiogenesis. On one hand, hyperglycemia is able to trigger EMT and enhance cell migration and invasion. On the other hand, hyperglycemia can induce vascular endothelial cell apoptosis, increase endothelial cell permeability and lead to angiopoiesis in a pathological way, which may create suitable conditions for tumor metastasis. ROS levels are also considered to be closely linked to the accelerated formation of metastasis. It is thought that metastasis facilitated by diabetes mellitus may be mediated by ROS. Managing hyperglycemia or inhibiting the production of ROS may prevent tumor recurrence not only locally but also at distant sites. New discoveries will elucidate the relationship between DM and cancer EMT and hold great promise for yielding novel therapeutic approaches for treating cancer.

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Abbreviations: EMT: epithelial-mesenchymal transition, MET: mesenchymal–epithelial transition, ROS: reactive oxygen species, DM: diabetes mellitus, HG: high glucose, PPAR-gamma: peroxisome proliferator-activated receptor gamma, TZDs: thiazolidinediones, ECM: cell-extracellular matrix, TGF-beta: transforming growth factor beta, AMPK: AMP-activated protein kinase, MAPK: mitogen-activated protein kinase, HIF-1alpha: hypoxia inducible factor-1 alpha, BMP-7: bone morphogenetic protein-7, MMPs: matrix metalloproteinases, NAC: N-acetylcystein, SOD:superoxide dismutase

Key Words: Metastasis, Hyperglycemia, Diabetes mellitus, Oxidative stress, Epithelial-mesenchymal transition, Angiogenesis, Pancreatic cancer, Review

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