**Name of Journal:** *World Journal of Gastrointestinal Oncology*

**Manuscript NO:** 68162

**Manuscript Type:** REVIEW

**Diabetes mellitus contribution to the remodeling of the tumor microenvironment in gastric cancer**

Rojas A *et al*. Diabetes and tumor microenvironment

Armando Rojas, Cristian Lindner, Iván Schneider, Ileana Gonzàlez, Hernan Araya, Erik Morales, Milibeth Gómez, Nelson Urdaneta, Paulina Araya, Miguel Angel Morales

**Armando Rojas, Cristian Lindner, Iván Schneider, Ileana Gonzàlez, Erik Morales, Paulina Araya,** Biomedical Research Lab., Medicine Faculty, Catholic University of Maule, Talca 34600000, Chile

**Hernan Araya, Milibeth Gómez, Nelson Urdaneta,** Department of Clinical Sciences, Medicine Faculty, Catholic University of Maule, Talca 34600000, Chile

**Hernan Araya, Milibeth Gómez, Nelson Urdaneta,** Servicio de Oncología, Hospital Regional de Talca, Talca 34600000, Chile

**Erik Morales,** Servicio de Anatomía Patologica, Hospital Regional de Talca, Talca 34600000, Chile

**Miguel Angel Morales,** Department of Molecular and Clinical Pharmacology Program, Institute of Biomedical Sciences, University of Chile, Santiago 8320000, Chile

**Author contributions:** All authors contributed to the original ideas and writing of this paper; Rojas A designed the report and wrote the paper; Lindner C contributed art-work and data acquisition, drafting and revising the manuscript; Schneider I, Gonzàlez I, Araya H, Morales E, Gómez M, Urdaneta N, Araya P and Morales MA contributed data acquisition, drafting and revising the manuscript.

**Corresponding author: Armando Rojas, PhD, Full Professor,** Biomedical Research Lab., Medicine Faculty, Catholic University of Maule, 3605 San Miguel Ave., Talca 34600000, Chile. arojasr@ucm.cl

**Received:** May 13, 2021

**Revised:** June 10, 2021

**Accepted: October 27, 2021**

**Published online:**

**Abstract**

Compelling pieces of evidence derived from both clinical and experimental research has demonstrated the crucial contribution of diabetes mellitus (DM) as a risk factor associated with increased cancer incidence and mortality in many human neoplasms, including gastric cancer (GC). DM is considered a systemic inflammatory disease and therefore, this inflammatory status may have profound effects on the tumor microenvironment (TME), particularly by driving many molecular mechanisms to generate a more aggressive TME. DM is an active driver in the modification of the behavior of many cell components of the TME as well as altering the mechanical properties of the extracellular matrix (ECM), leading to an increased ECM stiffening. Additionally, DM can alter many cellular signaling mechanisms and thus favoring tumor growth, invasion, and metastatic potential, as well as key elements in regulating cellular functions and cross-talks, such as the microRNAs network, the production, and cargo of exosomes, the metabolism of cell stroma and resistance to hypoxia. In the present review, we intend to highlight the mechanistic contributions of DM to the remodeling of TME in GC.

**Key Words:** Diabetes mellitus; Gastric cancer; Tumor microenvironment; Hyperglycemia; Chronic inflammation

Rojas A, Lindner C, Schneider I, Gonzàlez I, Araya H, Morales E, Gómez M, Urdaneta N, Araya P, Morales MA. Diabetes mellitus contribution to the remodeling of the tumor microenvironment in gastric cancer. *World J Gastrointest Oncol* 2021; In press

**Core Tip:** Compelling shreds of evidence support that diabetes mellitus (DM) is a crucial risk factor in human cancers. Due to its contribution to systemic inflammation, DM can sculpture the gastric tumor microenvironment through different mechanisms, which in turn, may generate highly malignant phenotypes in gastric cancer. We herein discuss the contribution of DM in the remodeling tumor microenvironment in GC, which may then leads to more aggressive tumor phenotypes.

**INTRODUCTION**

At present, a compelling body of evidence suggests that diabetes mellitus (DM) patients have not only increased incidence but also worse outcomes when they develop malignant neoplasm, especially those originating from gastrointestinal (GI) organs, such as the pancreas, colon, liver, and stomach[1].

Gastric cancer (GC) is the fifth most common cancer and the fourth most common cause of cancer death globally, with a poor 5-year survival < 20% for advanced stages[2].

Strikingly, data from different epidemiological data suggest that DM and chronic hyperglycemia may even increase the risk and mortality of GC patients[3,4]. Although there is compelling clinical data supporting this association, the molecular mechanisms underlying this association are not fully understood.

DM is considered a systemic inflammatory disorder[5], which triggers a dysregulated metabolism, and is characterized by sustained hyperglycemia[6]. However, the systemic pro-inflammatory effects induced by DM are not only mediated by chronic hyperglycemia but also enhanced by insulin resistance[7]. All these features drive critical modifications in extracellular elements such as ECM and favor the dysregulation of many intracellular signaling pathways[7-9].

Furthermore, DM not only interferes in intercellular communication increasing the biogenesis of exosomes but also altering the delivery of biomolecules to recipient cells and favors a pro-angiogenic and proliferative cross-talk between stromal cells, which could act as a key element in defining the fate of tumor development in these patients[9].

A crucial role in the tumor biology of gastric carcinoma plays the complex network established between cellular and non-cellular elements that composed the tumor microenvironment (TME), which drives the cancer cell fate and plays a critical role in the initiation, progression, and immune evasion[10].

A growing body of evidence suggests that these TME remodeling mechanisms can be crucial in favoring the development of highly malignant phenotypes in DM patients who develop GC[5,11].

In the present review, we intend to highlight the different mechanisms of the contribution of DM to the remodeling of TME in GC, which leads to more aggressive tumors.

**EPIDEMIOLOGICAL ASSOCIATION**

DM is considered an established risk factor for either higher incidence and increased long-term all-cause mortality rates in many cancer types[12,13], especially for those originating in the digestive tract[14,15].

Although several observational studies have demonstrated a controversial association between DM and CG[4,16] or restricted only to gender differences[17] a growing body of evidence including both meta-analyses of wide-population cohorts and case-control studies demonstrate an increased risk and mortality of GC in DM patients[3,18-21].

Furthermore, a recent study with a prospective endoscopic follow-up shows that DM is an independent risk factor for GC[3]. Noteworthy, this positive association remains significant even in patients who only present pre-diabetes and hyperglycemic events[22,23].

Additionally, several reports suggest that DM and hyperglycemia are not only associated with a higher incidence of GC but also increased mortality [21,24-26], and may even lead to drug resistance and tumor progression in GC patients[27-29].

At present*, Helicobacter pylori* (*H. pylori*) colonization is a crucial risk factor in the pathogenesis of GC. *H. pylori* infection leads to chronic inflammation of gastric mucosa and then leads to atrophy of the glands, intestinal metaplasia, and GC[30]. In 1994, *H. pylori* was classified as a Group 1 carcinogen by the International Agency for Research on Cancer[31].

Noteworthy, recent reports have not only demonstrated an association between DM and incidence of *H. pylori* infection[32-34] but also, as a higher risk of failure in eradication therapy[35-37]. Furthermore, sustained hyperglycemia influences the expressions of several *H. pylori* virulence factors, leading to promote carcinogenesis[38].

During the last decade, a growing body of evidence has shed light on the mechanisms underlying this epidemiological association (Figure 1).

**THE CONTRIBUTION OF DM IN REMODELING THE TME IN GC**

***Changing stroma cells behavior***

The TME is a complex tissue niche with a diverse repertoire of infiltrating host cells, mainly recruited by cancer cells, together with many secreted factors and components of the extracellular matrix, which profoundly influence tumor growth, and dissemination[39].

A convincing body of evidence supports that chronic inflammation caused by *H. pylori* infection is the major risk factor for the development of GC, and thus various types of cells in the gastric mucosa are exposed to an inflammatory environment for long periods. The robust inflammatory response triggered by infection, together with bacterial and host factors determines the transit from the early stages of inflammation through the development of metaplasia, dysplasia, and finally to invasive carcinoma[40].

In the GC microenvironment, the behavior of many cell types of the tumor stroma is influenced by diabetes or hyperglycemia. Noteworthy, all cellular components of tumor stroma express the receptor of advanced glycation end products (RAGE), including tumor cells, and a growing body of pieces of evidence supports the role of the RAGE/advanced glycation end products (AGEs) (RAGE/AGEs) axis on tumor growth. This important modifier of the TME will be covered in the cell signaling disturbances section.

Gastric epithelial homeostasis is maintained by long-lived stem cells surrounded by a supportive niche. Therefore, GC may arise from mutated stem cells that have been accumulating gene mutations during cell half-life, and the subsequent expansion of mutated clones[41]. In this context, the chronic inflammation induced by *H. pylori* infection may then damage gastric epithelial mucosa, followed by the recruitment of bone marrow-derived cells (BMDCs), which may then lead to tissue remodeling, transformation, and potential progression to malignancy[42].

Of note, the diabetic condition has been described to force BMDCs to express tumor necrosis factor-alpha (TNF-α) and thus they become a contributor to fuel inflammation instead of repairing the damaged gastric mucosa[43]. Tumor-associated mast cells are also part of the cell stroma in GC[44]. These infiltrating cells play crucial roles in remodeling the TME[45], by the release of large amounts of preformed and pre-activated inflammatory mediators through degranulation, and supporting tumor progression, immunosuppression, and angiogenesis[46,47].

Hyperglycemia and advanced glycation end-products are known to activate mast cells and increase the expression of proinflammatory cytokines such as TNF-α and favor the degranulation of mast cells[48].

Cancer-associated fibroblasts (CAFs) are prominent components of the TME, and play important roles in GC, such as tumor growth and progression, matrix remodeling, promoting angiogenesis as well as fueling inflammation[49].

CAFs are crucial cells in the production of a desmoplastic stroma, characterized by the formation of dense fibrosis and increased remodeling and deposition of ECM components. CAFs not only produce fibrillar collagens and other interstitial ECM components but also release matrix metalloproteinases[49,50].

Of note, desmoplasia is commonly found in patients with diabetes, where the hyperglycemic condition activates fibrogenic pathways, not only through direct stimulation of the synthesis of ECM components but also by triggering epithelial and endothelial cell conversion to a fibroblast-like phenotype[51].

Cancer cells can recruit and activate fibroblasts in the TME by the induction of their trans-differentiation into CAFs. Recently, the serine/threonine homeodomain-interacting protein kinase 2, has been reported as a crucial regulator of this process, and its downregulation favors tumor progression[52]. Noteworthy, hyperglycemia produces a sustained degradation of this protein[53] and thus favoring the transdifferentiating process.

CAFs play an important role in the progression of GC, by promoting migration and epithelial to mesenchymal transition (EMT) of GC cells, and EMT is fully potentiated by hyperglycemia[54].

Tumor-associated macrophages (TAMs) are crucial cells in sculpturing the TME[55,56]. Furthermore, TAMs have a prognostic significance for GC patients, when combined with the TNM staging system[57].

TAMs are crucial cells in tuning the machinery of inflammatory and host immune responses in TME. Once infiltrated, macrophages undergo a polarization process rendering distinct functional phenotypes, and where classically activated (M1) and alternatively activated (M2) macrophages represent two extreme phenotypes[55,58]. In GC, TAMs are predominantly bearing an M2 phenotype, which is associated with cancer metastasis and a worse prognosis in patients[56-59].

During diabetes, macrophages and other innate immune cells are known to have a pro-inflammatory phenotype, which is believed to contribute to the pathogenesis of various diabetic complications[60]. Noteworthy, hyperglycemia acts in synergy with hypoxia and sensitizes macrophage responses to cytokine stimuli[61], and generates particular M1/M2 cytokine profiles[62].

Recently, hyperglycemia is reported to induce an increased flux through the hexosamine biosynthetic pathway in TAMS resulting in an upregulation of O-GlcNAcylation, which in turn favors the alternative M2 polarization of TAMs and reduced anti-tumor immunity[63].

Tumor-infiltrating neutrophils are very abundant in the GC microenvironment, where they promote GC cell migration and invasion as well as the induction of EMT through the interleukin (IL)-17-mediated JAK2/STAT3 signaling activation, indicating that neutrophils may play an important role in GC metastasis[64,65].

Hyperglycemia is reported to impair granulocyte-colony stimulating factor secretion, thereby hindering the mobilization of antitumor neutrophils, which in turn, leads to increased survival of disseminated tumor cells and consequently increasing the metastatic burden[66].

Obesity is a common comorbidity of diabetes, and some authors have associated obesity with an increased risk of GC[67]. Obesity can impact the TME both locally, and systemically through many signals associated with visceral adipose tissue inflammation, as reported for adipokines, growth factors, and cytokines[68,69]. In this context, the activation of the STAT3 gastric signaling pathway, which is crucial in promoting the malignant transformation of epithelial cells[70], is induced by leptin and IL-6 in obese subjects[71,72].

***Modification of extracellular matrix***

ECM is known to be a complex non-cellular network composed mainly of glycosaminoglycans and fibrous proteins, such as collagens, fibronectin, elastin, and laminin, which give structural support to tissues and regulate diverse cellular functions such as survival, growth, migration, adhesion, and differentiation[73].

During these cellular-ECM interactions, a complex network of signaling pathways is activated through mechanotransduction receptors, which are capable of sensing changes in the stiffness of the ECM[74,75]. At present, ECM is considered a highly dynamic element that continuously undergoes remodeling induced by several conditions[76].

Compelling evidence support that tumor-associated ECM remodeling and stiffening, are key elements behind the TME of highly invasive phenotypes of several neoplastic cells[77-79]. Strikingly, tumor-associated ECM remodeling and the subsequent stiffening play a critical role in the behavior of cancer cells in the TME[80], and thus, supporting cancer cell survival, progression, and metastatic invasion[81].

Fibronectin and type I collagen are the most common and abundant fibrillar ECM proteins found in cancer-associated ECM[82,83]. Their increase is a result of excessive fibrotic remodeling, also referred to as desmoplasia, which is largely mediated by alpha-smooth muscle actin-expressing myofibroblasts[83,84].

Most ECM fibrous proteins are long-live potential targets for the higher rate of AGEs formation observed in DM and chronic hyperglycemic-state[85]. AGEs cross-links of load-bearing protein lead to ECM stiffening which favors not only tumor cell survival, but also high rates of proliferation, and metastatic cancer cell interaction with the endothelium[86,87].

Furthermore, the chronic hyperglycemia state not only mediates mechanical changes in ECM but also can generate a reservoir of AGEs with the potential to trigger a multitude of RAGE-dependent mechanisms[85].

In addition, *in vivo* studies support that these posttranslational modifications of ECM produced during hyperglycemia also favor cancer cell invasion by activation of mechanotransduction-dependent epidermal growth factor receptor (EGFR) signaling pathway[88,89]. The interplay between highly glycated-ECM and increased EGFR activity could be a key element in the enhanced cancer cell invasion in DM patients.

In this context, lysyl oxidase (LOX) plays a central role in modulating the formation of molecular cross-linkages of ECM components[90]. LOX is known to play a significant role in the GC microenvironment[91]. Interestingly, the DM milieu favors the overexpression of LOX[92], which is associated with increased ECM modifications and high invasion activity of GC in DM patients[93,94].

***Cellular signaling disturbances***

One of the earliest pieces of evidence supporting that DM represents an active landscape for cellular signaling disturbances, coming either from the complex network of mechanisms underlying diabetes complications and the altered insulin sensitivity observed in obesity and type 2 diabetes[95,96].

At present, a growing body of evidence supports that the hyperglycemic condition can activate different signaling mechanisms, such as the polyol pathway, the advanced-glycation end-product formation, and the subsequent activation of the RAGE/AGEs axis, as well as the activation of Protein Kinase C and hexosamine pathway. All these activated pathways may then lead to the over-expression of reactive oxygen species (ROS), activation of the transcriptional factors nuclear factor-κappa beta, and consequently the increased production of proinflammatory mediators, the activation of leukocytes, as well as increased apoptosis, and a desmoplastic reaction[97,98].

These pro-inflammatory signaling pathways have supported the new concept called meta-inflammation, which is characterized by a low-grade systemic and chronic inflammation and is associated with the pathogenesis of diabetic complications[99,100].

Hyperglycemia results in calpain-1 upregulation in the mitochondria, which in turn leads to a reduction in ATP synthase activity and increased mitochondrial ROS formation[101]. Mitochondrial ROS is crucial for the stabilization of hypoxia-inducible transcription and thus leading to an activation of a transcriptional profile supporting tumor angiogenesis[102]. Additionally, ROS is a well-known driver of myofibroblast differentiation, through the activation of the TGF-B pathway[103], and myofibroblasts are recognized as a major source of the CAFs[104].

Chronic hyperglycemia is the hallmark of DM. This condition leads to an accelerated formation of AGEs, a heterogeneous group of compounds resulting from the non-enzymatic reaction of reducing sugars with the free amino group of proteins lipids and nucleic acids[105].

The high rate of AGEs formation in DM patients favors the overexpression of RAGE, and the hyperactivation of the RAGE/AGE axis[98,106,107]. This receptor is involved not only in the adhesion of H. pylori to gastric epithelial cells but also in the inflammatory response to infection[108].

The activation of this signaling pathway is an important contributor to inflammation-related tumorigenesis through different signaling mechanisms, including the resistance to apoptotic insults and hypoxia, interfering with antitumor immunity, stimulating angiogenesis, and supporting invasiveness[109].

Interestingly, hyperglycemia can disturb cell cycle regulation not only in normal cells[110] but also in cancer cells[111]. High levels of glucose and insulin are reported to enhance cyclin D, cyclin-dependent kinase 4 (Cdk4), and Cdk2 expression and suppress cyclin-dependent kinase inhibitors p21 and p15/16[112].

On the other hand, the protein O-linked β-N-acetylglucosamine (O-GlcNAc) modification is a dynamic post-translational modification affecting a wide variety of proteins involved in cell cycle regulation, and this modification is considered as a major contributor to the deleterious effects of hyperglycemia[113]. This post-translational modification relies on the addition of a single N-acetyl-glucosamine molecule to the OH residues of serine or threonine by the action of the O-GlcNAc-transferase, and where some oncogenic factors, such as p53, Myc, and β-catenin, as well as other cell cycle regulators are O-GlcNAcylated[114,115] and is increased in many human neoplasias, including GC[116,117].

A growing body of evidence supports the role of the Wnt/β-catenin pathway in the development, progression, and metastasis of GC[118,119]. High glucose levels can produce profound effects on Wnt/β-catenin signaling in cancer cells, leading to an increased expression of WNT target genes[120] by either a sustained increment of the p300 acetyltransferase activity or decreased sirtuin 1 deacetylase activity. In this way, hyperglycemia renders high levels of β-catenin acetylation, which in turn, allows nuclear accumulation and transcriptional activation of Wnt-target genes[121].

An overactive TGF-β1 signaling pathway has been reported in diabetes patients[122] and its role as a critical profibrotic factor in the progression of chronic kidney disease in diabetes is widely documented[27,123]. The role of TGF-β in the biology of GI cancers has been extensively studied showing crucial roles in regulating processes such as tumor progression, evasion of growth suppressors, and resistance to cell death, angiogenesis, invasion, and metastasis[124].

TGF-β1 is overexpressed in GCs and the stromal tissues surrounding the cancer cells[125,126]. The main source of TGF-β1 is stromal cells, such as fibroblasts, lymphocytes, and macrophages[127], and therefore, the coexistence of the burden due to diabetes reinforces its impact on the TME.

Another key element in the signaling network in the gastric TME is the EGFR family, which consists of four related receptor tyrosine kinases (ErbB1 to ErbB4)[128], and all members of the family are expressed in gastric tumors[129].

On the other hand, diabetic kidney disease is a common microvascular complication of DM and the leading cause of end-stage renal disease[130]. Activation of the EGFR signaling pathway is linked to the onset and progression of renal damage in DM, by promoting cell proliferation, inflammatory processes, and ECM modification[131]. Interestingly, these signaling pathways can be activated by several ligands, but also by other biological mediators such as ROS, TGF-β, and PKC, all of which are upregulated in DM[122,132,133].

The COX-2/PGE2 signaling pathway plays a critical role in the inflammatory nature of gastric tumors. COX-2 is upregulated in GC and its precursor lesions, and it provides valuable clinical information as a prognostic factor[134]. Of note, the high levels of COX-2 expression are an earlier event reported during the *H. pylori* infection of gastric mucosa[135].

Many PGE2-mediated mechanisms supporting tumor growth, new vessel formation, and enhancing metastasis have been described[136]. Additionally, COX-2 /PGE2-mediated signaling pathways are key contributors to many diabetes complications[137,138].

Noteworthy, the activation of the RAGE/AGEs axis, which is highly expressed in diabetic tissues and cells, can significantly increase both COX-2 messenger RNA and protein expression, together with a rise in PGE2 Levels[139].

Hyperinsulinemia is strongly associated with type 2 diabetes and it has been recently postulated to be a risk factor for GC[140] Emerging data suggest that insulin may be a crucial regulator in some human neoplasias, including GC[141-145].

In addition, hyperinsulinemia also increases the hepatic production and systemic bioavailability of IGF1 but also reduces the hepatic protein production of the insulin-like growth factor binding proteins 1 (IGFBP-1) and 2 (IGFBP-2). These two coordinated actions may, in turn, hyperactivate the Ins-R/IGF1-R system, and thus triggering their proliferative and anti-apoptotic programs in cancer cells[142]. Additionally, the activation of the RAGE/AGEs axis also upregulates the expression of both IGF1 mRNA and protein levels[143].

***Disturbances in microRNAs network***

MicroRNAs (miRNAs) are a class of small non-coding RNAs, which act as posttranscriptional regulators of gene expression[146], and are involved in several cellular activities such as cell growth, differentiation, development, and apoptosis in many cancer types[147]. Notably, recent research has demonstrated that dysregulation in the miRNAs network has crucial consequences in the cellular behavior of neoplastic cells[147], by modulating multiple signaling pathways, especially within the gastric TME[148].

Noteworthy, hyperglycemia, and hyperinsulinemia in DM patients are two conditions that induce major changes in miRNA expression profile, especially those that are involved in gastric carcinogenesis[149].

DM patients have a particularly pro-tumoral miRNA profile, characterized by downregulation of tumor suppressor miRNAs such miR-497, miR-495p, and miR-203, which can inhibit tumor cell proliferation and migration[150,151], and its decreased expression has been associated with poor prognosis in GC patients[152,153].

In addition, the expression of some members of the family of Let-7 miRNAs, which are known by their roles in regulating oncogenes and controlling cellular differentiation and apoptosis[154], is often downregulated in several cancers, and thus derepressing some relevant oncogenic targets in GC, such as K-ras, and c-Myc[155]. Noteworthy, Let-7 miRNAs are downregulated under DM conditions not only by hyperglycemia but also by insulin resistance[151].

Conversely, a diabetogenic milieu and chronic hyperglycemia favor the overexpression of some oncomiRs, such as miR-17-5p[150,156]. Furthermore, recent research support that increased stiffness of ECM significantly induces the expression of miR-17-5p and thus rendering a loop towards the support of tumor growth and invasion[157].

***Altered exosomes production and cargo***

Exosomes are submicron-sized extracellular vesicles that are involved in cell-to-cell and organ-to-organ communication[158]. Recently, exosomes are involved in the pathogenesis of various disorders, including inflammatory diseases and cancer[159].

In addition, these small vesicles are now emerging as important modulators of the interchange of bioactive molecules within the TME[148].

At present, a growing body of evidence supports that either chronic hyperglycemic or hyperinsulinemic state alters not only the molecular cargo of exosomes but also their production in DM patients. These changes consequently induce critical changes in cellular function that enhance the cross-talk communication between neoplastic and non-neoplastic stromal cells[9,160].

Noteworthy, recent studies suggest that exosome release from individuals with diabetes expresses a skewed profile of pro-inflammatory molecular cargo[160,161], which influences the neoplastic transformation and favors cancer cell dissemination, especially in gastric tumors[162].

In addition, the altered exosomes-profile in a hyperglycemic milieu drives an increased expression of pro-angiogenic factors such as VEGF and HIF-1[160,161], which give rise to an increased intercellular cross-talk between endothelial cells, and subsequently leading to a highly angiogenic gastric microenvironment phenotype, thus promoting cancer growth and progression[163].

Besides the alterations in the molecular cargo of exosomes in the DM milieu, the increased release rate of exosomes due to hyperinsulinemia could enhance the exosome-dependent molecular transfer associated with the peritoneal dissemination of GC[160,161,164], and thus affecting the prognosis of DM patients who develop GC[165].

***Altered metabolism***

The Warburg effect refers to the enhanced glucose uptake and lactate production observed in cancer cells, even in the presence of oxygen and fully functioning mitochondria, also known as aerobic glycolysis[166]. Aerobic glycolysis provides glycolytic intermediates, which function as important precursors required for the synthesis of carbohydrates, fats, and proteins by cancer cells[167].

In the context of hyperglycemia, all these requirements are covered; however, hyperglycemia also promotes glycolysis by inducing the expression of glycolytic-related genes[168-170]. However, the metabolic effects of hyperglycemia on cancer cells can go further than the Warburg effect, considering that the activation of some oncogenes can subsequently proceed to an increase in ATP production[171].

Hyperglycemia also enhances the expression of the carbohydrate-responsive element-binding protein (ChREBP) in cancer cells, a well-known promoter of lipogenesis[172]. This is particularly interesting considering many tumor cells produce *de novo* almost the total of the monounsaturated and saturated fatty acids required, which are used in many cellular events crucial for tumor growth and progression[173].

In tumor cells, high glucose levels can promote HIF-1α expression under both normoxic and hypoxic conditions[168,174]. In the GC microenvironment, the HIF-1 complex activates the transcription of crucial target genes in conferring the adaptation to the hypoxic milieu and its expression correlates with an aggressive tumor phenotype and a poor prognosis[175].

In summary, DM contributes through a myriad of molecular mechanisms to the remodeling of the GC microenvironment and thus renders crucial phenotypical changes, which in turn generates tumors that are more aggressive (Figure 2).

**CONCLUSION**

At present, a compelling body of evidence supports the contribution of DM not only to higher cancer incidence but also to an increased mortality rate of DM patients who develops GC.

In recent years, considerable efforts in experimental research have allowed elucidating the molecular mechanisms underlying this association. In this regard, growing data suggest that the mechanical alterations induced in ECM by AGEs-mediated cross-linking and the profound changes in stromal cell behavior influenced by diabetes are pivotal elements in supporting tumor growth and progression.

Furthermore, the underlying pro-inflammatory signaling supporting the meta-inflammation in DM patients, favors several disturbances in intra- and intercellular signaling pathways, which ultimately converge in favor of the development, progression, and dissemination of GC. In addition, the chronic metabolic dysregulation observed in DM patients favors crucial changes in tumor cell metabolism that will ultimately contribute to highly hypoxic-resistant neoplastic cells as well as to a more aggressive tumoral phenotype.

Although in recent years crucial advances have been made in the knowledge of the mechanisms induced by DM in generating a TME that is supportive of tumor growth and spread, the strengthening of clinical research is essential to achieving a better understanding of the mechanisms underlying this epidemiological association.

**REFERENCES**

1 **Ling S**, Brown K, Miksza JK, Howells L, Morrison A, Issa E, Yates T, Khunti K, Davies MJ, Zaccardi F. Association of Type 2 Diabetes With Cancer: A Meta-analysis With Bias Analysis for Unmeasured Confounding in 151 Cohorts Comprising 32 Million People. *Diabetes Care* 2020; **43**: 2313-2322 [PMID: 32910779 DOI: 10.2337/dc20-0204]

2 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

3 **Yang HJ**, Kang D, Chang Y, Ahn J, Ryu S, Cho J, Guallar E, Sohn CI. Diabetes mellitus is associated with an increased risk of gastric cancer: a cohort study. *Gastric Cancer* 2020; **23**: 382-390 [PMID: 31853749 DOI: 10.1007/s10120-019-01033-8]

4 **Miao ZF**, Xu H, Xu YY, Wang ZN, Zhao TT, Song YX, Xu HM. Diabetes mellitus and the risk of gastric cancer: a meta-analysis of cohort studies. *Oncotarget* 2017; **8**: 44881-44892 [PMID: 28415651 DOI: 10.18632/oncotarget.16487]

5 **Donath MY**, Shoelson SE. Type 2 diabetes as an inflammatory disease. *Nat Rev Immunol* 2011; **11**: 98-107 [PMID: 21233852 DOI: 10.1038/nri2925]

6 **Hameed I**, Masoodi SR, Mir SA, Nabi M, Ghazanfar K, Ganai BA. Type 2 diabetes mellitus: From a metabolic disorder to an inflammatory condition. *World J Diabetes* 2015; **6**: 598-612 [PMID: 25987957 DOI: 10.4239/wjd.v6.i4.598]

7 **Gross B**, Pawlak M, Lefebvre P, Staels B. PPARs in obesity-induced T2DM, dyslipidaemia and NAFLD. *Nat Rev Endocrinol* 2017; **13**: 36-49 [PMID: 27636730 DOI: 10.1038/nrendo.2016.135]

8 **Yaribeygi H**, Sathyapalan T, Atkin SL, Sahebkar A. Molecular Mechanisms Linking Oxidative Stress and Diabetes Mellitus. *Oxid Med Cell Longev* 2020; **2020**: 8609213 [PMID: 32215179 DOI: 10.1155/2020/8609213]

9 **Noren Hooten N**, Evans MK. Extracellular vesicles as signaling mediators in type 2 diabetes mellitus. *Am J Physiol Cell Physiol* 2020; **318**: C1189-C1199 [PMID: 32348178 DOI: 10.1152/ajpcell.00536.2019]

10 **Oya Y**, Hayakawa Y, Koike K. Tumor microenvironment in gastric cancers. *Cancer Sci* 2020; **111**: 2696-2707 [PMID: 32519436 DOI: 10.1111/cas.14521]

11 **Tseng CH**, Tseng FH. Diabetes and gastric cancer: the potential links. *World J Gastroenterol* 2014; **20**: 1701-1711 [PMID: 24587649 DOI: 10.3748/wjg.v20.i7.1701]

12 **Barone BB**, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL. Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. *JAMA* 2008; **300**: 2754-2764 [PMID: 19088353 DOI: 10.1001/jama.2008.824]

13 **Harding JL**, Andes LJ, Gregg EW, Cheng YJ, Weir HK, Bullard KM, Burrows NR, Imperatore G. Trends in cancer mortality among people with *vs* without diabetes in the USA, 1988-2015. *Diabetologia* 2020; **63**: 75-84 [PMID: 31511931 DOI: 10.1007/s00125-019-04991-x]

14 **Goto A**, Yamaji T, Sawada N, Momozawa Y, Kamatani Y, Kubo M, Shimazu T, Inoue M, Noda M, Tsugane S, Iwasaki M. Diabetes and cancer risk: A Mendelian randomization study. *Int J Cancer* 2020; **146**: 712-719 [PMID: 30927373 DOI: 10.1002/ijc.32310]

15 **Ling S**, Brown K, Miksza JK, Howells LM, Morrison A, Issa E, Yates T, Khunti K, Davies MJ, Zaccardi F. Risk of cancer incidence and mortality associated with diabetes: A systematic review with trend analysis of 203 cohorts. *Nutr Metab Cardiovasc Dis* 2021; **31**: 14-22 [PMID: 33223399 DOI: 10.1016/j.numecd.2020.09.023]

16 **Khan M**, Mori M, Fujino Y, Shibata A, Sakauchi F, Washio M, Tamakoshi A; Japan Collaborative Cohort Study Group. Site-specific cancer risk due to diabetes mellitus history: evidence from the Japan Collaborative Cohort (JACC) Study. *Asian Pac J Cancer Prev* 2006; **7**: 253-259 [PMID: 16839219]

17 **Inoue M**, Iwasaki M, Otani T, Sasazuki S, Noda M, Tsugane S. Diabetes mellitus and the risk of cancer: results from a large-scale population-based cohort study in Japan. *Arch Intern Med* 2006; **166**: 1871-1877 [PMID: 17000944 DOI: 10.1001/archinte.166.17.1871]

18 **Hong SH**, Noh E, Kim J, Hwang SY, Kim JA, Lee YB, Roh E, Choi KM, Baik SH, Cho GJ, Yoo HJ. Fasting Plasma Glucose Variability and Gastric Cancer Risk in Individuals Without Diabetes Mellitus: A Nationwide Population-Based Cohort Study. *Clin Transl Gastroenterol* 2020; **11**: e00221 [PMID: 32858572 DOI: 10.14309/ctg.0000000000000221]

19 **Ge Z**, Ben Q, Qian J, Wang Y, Li Y. Diabetes mellitus and risk of gastric cancer: a systematic review and meta-analysis of observational studies. *Eur J Gastroenterol Hepatol* 2011; **23**: 1127-1135 [PMID: 21934509 DOI: 10.1097/MEG.0b013e32834b8d73]

20 **Shimoyama S**. Diabetes mellitus carries a risk of gastric cancer: a meta-analysis. *World J Gastroenterol* 2013; **19**: 6902-6910 [PMID: 24187468 DOI: 10.3748/wjg.v19.i40.6902]

21 **Tian T**, Zhang LQ, Ma XH, Zhou JN, Shen J. Diabetes mellitus and incidence and mortality of gastric cancer: a meta-analysis. *Exp Clin Endocrinol Diabetes* 2012; **120**: 217-223 [PMID: 22187293 DOI: 10.1055/s-0031-1297969]

22 **Ikeda F**, Doi Y, Yonemoto K, Ninomiya T, Kubo M, Shikata K, Hata J, Tanizaki Y, Matsumoto T, Iida M, Kiyohara Y. Hyperglycemia increases risk of gastric cancer posed by Helicobacter pylori infection: a population-based cohort study. *Gastroenterology* 2009; **136**: 1234-1241 [PMID: 19236964 DOI: 10.1053/j.gastro.2008.12.045]

23 **Huang Y**, Cai X, Qiu M, Chen P, Tang H, Hu Y, Huang Y. Prediabetes and the risk of cancer: a meta-analysis. *Diabetologia* 2014; **57**: 2261-2269 [PMID: 25208757 DOI: 10.1007/s00125-014-3361-2]

24 **Tseng CH**. Diabetes conveys a higher risk of gastric cancer mortality despite an age-standardised decreasing trend in the general population in Taiwan. *Gut* 2011; **60**: 774-779 [PMID: 21193459 DOI: 10.1136/gut.2010.226522]

25 **Li PF**, Chen WL. Are the Different Diabetes Subgroups Correlated With All-Cause, Cancer-Related, and Cardiovascular-Related Mortality? *J Clin Endocrinol Metab* 2020; **105** [PMID: 32893854 DOI: 10.1210/clinem/dgaa628]

26 . Population-based cohort study of diabetes mellitus and mortality in gastric adenocarcinoma. *Br J Surg* 2020; **107**: 1012 [PMID: 32539215 DOI: 10.1002/bjs.11884]

27 **Zhao W**, Chen R, Zhao M, Li L, Fan L, Che XM. High glucose promotes gastric cancer chemoresistance *in vivo* and in vitro. *Mol Med Rep* 2015; **12**: 843-850 [PMID: 25815791 DOI: 10.3892/mmr.2015.3522]

28 **Li W**, Zhang X, Sang H, Zhou Y, Shang C, Wang Y, Zhu H. Effects of hyperglycemia on the progression of tumor diseases. *J Exp Clin Cancer Res* 2019; **38**: 327 [PMID: 31337431 DOI: 10.1186/s13046-019-1309-6]

29 **Xu X**, Chen B, Zhu S, Zhang J, He X, Cao G, Chen B. Hyperglycemia promotes Snail-induced epithelial-mesenchymal transition of gastric cancer *via* activating ENO1 expression. *Cancer Cell Int* 2019; **19**: 344 [PMID: 31889896 DOI: 10.1186/s12935-019-1075-8]

30 **Correa P**. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res* 1992; **52**: 6735-6740 [PMID: 1458460]

31 Schistosomes, liver flukes and Helicobacter pylori. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 7-14 June 1994. *IARC Monogr Eval Carcinog Risks Hum* 1994; **61**: 1-241 [PMID: 7715068]

32 **Chen J**, Xing Y, Zhao L, Ma H. The Association between Helicobacter pylori Infection and Glycated Hemoglobin A in Diabetes: A Meta-Analysis. *J Diabetes Res* 2019; **2019**: 3705264 [PMID: 31583248 DOI: 10.1155/2019/3705264]

33 **Youn Nam S**, Park BJ, Nam JH, Ryu KH, Kook MC, Kim J, Lee WK. Association of current *Helicobacter pylori* infection and metabolic factors with gastric cancer in 35,519 subjects: A cross-sectional study. *United European Gastroenterol J* 2019; **7**: 287-296 [PMID: 31080613 DOI: 10.1177/2050640618819402]

34 **Mansori K**, Dehghanbanadaki H, Naderpour S, Rashti R, Moghaddam AB, Moradi Y. A systematic review and meta-analysis of the prevalence of Helicobacter pylori in patients with diabetes. *Diabetes Metab Syndr* 2020; **14**: 601-607 [PMID: 32417710 DOI: 10.1016/j.dsx.2020.05.009]

35 **Nam SJ**, Park SC, Lee SH, Choi DW, Lee SJ, Bang CS, Baik GH, Park JK. *Helicobacter pylori* eradication in patients with type 2 diabetes mellitus: Multicenter prospective observational study. *SAGE Open Med* 2019; **7**: 2050312119832093 [PMID: 30815260 DOI: 10.1177/2050312119832093]

36 **Yao CC**, Kuo CM, Hsu CN, Yang SC, Wu CK, Tai WC, Liang CM, Wu KL, Huang CF, Bi KW, Lee CH, Chuah SK. First-line *Helicobacter pylori* eradication rates are significantly lower in patients with than those without type 2 diabetes mellitus. *Infect Drug Resist* 2019; **12**: 1425-1431 [PMID: 31239721 DOI: 10.2147/IDR.S194584]

37 **Ojetti V**, Pitocco D, Bartolozzi F, Danese S, Migneco A, Lupascu A, Pola P, Ghirlanda G, Gasbarrini G, Gasbarrini A. High rate of helicobacter pylori re-infection in patients affected by type 1 diabetes. *Diabetes Care* 2002; **25**: 1485 [PMID: 12145262 DOI: 10.2337/diacare.25.8.1485]

38 **Sheu SM**, Cheng H, Kao CY, Yang YJ, Wu JJ, Sheu BS. Higher glucose level can enhance the H. pylori adhesion and virulence related with type IV secretion system in AGS cells. *J Biomed Sci* 2014; **21**: 96 [PMID: 25296847 DOI: 10.1186/s12929-014-0096-9]

39 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

40 **Correa P**, Piazuelo MB. The gastric precancerous cascade. *J Dig Dis* 2012; **13**: 2-9 [PMID: 22188910 DOI: 10.1111/j.1751-2980.2011.00550.x]

41 **Brungs D**, Aghmesheh M, Vine KL, Becker TM, Carolan MG, Ranson M. Gastric cancer stem cells: evidence, potential markers, and clinical implications. *J Gastroenterol* 2016; **51**: 313-326 [PMID: 26428661 DOI: 10.1007/s00535-015-1125-5]

42 **Houghton J**, Stoicov C, Nomura S, Rogers AB, Carlson J, Li H, Cai X, Fox JG, Goldenring JR, Wang TC. Gastric cancer originating from bone marrow-derived cells. *Science* 2004; **306**: 1568-1571 [PMID: 15567866 DOI: 10.1126/science.1099513]

43 **Nobuta H**, Katagi M, Kume S, Terashima T, Araki SI, Maegawa H, Kojima H, Nakagawa T. A role for bone marrow-derived cells in diabetic nephropathy. *FASEB J* 2019; **33**: 4067-4076 [PMID: 30496699 DOI: 10.1096/fj.201801825R]

44 **Ribatti D**, Guidolin D, Marzullo A, Nico B, Annese T, Benagiano V, Crivellato E. Mast cells and angiogenesis in gastric carcinoma. *Int J Exp Pathol* 2010; **91**: 350-356 [PMID: 20412338 DOI: 10.1111/j.1365-2613.2010.00714.x]

45 **Liu J**, Zhang Y, Zhao J, Yang Z, Li D, Katirai F, Huang B. Mast cell: insight into remodeling a tumor microenvironment. *Cancer Metastasis Rev* 2011; **30**: 177-184 [PMID: 21267769 DOI: 10.1007/s10555-011-9276-1]

46 **Zhong B**, Li Y, Liu X, Wang D. Association of mast cell infiltration with gastric cancer progression. *Oncol Lett* 2018; **15**: 755-764 [PMID: 29422964 DOI: 10.3892/ol.2017.7380]

47 **Lv Y**, Zhao Y, Wang X, Chen N, Mao F, Teng Y, Wang T, Peng L, Zhang J, Cheng P, Liu Y, Kong H, Chen W, Hao C, Han B, Ma Q, Zou Q, Chen J, Zhuang Y. Increased intratumoral mast cells foster immune suppression and gastric cancer progression through TNF-α-PD-L1 pathway. *J Immunother Cancer* 2019; **7**: 54 [PMID: 30808413 DOI: 10.1186/s40425-019-0530-3]

48 **Nagai K**, Fukushima T, Oike H, Kobori M. High glucose increases the expression of proinflammatory cytokines and secretion of TNFα and β-hexosaminidase in human mast cells. *Eur J Pharmacol* 2012; **687**: 39-45 [PMID: 22575517 DOI: 10.1016/j.ejphar.2012.04.038]

49 **Ping Q**, Yan R, Cheng X, Wang W, Zhong Y, Hou Z, Shi Y, Wang C, Li R. Cancer-associated fibroblasts: overview, progress, challenges, and directions. *Cancer Gene Ther* 2021; **28**: 984-999 [PMID: 33712707 DOI: 10.1038/s41417-021-00318-4]

50 **Kalluri R**. The biology and function of fibroblasts in cancer. *Nat Rev Cancer* 2016; **16**: 582-598 [PMID: 27550820 DOI: 10.1038/nrc.2016.73]

51 **Tuleta I**, Frangogiannis NG. Diabetic fibrosis. *Biochim Biophys Acta Mol Basis Dis* 2021; **1867**: 166044 [PMID: 33378699 DOI: 10.1016/j.bbadis.2020.166044]

52 **Garufi A**, Traversi G, Cirone M, D'Orazi G. HIPK2 role in the tumor-host interaction: Impact on fibroblasts transdifferentiation CAF-like. *IUBMB Life* 2019; **71**: 2055-2061 [PMID: 31414572 DOI: 10.1002/iub.2144]

53 **Baldari S**, Garufi A, Granato M, Cuomo L, Pistritto G, Cirone M, D'Orazi G. Hyperglycemia triggers HIPK2 protein degradation. *Oncotarget* 2017; **8**: 1190-1203 [PMID: 27901482 DOI: 10.18632/oncotarget.13595]

54 **Osório H**, Silva C, Ferreira M, Gullo I, Máximo V, Barros R, Mendonça F, Oliveira C, Carneiro F. Proteomics Analysis of Gastric Cancer Patients with Diabetes Mellitus. *J Clin Med* 2021; **10** [PMID: 33494396 DOI: 10.3390/jcm10030407]

55 **Mantovani A**, Sozzani S, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol* 2002; **23**: 549-555 [PMID: 12401408 DOI: 10.1016/s1471-4906(02)02302-5]

56 **Gambardella V**, Castillo J, Tarazona N, Gimeno-Valiente F, Martínez-Ciarpaglini C, Cabeza-Segura M, Roselló S, Roda D, Huerta M, Cervantes A, Fleitas T. The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target. *Cancer Treat Rev* 2020; **86**: 102015 [PMID: 32248000 DOI: 10.1016/j.ctrv.2020.102015]

57 **Zhang QW**, Liu L, Gong CY, Shi HS, Zeng YH, Wang XZ, Zhao YW, Wei YQ. Prognostic significance of tumor-associated macrophages in solid tumor: a meta-analysis of the literature. *PLoS One* 2012; **7**: e50946 [PMID: 23284651 DOI: 10.1371/journal.pone.0050946]

58 **Biswas SK**, Mantovani A. Macrophage plasticity and interaction with lymphocyte subsets: cancer as a paradigm. *Nat Immunol* 2010; **11**: 889-896 [PMID: 20856220 DOI: 10.1038/ni.1937]

59 **Yamaguchi T**, Fushida S, Yamamoto Y, Tsukada T, Kinoshita J, Oyama K, Miyashita T, Tajima H, Ninomiya I, Munesue S, Harashima A, Harada S, Yamamoto H, Ohta T. Tumor-associated macrophages of the M2 phenotype contribute to progression in gastric cancer with peritoneal dissemination. *Gastric Cancer* 2016; **19**: 1052-1065 [PMID: 26621525 DOI: 10.1007/s10120-015-0579-8]

60 **Tesch GH**. Role of macrophages in complications of type 2 diabetes. *Clin Exp Pharmacol Physiol* 2007; **34**: 1016-1019 [PMID: 17714088 DOI: 10.1111/j.1440-1681.2007.04729.x]

61 **Pavlou S**, Lindsay J, Ingram R, Xu H, Chen M. Sustained high glucose exposure sensitizes macrophage responses to cytokine stimuli but reduces their phagocytic activity. *BMC Immunol* 2018; **19**: 24 [PMID: 29996768 DOI: 10.1186/s12865-018-0261-0]

62 **Moganti K**, Li F, Schmuttermaier C, Riemann S, Klüter H, Gratchev A, Harmsen MC, Kzhyshkowska J. Hyperglycemia induces mixed M1/M2 cytokine profile in primary human monocyte-derived macrophages. *Immunobiology* 2017; **222**: 952-959 [PMID: 27492721 DOI: 10.1016/j.imbio.2016.07.006]

63 **Rodrigues Mantuano N**, Stanczak MA, Oliveira IA, Kirchhammer N, Filardy AA, Monaco G, Santos RC, Fonseca AC, Fontes M, Bastos CS Jr, Dias WB, Zippelius A, Todeschini AR, Läubli H. Hyperglycemia Enhances Cancer Immune Evasion by Inducing Alternative Macrophage Polarization through Increased O-GlcNAcylation. *Cancer Immunol Res* 2020; **8**: 1262-1272 [PMID: 32819969 DOI: 10.1158/2326-6066.CIR-19-0904]

64 **Zhang W**, Gu J, Chen J, Zhang P, Ji R, Qian H, Xu W, Zhang X. Interaction with neutrophils promotes gastric cancer cell migration and invasion by inducing epithelial-mesenchymal transition. *Oncol Rep* 2017; **38**: 2959-2966 [PMID: 28901479 DOI: 10.3892/or.2017.5942]

65 **Li S**, Cong X, Gao H, Lan X, Li Z, Wang W, Song S, Wang Y, Li C, Zhang H, Zhao Y, Xue Y. Tumor-associated neutrophils induce EMT by IL-17a to promote migration and invasion in gastric cancer cells. *J Exp Clin Cancer Res* 2019; **38**: 6 [PMID: 30616627 DOI: 10.1186/s13046-018-1003-0]

66 **Fainsod-Levi T**, Gershkovitz M, Völs S, Kumar S, Khawaled S, Sagiv JY, Sionov RV, Grunewald M, Keshet E, Granot Z. Hyperglycemia Impairs Neutrophil Mobilization Leading to Enhanced Metastatic Seeding. *Cell Rep* 2017; **21**: 2384-2392 [PMID: 29186678 DOI: 10.1016/j.celrep.2017.11.010]

67 **Yang P**, Zhou Y, Chen B, Wan HW, Jia GQ, Bai HL, Wu XT. Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur J Cancer* 2009; **45**: 2867-2873 [PMID: 19427197 DOI: 10.1016/j.ejca.2009.04.019]

68 **Nieman KM**, Romero IL, Van Houten B, Lengyel E. Adipose tissue and adipocytes support tumorigenesis and metastasis. *Biochim Biophys Acta* 2013; **1831**: 1533-1541 [PMID: 23500888 DOI: 10.1016/j.bbalip.2013.02.010]

69 **Dumas JF**, Brisson L. Interaction between adipose tissue and cancer cells: role for cancer progression. *Cancer Metastasis Rev* 2021; **40**: 31-46 [PMID: 33009650 DOI: 10.1007/s10555-020-09934-2]

70 **Iliopoulos D**, Jaeger SA, Hirsch HA, Bulyk ML, Struhl K. STAT3 activation of miR-21 and miR-181b-1 *via* PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer. *Mol Cell* 2010; **39**: 493-506 [PMID: 20797623 DOI: 10.1016/j.molcel.2010.07.023]

71 **Zheng J**, Zhao M, Li J, Lou G, Yuan Y, Bu S, Xi Y. Obesity-associated digestive cancers: A review of mechanisms and interventions. *Tumour Biol* 2017; **39**: 1010428317695020 [PMID: 28351315 DOI: 10.1177/1010428317695020]

72 **O'Sullivan J**, Lysaght J, Donohoe CL, Reynolds JV. Obesity and gastrointestinal cancer: the interrelationship of adipose and tumour microenvironments. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 699-714 [PMID: 30323319 DOI: 10.1038/s41575-018-0069-7]

73 **McKee TJ**, Perlman G, Morris M, Komarova SV. Extracellular matrix composition of connective tissues: a systematic review and meta-analysis. *Sci Rep* 2019; **9**: 10542 [PMID: 31332239 DOI: 10.1038/s41598-019-46896-0]

74 **Romani P**, Valcarcel-Jimenez L, Frezza C, Dupont S. Crosstalk between mechanotransduction and metabolism. *Nat Rev Mol Cell Biol* 2021; **22**: 22-38 [PMID: 33188273 DOI: 10.1038/s41580-020-00306-w]

75 **Winkler J**, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z. Concepts of extracellular matrix remodelling in tumour progression and metastasis. *Nat Commun* 2020; **11**: 5120 [PMID: 33037194 DOI: 10.1038/s41467-020-18794-x]

76 **Manou D**, Caon I, Bouris P, Triantaphyllidou IE, Giaroni C, Passi A, Karamanos NK, Vigetti D, Theocharis AD. The Complex Interplay Between Extracellular Matrix and Cells in Tissues. *Methods Mol Biol* 2019; **1952**: 1-20 [PMID: 30825161 DOI: 10.1007/978-1-4939-9133-4\_1]

77 **Najafi M**, Farhood B, Mortezaee K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J Cell Biochem* 2019; **120**: 2782-2790 [PMID: 30321449 DOI: 10.1002/jcb.27681]

78 **Poltavets V**, Kochetkova M, Pitson SM, Samuel MS. The Role of the Extracellular Matrix and Its Molecular and Cellular Regulators in Cancer Cell Plasticity. *Front Oncol* 2018; **8**: 431 [PMID: 30356678 DOI: 10.3389/fonc.2018.00431]

79 **Walker C**, Mojares E, Del Río Hernández A. Role of Extracellular Matrix in Development and Cancer Progression. *Int J Mol Sci* 2018; **19** [PMID: 30287763 DOI: 10.3390/ijms19103028]

80 **Rigoglio NN**, Rabelo ACS, Borghesi J, de Sá Schiavo Matias G, Fratini P, Prazeres PHDM, Pimentel CMMM, Birbrair A, Miglino MA. The Tumor Microenvironment: Focus on Extracellular Matrix. *Adv Exp Med Biol* 2020; **1245**: 1-38 [PMID: 32266651 DOI: 10.1007/978-3-030-40146-7\_1]

81 **Dandia H**, Makkad K, Tayalia P. Glycated collagen - a 3D matrix system to study pathological cell behavior. *Biomater Sci* 2019; **7**: 3480-3488 [PMID: 31282511 DOI: 10.1039/c9bm00184k]

82 **Spada S**, Tocci A, Di Modugno F, Nisticò P. Fibronectin as a multiregulatory molecule crucial in tumor matrisome: from structural and functional features to clinical practice in oncology. *J Exp Clin Cancer Res* 2021; **40**: 102 [PMID: 33731188 DOI: 10.1186/s13046-021-01908-8]

83 **Kobayashi H**, Enomoto A, Woods SL, Burt AD, Takahashi M, Worthley DL. Cancer-associated fibroblasts in gastrointestinal cancer. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 282-295 [PMID: 30778141 DOI: 10.1038/s41575-019-0115-0]

84 **Mohan V**, Das A, Sagi I. Emerging roles of ECM remodeling processes in cancer. *Semin Cancer Biol* 2020; **62**: 192-200 [PMID: 31518697 DOI: 10.1016/j.semcancer.2019.09.004]

85 **Rojas A**, Añazco C, González I, Araya P. Extracellular matrix glycation and receptor for advanced glycation end-products activation: a missing piece in the puzzle of the association between diabetes and cancer. *Carcinogenesis* 2018; **39**: 515-521 [PMID: 29373651 DOI: 10.1093/carcin/bgy012]

86 **Moreira AM**, Pereira J, Melo S, Fernandes MS, Carneiro P, Seruca R, Figueiredo J. The Extracellular Matrix: An Accomplice in Gastric Cancer Development and Progression. *Cells* 2020; **9** [PMID: 32046329 DOI: 10.3390/cells9020394]

87 **Suh YJ**, Hall MS, Huang YL, Moon SY, Song W, Ma M, Bonassar LJ, Segall JE, Wu M. Glycation of collagen matrices promotes breast tumor cell invasion. *Integr Biol (Camb)* 2019 [PMID: 31041443 DOI: 10.1093/intbio/zyz011]

88 **Grasset EM**, Bertero T, Bozec A, Friard J, Bourget I, Pisano S, Lecacheur M, Maiel M, Bailleux C, Emelyanov A, Ilie M, Hofman P, Meneguzzi G, Duranton C, Bulavin DV, Gaggioli C. Matrix Stiffening and EGFR Cooperate to Promote the Collective Invasion of Cancer Cells. *Cancer Res* 2018; **78**: 5229-5242 [PMID: 30026329 DOI: 10.1158/0008-5472.CAN-18-0601]

89 **Wei SC**, Fattet L, Tsai JH, Guo Y, Pai VH, Majeski HE, Chen AC, Sah RL, Taylor SS, Engler AJ, Yang J. Matrix stiffness drives epithelial-mesenchymal transition and tumour metastasis through a TWIST1-G3BP2 mechanotransduction pathway. *Nat Cell Biol* 2015; **17**: 678-688 [PMID: 25893917 DOI: 10.1038/ncb3157]

90 **Laczko R**, Csiszar K. Lysyl Oxidase (LOX): Functional Contributions to Signaling Pathways. *Biomolecules* 2020; **10** [PMID: 32708046 DOI: 10.3390/biom10081093]

91 **Añazco C**, Delgado-López F, Araya P, González I, Morales E, Pérez-Castro R, Romero J, Rojas A. Lysyl oxidase isoforms in gastric cancer. *Biomark Med* 2016; **10**: 987-998 [PMID: 27564724 DOI: 10.2217/bmm-2016-0075]

92 **Chronopoulos A**, Tang A, Beglova E, Trackman PC, Roy S. High glucose increases lysyl oxidase expression and activity in retinal endothelial cells: mechanism for compromised extracellular matrix barrier function. *Diabetes* 2010; **59**: 3159-3166 [PMID: 20823103 DOI: 10.2337/db10-0365]

93 **Li Q**, Zhu CC, Ni B, Zhang ZZ, Jiang SH, Hu LP, Wang X, Zhang XX, Huang PQ, Yang Q, Li J, Gu JR, Xu J, Luo KQ, Zhao G, Zhang ZG. Lysyl oxidase promotes liver metastasis of gastric cancer *via* facilitating the reciprocal interactions between tumor cells and cancer associated fibroblasts. *EBioMedicine* 2019; **49**: 157-171 [PMID: 31678002 DOI: 10.1016/j.ebiom.2019.10.037]

94 **Trackman PC**. Lysyl Oxidase Isoforms and Potential Therapeutic Opportunities for Fibrosis and Cancer. *Expert Opin Ther Targets* 2016; **20**: 935-945 [PMID: 26848785 DOI: 10.1517/14728222.2016.1151003]

95 **Zand H**, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. *Diabetes Metab Syndr* 2017; **11 Suppl 1**: S307-S309 [PMID: 28365222 DOI: 10.1016/j.dsx.2017.03.006]

96 **Cheng F**, Carroll L, Joglekar MV, Januszewski AS, Wong KK, Hardikar AA, Jenkins AJ, Ma RCW. Diabetes, metabolic disease, and telomere length. *Lancet Diabetes Endocrinol* 2021; **9**: 117-126 [PMID: 33248477 DOI: 10.1016/S2213-8587(20)30365-X]

97 **Brownlee M**. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001; **414**: 813-820 [PMID: 11742414 DOI: 10.1038/414813a]

98 **Yan SF**, Ramasamy R, Naka Y, Schmidt AM. Glycation, inflammation, and RAGE: a scaffold for the macrovascular complications of diabetes and beyond. *Circ Res* 2003; **93**: 1159-1169 [PMID: 14670831 DOI: 10.1161/01.RES.0000103862.26506.3D]

99 **Hotamisligil GS**. Inflammation and metabolic disorders. *Nature* 2006; **444**: 860-867 [PMID: 17167474 DOI: 10.1038/nature05485]

100 **Diedisheim M**, Carcarino E, Vandiedonck C, Roussel R, Gautier JF, Venteclef N. Regulation of inflammation in diabetes: From genetics to epigenomics evidence. *Mol Metab* 2020; **41**: 101041 [PMID: 32603690 DOI: 10.1016/j.molmet.2020.101041]

101 **Ni R**, Zheng D, Xiong S, Hill DJ, Sun T, Gardiner RB, Fan GC, Lu Y, Abel ED, Greer PA, Peng T. Mitochondrial Calpain-1 Disrupts ATP Synthase and Induces Superoxide Generation in Type 1 Diabetic Hearts: A Novel Mechanism Contributing to Diabetic Cardiomyopathy. *Diabetes* 2016; **65**: 255-268 [PMID: 26470784 DOI: 10.2337/db15-0963]

102 **Weinberg F**, Ramnath N, Nagrath D. Reactive Oxygen Species in the Tumor Microenvironment: An Overview. *Cancers (Basel)* 2019; **11** [PMID: 31426364 DOI: 10.3390/cancers11081191]

103 **Jain M**, Rivera S, Monclus EA, Synenki L, Zirk A, Eisenbart J, Feghali-Bostwick C, Mutlu GM, Budinger GR, Chandel NS. Mitochondrial reactive oxygen species regulate transforming growth factor-β signaling. *J Biol Chem* 2013; **288**: 770-777 [PMID: 23204521 DOI: 10.1074/jbc.M112.431973]

104 **Schmitt-Gräff A**, Desmoulière A, Gabbiani G. Heterogeneity of myofibroblast phenotypic features: an example of fibroblastic cell plasticity. *Virchows Arch* 1994; **425**: 3-24 [PMID: 7921410 DOI: 10.1007/BF00193944]

105 **Vlassara H**, Palace MR. Diabetes and advanced glycation endproducts. *J Intern Med* 2002; **251**: 87-101 [PMID: 11905595 DOI: 10.1046/j.1365-2796.2002.00932.x]

106 **Yan SF**, Ramasamy R, Schmidt AM. The RAGE axis: a fundamental mechanism signaling danger to the vulnerable vasculature. *Circ Res* 2010; **106**: 842-853 [PMID: 20299674 DOI: 10.1161/CIRCRESAHA.109.212217]

107 **Yan SF**, Ramasamy R, Schmidt AM. Mechanisms of disease: advanced glycation end-products and their receptor in inflammation and diabetes complications. *Nat Clin Pract Endocrinol Metab* 2008; **4**: 285-293 [PMID: 18332897 DOI: 10.1038/ncpendmet0786]

108 **Rojas A**, González I, Rodríguez B, Romero J, Figueroa H, Llanos J, Morales E, Pérez-Castro R. Evidence of involvement of the receptor for advanced glycation end-products (RAGE) in the adhesion of Helicobacter pylori to gastric epithelial cells. *Microbes Infect* 2011; **13**: 818-823 [PMID: 21609778 DOI: 10.1016/j.micinf.2011.04.005]

109 **Rojas A**, Figueroa H, Morales E. Fueling inflammation at tumor microenvironment: the role of multiligand/RAGE axis. *Carcinogenesis* 2010; **31**: 334-341 [PMID: 20028726 DOI: 10.1093/carcin/bgp322]

110 **Wolf G**. Cell cycle regulation in diabetic nephropathy. *Kidney Int Suppl* 2000; **77**: S59-S66 [PMID: 10997692 DOI: 10.1046/j.1523-1755.2000.07710.x]

111 **Li X**, Li J, Cai Y, Peng S, Wang J, Xiao Z, Wang Y, Tao Y, Li J, Leng Q, Wu D, Yang S, Ji Z, Han Y, Li L, Gao X, Zeng C, Wen X. Hyperglycaemia-induced miR-301a promotes cell proliferation by repressing p21 and Smad4 in prostate cancer. *Cancer Lett* 2018; **418**: 211-220 [PMID: 29331421 DOI: 10.1016/j.canlet.2018.01.031]

112 **Kim D**, Ahn BN, Kim Y, Hur DY, Yang JW, Park GB, Jang JE, Lee EJ, Kwon MJ, Kim TN, Kim MK, Park JH, Rhee BD, Lee SH. High Glucose with Insulin Induces Cell Cycle Progression and Activation of Oncogenic Signaling of Bladder Epithelial Cells Cotreated with Metformin and Pioglitazone. *J Diabetes Res* 2019; **2019**: 2376512 [PMID: 30729133 DOI: 10.1155/2019/2376512]

113 **Nagy T**, Fisi V, Frank D, Kátai E, Nagy Z, Miseta A. Hyperglycemia-Induced Aberrant Cell Proliferation; A Metabolic Challenge Mediated by Protein O-GlcNAc Modification. *Cells* 2019; **8** [PMID: 31466420 DOI: 10.3390/cells8090999]

114 **Sakabe K**, Wang Z, Hart GW. Beta-N-acetylglucosamine (O-GlcNAc) is part of the histone code. *Proc Natl Acad Sci U S A* 2010; **107**: 19915-19920 [PMID: 21045127 DOI: 10.1073/pnas.1009023107]

115 **Fardini Y**, Dehennaut V, Lefebvre T, Issad T. O-GlcNAcylation: A New Cancer Hallmark? *Front Endocrinol (Lausanne)* 2013; **4**: 99 [PMID: 23964270 DOI: 10.3389/fendo.2013.00099]

116 **Forma E**, Jóźwiak P, Bryś M, Krześlak A. The potential role of O-GlcNAc modification in cancer epigenetics. *Cell Mol Biol Lett* 2014; **19**: 438-460 [PMID: 25141978 DOI: 10.2478/s11658-014-0204-6]

117 **Jiang M**, Qiu Z, Zhang S, Fan X, Cai X, Xu B, Li X, Zhou J, Zhang X, Chu Y, Wang W, Liang J, Horvath T, Yang X, Wu K, Nie Y, Fan D. Elevated O-GlcNAcylation promotes gastric cancer cells proliferation by modulating cell cycle related proteins and ERK 1/2 signaling. *Oncotarget* 2016; **7**: 61390-61402 [PMID: 27542217 DOI: 10.18632/oncotarget.11359]

118 **Chiurillo MA**. Role of the Wnt/β-catenin pathway in gastric cancer: An in-depth literature review. *World J Exp Med* 2015; **5**: 84-102 [PMID: 25992323 DOI: 10.5493/wjem.v5.i2.84]

119 **Zhan T**, Rindtorff N, Boutros M. Wnt signaling in cancer. *Oncogene* 2017; **36**: 1461-1473 [PMID: 27617575 DOI: 10.1038/onc.2016.304]

120 **Chocarro-Calvo A**, García-Martínez JM, Ardila-González S, De la Vieja A, García-Jiménez C. Glucose-induced β-catenin acetylation enhances Wnt signaling in cancer. *Mol Cell* 2013; **49**: 474-486 [PMID: 23273980 DOI: 10.1016/j.molcel.2012.11.022]

121 **García-Jiménez C**, García-Martínez JM, Chocarro-Calvo A, De la Vieja A. A new link between diabetes and cancer: enhanced WNT/β-catenin signaling by high glucose. *J Mol Endocrinol* 2014; **52**: R51-R66 [PMID: 24049067 DOI: 10.1530/JME-13-0152]

122 **Ma X**, Cui Z, Du Z, Lin H. Transforming growth factor-β signaling, a potential mechanism associated with diabetes mellitus and pancreatic cancer? *J Cell Physiol* 2020; **235**: 5882-5892 [PMID: 32017070 DOI: 10.1002/jcp.29605]

123 **Zhao L**, Zou Y, Liu F. Transforming Growth Factor-Beta1 in Diabetic Kidney Disease. *Front Cell Dev Biol* 2020; **8**: 187 [PMID: 32266267 DOI: 10.3389/fcell.2020.00187]

124 **Achyut BR**, Yang L. Transforming growth factor-β in the gastrointestinal and hepatic tumor microenvironment. *Gastroenterology* 2011; **141**: 1167-1178 [PMID: 21839702 DOI: 10.1053/j.gastro.2011.07.048]

125 **Ebert MP**, Yu J, Miehlke S, Fei G, Lendeckel U, Ridwelski K, Stolte M, Bayerdörffer E, Malfertheiner P. Expression of transforming growth factor beta-1 in gastric cancer and in the gastric mucosa of first-degree relatives of patients with gastric cancer. *Br J Cancer* 2000; **82**: 1795-1800 [PMID: 10839293 DOI: 10.1054/bjoc.1999.1107]

126 **Naef M**, Ishiwata T, Friess H, Büchler MW, Gold LI, Korc M. Differential localization of transforming growth factor-beta isoforms in human gastric mucosa and overexpression in gastric carcinoma. *Int J Cancer* 1997; **71**: 131-137 [PMID: 9139831 DOI: 10.1002/(sici)1097-0215(19970410)71:2<131::aid-ijc1>3.0.co;2-1]

127 **Ikushima H**, Miyazono K. TGFbeta signalling: a complex web in cancer progression. *Nat Rev Cancer* 2010; **10**: 415-424 [PMID: 20495575 DOI: 10.1038/nrc2853]

128 **Hynes NE**, MacDonald G. ErbB receptors and signaling pathways in cancer. *Curr Opin Cell Biol* 2009; **21**: 177-184 [PMID: 19208461 DOI: 10.1016/j.ceb.2008.12.010]

129 **Arienti C**, Pignatta S, Tesei A. Epidermal Growth Factor Receptor Family and its Role in Gastric Cancer. *Front Oncol* 2019; **9**: 1308 [PMID: 31850207 DOI: 10.3389/fonc.2019.01308]

130 **Thomas MC**, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, Rossing P, Groop PH, Cooper ME. Diabetic kidney disease. *Nat Rev Dis Primers* 2015; **1**: 15018 [PMID: 27188921 DOI: 10.1038/nrdp.2015.18]

131 **Rayego-Mateos S**, Rodrigues-Diez R, Morgado-Pascual JL, Valentijn F, Valdivielso JM, Goldschmeding R, Ruiz-Ortega M. Role of Epidermal Growth Factor Receptor (EGFR) and Its Ligands in Kidney Inflammation and Damage. *Mediators Inflamm* 2018; **2018**: 8739473 [PMID: 30670929 DOI: 10.1155/2018/8739473]

132 **Dos Santos JM**, Tewari S, Mendes RH. The Role of Oxidative Stress in the Development of Diabetes Mellitus and Its Complications. *J Diabetes Res* 2019; **2019**: 4189813 [PMID: 31192263 DOI: 10.1155/2019/4189813]

133 **Yuan T**, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W, Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. *Redox Biol* 2019; **20**: 247-260 [PMID: 30384259 DOI: 10.1016/j.redox.2018.09.025]

134 **Wang Z**, Chen JQ, Liu JL. COX-2 Inhibitors and Gastric Cancer. *Gastroenterol Res Pract* 2014; **2014**: 132320 [PMID: 25371669 DOI: 10.1155/2014/132320]

135 **Sung JJ**, Leung WK, Go MY, To KF, Cheng AS, Ng EK, Chan FK. Cyclooxygenase-2 expression in Helicobacter pylori-associated premalignant and malignant gastric lesions. *Am J Pathol* 2000; **157**: 729-735 [PMID: 10980112 DOI: 10.1016/S0002-9440(10)64586-5]

136 **Oshima H**, Oshima M. The role of PGE2-associated inflammatory responses in gastric cancer development. *Semin Immunopathol* 2013; **35**: 139-150 [PMID: 23053397 DOI: 10.1007/s00281-012-0353-5]

137 **Nasrallah R**, Hassouneh R, Hébert RL. PGE2, Kidney Disease, and Cardiovascular Risk: Beyond Hypertension and Diabetes. *J Am Soc Nephrol* 2016; **27**: 666-676 [PMID: 26319242 DOI: 10.1681/ASN.2015050528]

138 **Wang Y**, Tao J, Yao Y. Prostaglandin E2 Activates NLRP3 Inflammasome in Endothelial Cells to Promote Diabetic Retinopathy. *Horm Metab Res* 2018; **50**: 704-710 [PMID: 30142638 DOI: 10.1055/a-0664-0699]

139 **Shanmugam N**, Kim YS, Lanting L, Natarajan R. Regulation of cyclooxygenase-2 expression in monocytes by ligation of the receptor for advanced glycation end products. *J Biol Chem* 2003; **278**: 34834-34844 [PMID: 12837757 DOI: 10.1074/jbc.M302828200]

140 **Kwon HJ**, Park MI, Park SJ, Moon W, Kim SE, Kim JH, Choi YJ, Lee SK. Insulin Resistance Is Associated with Early Gastric Cancer: A Prospective Multicenter Case Control Study. *Gut Liver* 2019; **13**: 154-160 [PMID: 30400721 DOI: 10.5009/gnl17556]

141 **Yi HK**, Hwang PH, Yang DH, Kang CW, Lee DY. Expression of the insulin-like growth factors (IGFs) and the IGF-binding proteins (IGFBPs) in human gastric cancer cells. *Eur J Cancer* 2001; **37**: 2257-2263 [PMID: 11677116 DOI: 10.1016/S0959-8049(01)00269-6]

142 **Choi YJ**. Insulin Resistance: A Hidden Risk Factor for Gastric Cancer? *Gut Liver* 2019; **13**: 133-134 [PMID: 30893982 DOI: 10.5009/gnl19060]

143 **Tsujimoto T**, Kajio H, Sugiyama T. Association between hyperinsulinemia and increased risk of cancer death in nonobese and obese people: A population-based observational study. *Int J Cancer* 2017; **141**: 102-111 [PMID: 28390156 DOI: 10.1002/ijc.30729]

144 **Garay-Sevilla ME**, Gomez-Ojeda A, González I, Luévano-Contreras C, Rojas A. Contribution of RAGE axis activation to the association between metabolic syndrome and cancer. *Mol Cell Biochem* 2021; **476**: 1555-1573 [PMID: 33398664 DOI: 10.1007/s11010-020-04022-z]

145 **Pollak M**. Insulin and insulin-like growth factor signalling in neoplasia. *Nat Rev Cancer* 2008; **8**: 915-928 [PMID: 19029956 DOI: 10.1038/nrc2536]

146 **Saliminejad K**, Khorram Khorshid HR, Soleymani Fard S, Ghaffari SH. An overview of microRNAs: Biology, functions, therapeutics, and analysis methods. *J Cell Physiol* 2019; **234**: 5451-5465 [PMID: 30471116 DOI: 10.1002/jcp.27486]

147 **Ali Syeda Z**, Langden SSS, Munkhzul C, Lee M, Song SJ. Regulatory Mechanism of MicroRNA Expression in Cancer. *Int J Mol Sci* 2020; **21** [PMID: 32138313 DOI: 10.3390/ijms21051723]

148 **Rojas A**, Araya P, Gonzalez I, Morales E. Gastric Tumor Microenvironment. *Adv Exp Med Biol* 2020; **1226**: 23-35 [PMID: 32030673 DOI: 10.1007/978-3-030-36214-0\_2]

149 **Link A**, Schirrmeister W, Langner C, Varbanova M, Bornschein J, Wex T, Malfertheiner P. Differential expression of microRNAs in preneoplastic gastric mucosa. *Sci Rep* 2015; **5**: 8270 [PMID: 25652892 DOI: 10.1038/srep08270]

150 **Kim M**, Zhang X. The Profiling and Role of miRNAs in Diabetes Mellitus. *J Diabetes Clin Res* 2019; **1**: 5-23 [PMID: 32432227 DOI: 10.33696/diabetes.1.003]

151 **Chen B**, Li J, Chi D, Sahnoune I, Calin S, Girnita L, Calin GA. Non-Coding RNAs in IGF-1R Signaling Regulation: The Underlying Pathophysiological Link between Diabetes and Cancer. *Cells* 2019; **8** [PMID: 31847392 DOI: 10.3390/cells8121638]

152 **Liang M**, Shi B, Liu J, He L, Yi G, Zhou L, Yu G, Zhou X. Downregulation of miR203 induces overexpression of PIK3CA and predicts poor prognosis of gastric cancer patients. *Drug Des Devel Ther* 2015; **9**: 3607-3616 [PMID: 26213461 DOI: 10.2147/DDDT.S85525]

153 **Feng L**, Cheng K, Zang R, Wang Q, Wang J. miR-497-5p inhibits gastric cancer cell proliferation and growth through targeting PDK3. *Biosci Rep* 2019; **39** [PMID: 31409724 DOI: 10.1042/BSR20190654]

154 **Wang BG**, Jiang LY, Xu Q. A comprehensive evaluation for polymorphisms in *let-7* family in cancer risk and prognosis: a system review and meta-analysis. *Biosci Rep* 2018; **38** [PMID: 29717029 DOI: 10.1042/BSR20180273]

155 **Zhu P**, Liu J, Lu M, Wu G, Lin X, Cai L, Zhang X. Influence and mechanism of miR-99a suppressing development of colorectal cancer (CRC) with diabetes mellitus (DM). *Onco Targets Ther* 2019; **12**: 10311-10321 [PMID: 31819515 DOI: 10.2147/OTT.S190998]

156 **Coucha M**, Mohamed IN, Elshaer SL, Mbata O, Bartasis ML, El-Remessy AB. High fat diet dysregulates microRNA-17-5p and triggers retinal inflammation: Role of endoplasmic-reticulum-stress. *World J Diabetes* 2017; **8**: 56-65 [PMID: 28265343 DOI: 10.4239/wjd.v8.i2.56]

157 **Gao X**, Qiao X, Xing X, Huang J, Qian J, Wang Y, Zhang Y, Zhang X, Li M, Cui J, Yang Y. Matrix Stiffness-Upregulated MicroRNA-17-5p Attenuates the Intervention Effects of Metformin on HCC Invasion and Metastasis by Targeting the PTEN/PI3K/Akt Pathway. *Front Oncol* 2020; **10**: 1563 [PMID: 32974191 DOI: 10.3389/fonc.2020.01563]

158 **Zhang L**, Yu D. Exosomes in cancer development, metastasis, and immunity. *Biochim Biophys Acta Rev Cancer* 2019; **1871**: 455-468 [PMID: 31047959 DOI: 10.1016/j.bbcan.2019.04.004]

159 **Kalluri R**, LeBleu VS. The biology**,** function**,** and biomedical applications of exosomes. *Science* 2020; **367** [PMID: 32029601 DOI: 10.1126/science.aau6977]

160 **Wu SF**, Noren Hooten N, Freeman DW, Mode NA, Zonderman AB, Evans MK. Extracellular vesicles in diabetes mellitus induce alterations in endothelial cell morphology and migration. *J Transl Med* 2020; **18**: 230 [PMID: 32517700 DOI: 10.1186/s12967-020-02398-6]

161 **Freeman DW**, Noren Hooten N, Eitan E, Green J, Mode NA, Bodogai M, Zhang Y, Lehrmann E, Zonderman AB, Biragyn A, Egan J, Becker KG, Mattson MP, Ejiogu N, Evans MK. Altered Extracellular Vesicle Concentration, Cargo, and Function in Diabetes. *Diabetes* 2018; **67**: 2377-2388 [PMID: 29720498 DOI: 10.2337/db17-1308]

162 **Huang T**, Song C, Zheng L, Xia L, Li Y, Zhou Y. The roles of extracellular vesicles in gastric cancer development, microenvironment, anti-cancer drug resistance, and therapy. *Mol Cancer* 2019; **18**: 62 [PMID: 30925929 DOI: 10.1186/s12943-019-0967-5]

163 **Hsieh HL**, Tsai MM. Tumor progression-dependent angiogenesis in gastric cancer and its potential application. *World J Gastrointest Oncol* 2019; **11**: 686-704 [PMID: 31558974 DOI: 10.4251/wjgo.v11.i9.686]

164 **Chen KB**, Chen J, Jin XL, Huang Y, Su QM, Chen L. Exosome-mediated peritoneal dissemination in gastric cancer and its clinical applications. *Biomed Rep* 2018; **8**: 503-509 [PMID: 29774141 DOI: 10.3892/br.2018.1088]

165 **Deng G**, Qu J, Zhang Y, Che X, Cheng Y, Fan Y, Zhang S, Na D, Liu Y, Qu X. Gastric cancer-derived exosomes promote peritoneal metastasis by destroying the mesothelial barrier. *FEBS Lett* 2017; **591**: 2167-2179 [PMID: 28643334 DOI: 10.1002/1873-3468.12722]

166 **WARBURG O**. On the origin of cancer cells. *Science* 1956; **123**: 309-314 [PMID: 13298683 DOI: 10.1126/science.123.3191.309]

167 **Burns JS**, Manda G. Metabolic Pathways of the Warburg Effect in Health and Disease: Perspectives of Choice, Chain or Chance. *Int J Mol Sci* 2017; **18** [PMID: 29257069 DOI: 10.3390/ijms18122755]

168 **Liu Z**, Jia X, Duan Y, Xiao H, Sundqvist KG, Permert J, Wang F. Excess glucose induces hypoxia-inducible factor-1α in pancreatic cancer cells and stimulates glucose metabolism and cell migration. *Cancer Biol Ther* 2013; **14**: 428-435 [PMID: 23377827 DOI: 10.4161/cbt.23786]

169 **Huang YL**, Lin YC, Lin CC, Chen WM, Chen BPC, Lee H. High Glucose Induces VEGF-C Expression *via* the LPA1/3-Akt-ROS-LEDGF Signaling Axis in Human Prostate Cancer PC-3 Cells. *Cell Physiol Biochem* 2018; **50**: 597-611 [PMID: 30317243 DOI: 10.1159/000494177]

170 **Yang W**, Lu Z. Regulation and function of pyruvate kinase M2 in cancer. *Cancer Lett* 2013; **339**: 153-158 [PMID: 23791887 DOI: 10.1016/j.canlet.2013.06.008]

171 **Ramteke P**, Deb A, Shepal V, Bhat MK. Hyperglycemia Associated Metabolic and Molecular Alterations in Cancer Risk, Progression, Treatment, and Mortality. *Cancers (Basel)* 2019; **11** [PMID: 31546918 DOI: 10.3390/cancers11091402]

172 **Lei Y**, Zhou S, Hu Q, Chen X, Gu J. Carbohydrate response element binding protein (ChREBP) correlates with colon cancer progression and contributes to cell proliferation. *Sci Rep* 2020; **10**: 4233 [PMID: 32144313 DOI: 10.1038/s41598-020-60903-9]

173 **Kuhajda FP**. Fatty acid synthase and cancer: new application of an old pathway. *Cancer Res* 2006; **66**: 5977-5980 [PMID: 16778164 DOI: 10.1158/0008-5472.CAN-05-4673]

174 **Vordermark D**, Kraft P, Katzer A, Bölling T, Willner J, Flentje M. Glucose requirement for hypoxic accumulation of hypoxia-inducible factor-1alpha (HIF-1alpha). *Cancer Lett* 2005; **230**: 122-133 [PMID: 16253768 DOI: 10.1016/j.canlet.2004.12.040]

175 **Kitajima Y**, Miyazaki K. The Critical Impact of HIF-1a on Gastric Cancer Biology. *Cancers (Basel)* 2013; **5**: 15-26 [PMID: 24216696 DOI: 10.3390/cancers5010015]

**Footnotes**

**Conflict-of-interest statement:** The authors declare that there is no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** May 13, 2021

**First decision:** June 5, 2021

**Article in press:**

**Specialty type:** Oncology

**Country/Territory of origin:** Chile

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

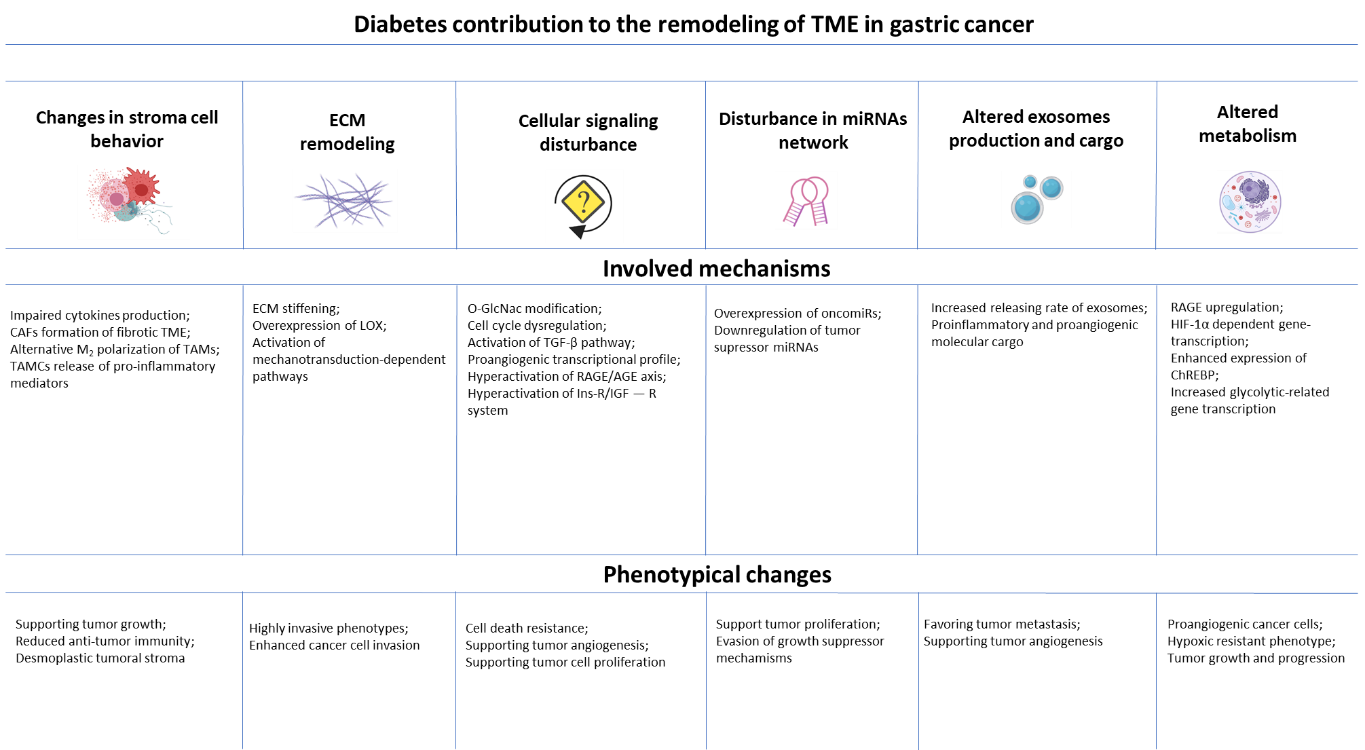
Grade C (Good): 0

Grade D (Fair): 0

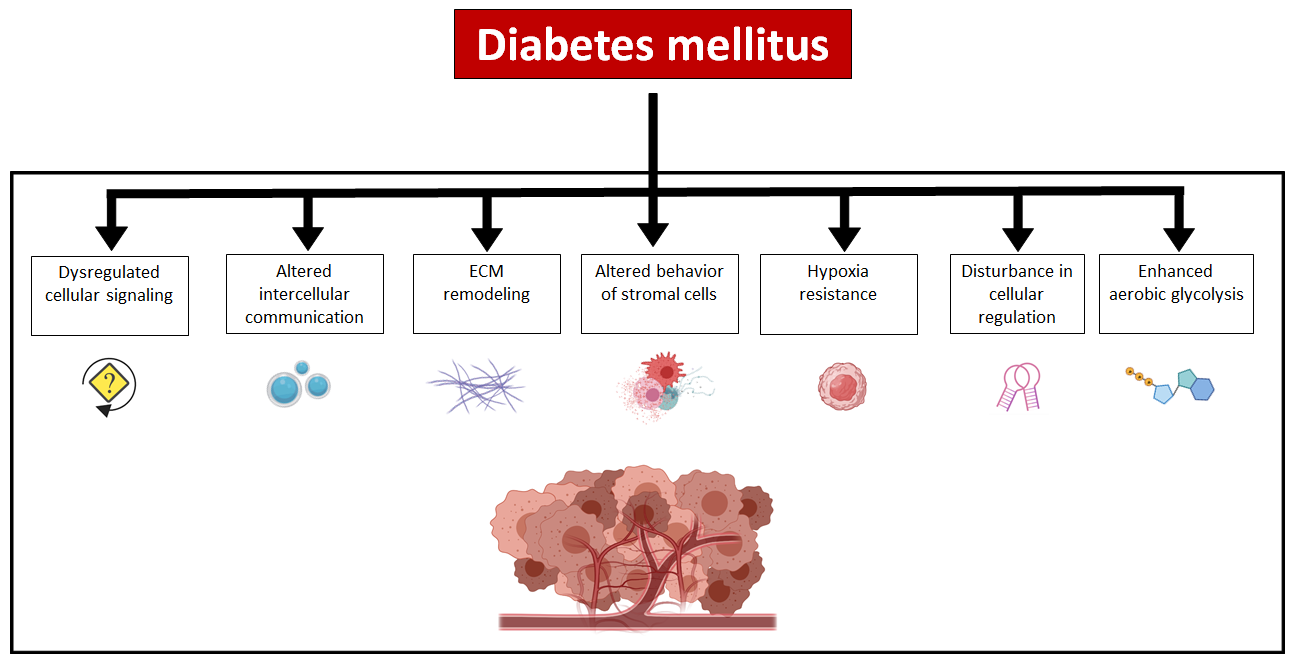
Grade E (Poor): 0

**P-Reviewer:** Ugo O **S-Editor:** Gao CC **L-Editor: P-Editor:**

**Figure Legends**

****

**Figure 1 Diabetes mellitus can sculpture the tumor microenvironment of gastric cancer through a myriad of different molecular mechanisms ranging from dysregulation of cellular signaling pathways to marked metabolic disturbances.** TME: Tumor microenvironment; ECM: Extracellular matrix; miRNAs: MicroRNAs; CAFs: Cancer-associated fibroblasts; TAMCs: Tumor-associated mast cells; LOX: Lysyl oxidase; TGF-β: Transforming growth factor β; RAGE: Receptor of advanced glycation end products; AGE: Advanced glycation end product; ChREBP: Carbohydrate-responsive element-binding protein.



**Figure 2 The molecular mechanisms involved in the contribution of diabetes mellitus to the remodeling of gastric cancer microenvironment determine crucial phenotypical changes not only on tumor cells but also in many other infiltrating cells.** All changes may then result in a supporting tumor-growth niche that favors angiogenesis, invasion, and metastasis, as well as interference with anti-tumor immunity and thus generating more aggressive tumor phenotypes. ECM: Extracellular matrix.