

Interlinking Pathological Pathways of Diabetes and Cancer – Identification of Novel Leads: A Review ArticleAnin G S Queency Stylin¹, B. Shanthi², Angeline Julius³, P. Sandhya⁴, W. Jincy⁵¹Tutor, Dept. of Biochemistry, Sree Balaji Medical College and Hospital, BIHER²Professor & HOD, Dept. of Biochemistry, Sree Balaji Medical College and Hospital, BIHER³Assistant Professor, (Centre for Materials Engineering and Regenerative Medicine), Bharath Institute of Higher Education and Research.⁴ Tutor, Dept. of Biochemistry, Sree Balaji Medical College and Hospital, BIHER.⁵Assistant Professor, ACS Medical College and Hospital, Dr. M.G.R. Educational And Research Institute

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Abstract:

Diabetes Mellitus is a global disorder that specifies the hyperglycemic condition in an individual, which is related to the secretion and action of insulin hormone. Many Epidemiological studies have significantly manifested the prevalence of being affected by different types of cancer by a diabetic patient. Many Signaling pathways were shared by diabetes and cancer. Signaling pathways like TNF- α , IL-1b, IL-8, PI3K, MAPK/ERK, VEGF, VEGFR, Estrogen/ER/SHBG, IRS I, PI3K, PIP3, AKT, SOS, RAS, C-Raf, MEK1/2, ERK, etc were disturbed in hyperglycemia which leads to the root cause of deadly diseases like Lung cancer, Hepatocellular cancer, Endometrial cancer, Breast cancer, Pancreatic cancer, etc. Besides many observational studies shows that some drugs used to treat diabetes were related to higher and lower risk of cancer. Recent studies have explained the role of the antidiabetic drug in reducing the effect of cancer. Common antidiabetic drugs like Metformin and thiazolidinediones (TZDs) were found to give a good result in reducing the risk of cancer. On the other hand, some studies have shown the effect of anti-diabetic drugs like Insulin, Sulfonylureas, and GLP – I agonists can develop tumorigenesis in the IGF -1 Signaling pathway. To identify the interlinking pathways and common medications for Diabetes and cancer, a systemic review was performed. By this review, it is found that the Synchronism of the deadly disease cancer and diabetes mellitus could be related in regards to the interlinking pathways and medications. But the results from most of the studies are dubious and colliding. Hence strong research work should be made shortly to relate diabetes and cancer which can be reliable.

Keywords: Diabetes, Cancer, Signaling Pathway, Insulin, Metformin.

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Introduction

Diabetes Mellitus is a metabolic disease that leads to hyperglycemia. It results in elevated levels of sugar in the blood and dysfunction of β -cells in the pancreas. Lack of insulin or insulin action plays an important role in metabolic activities, which is the fundamental cause of diabetes mellitus [1]. The hormone insulin produced by β -cells of the pancreas helps in the metabolism of sugar, in turn, reduces the blood sugar level. Classification of diabetes is more important for diagnosis and treatment. [2] Diabetes mellitus is of two types, they are 1. Type I Diabetes Mellitus or juvenile diabetes 2. Type II Diabetes Mellitus or Insulin dependent diabetes Mellitus. [3] Type I diabetes mellitus is more prevalent in children and Type II diabetes mellitus in adults.

The widespread presence of diabetes mellitus has increased tremendously; nearly 420 million

individuals are affected by this disease. The International Diabetes Federation released a report in which 415 million people were affected by diabetes mellitus and the count would increase to 642 million by 2040. [4] Type II diabetes mellitus is associated with enormous diseases like renal disease, Stroke, coronary heart disease, etc and it is also related to deadly diseases like cancer. Evidence from observational studies has shown the relationship with different types of cancer like endometrial cancer, colorectal cancer, breast cancer, gall bladder cancer, lung cancer, and pancreatic cancer. Nearly 18.1 million cancer cases were found worldwide with the highest cause of mortality. According to a recent report, across the world, nearly 293,000 cancer cases were associated with diabetes mellitus. [5]

The link between diabetes and cancer is not well known, but various studies have shown their common risk factors which involve proliferation and apoptosis. Diabetes initiates cell damage responses, glucotoxicity, lipotoxicity, and oxidative stress. Certainly hyperglycemia, hyperinsulinemia, and inflammation seen in diabetic patients pave the way for the progression of neoplasia. Added to that, results from observational and experimental studies indicate the drugs used for diabetes are related to the reduced risk of cancer. [6]

Diabetes Mellitus and Hepatocellular Carcinoma: Hepatocellular carcinoma (HCC) is

the most common liver cancer with a high mortality rate across the globe.

Patients affected by hepatocellular carcinoma are mostly with Chronic liver disease and fibrosis. [7] Figure 1 explains the association between diabetes and hepatocellular carcinoma. [2]. Here Virus, genetic susceptibility, and environmental factor shows their action on pancreatic beta cell, which in turn releases proinflammatory cytokines (TNF- α , IL-1b, IL-8) which leads to a decrease in insulin resistance and then finally Hepatocellular carcinoma.

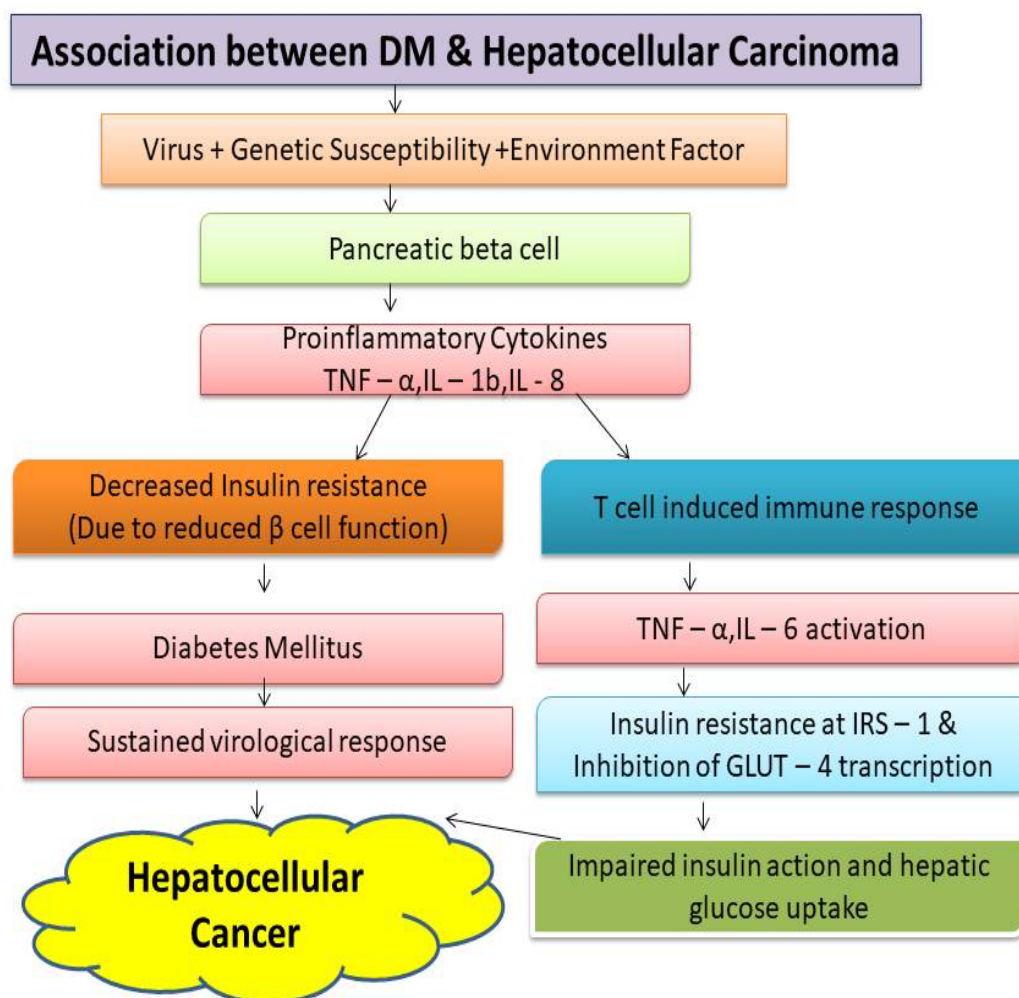


Figure 1: Pathways associated between DM and Hepatocellular Carcinoma

Figure 1: Shows the pathogenesis of hepatitis C-induced Type II Diabetes Mellitus, Virus acts on a pancreatic beta cell which releases the proinflammatory cytokines and it decreases insulin resistance (diabetes mellitus).

At the same time, Proinflammatory cytokines activate the signaling factors which induce Insulin resistance at IRS-1, All these factors lead to

diabetic Mellitus and finally Hepatocellular cancer. [4]

Diabetes mellitus and endometrial carcinoma: Diabetic patients have twice the chance of getting endometrial carcinoma. The progression of endometrial carcinoma is due to the high sugar level, insulin resistance, hyperinsulinemia, glycolysis, chronic inflammation, obesity, and initiation of signaling pathways. Figure 2 shows the

prevalence of getting endometrial carcinoma in a diabetes patient. The blue box shows the biological mechanism of diabetes and changes observed due

to diabetes including signaling pathways that end up in endometrial carcinoma.

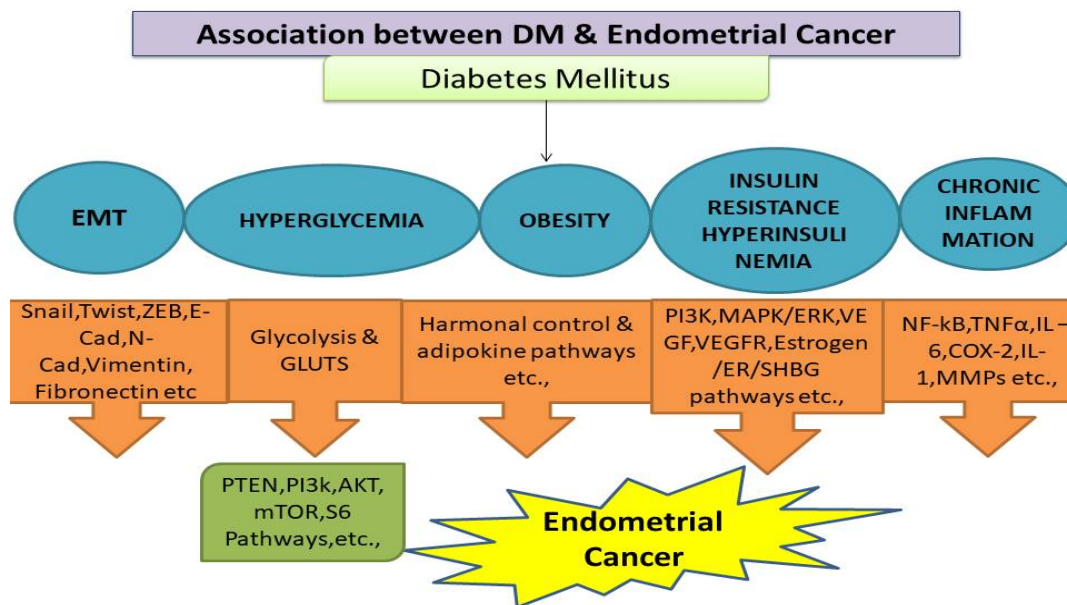


Figure 2: Pathways associated between DM & Endometrial Cancer

Figure 2: Diabetes leads to epithelial-mesenchymal transition (EMT), Hyperglycemia, Obesity, Insulin resistance & chronic inflammation which in turn pave the way for the activation of signaling pathways that leads to Endometrial Cancer. [8]

Diabetes mellitus and lung cancer: Diabetes patients are at high risk of developing lung cancer. Type I and Type II diabetic patients are related to

lung cancer. Like other diseases, diabetes disturbs the cell signaling process, which leads to tumorigenesis. [3]

Figure 3 explains the consequence of diabetic Mellitus which leads to the signaling pathway like the glycation end product, inflammation, oxidative stress, angiogenesis & hypoxia leads to lung cancer.

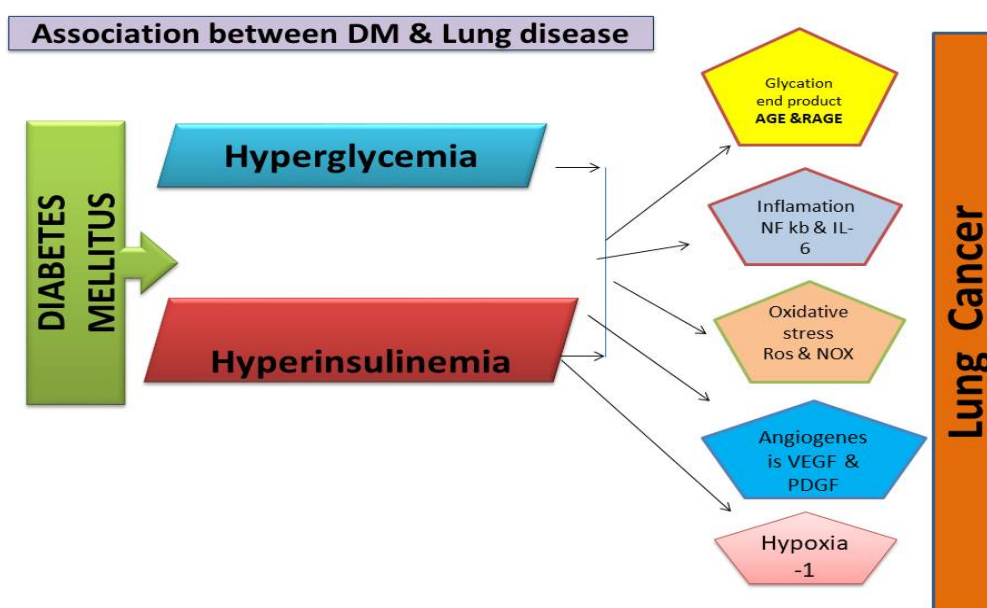


Figure 3: Pathways associated between diabetes Mellitus and Lung cancer

Diabetes mellitus and Breast cancer: Across the world, the United States of America holds the second rank for the incidence of breast cancer. A huge women population is affected by this disease. [9] Diabetic women are at high risk for the prevalence of getting breast cancer than a woman without diabetes. [10]. One of the studies on

diabetes and breast cancer shows a significant relationship between diabetes and breast cancer in Europe and the United States, but no such significant relationship was not seen in Asia. [11]

Figure 4 shows the schematic representation of signaling factors released due to diabetes mellitus which is responsible for breast cancer.

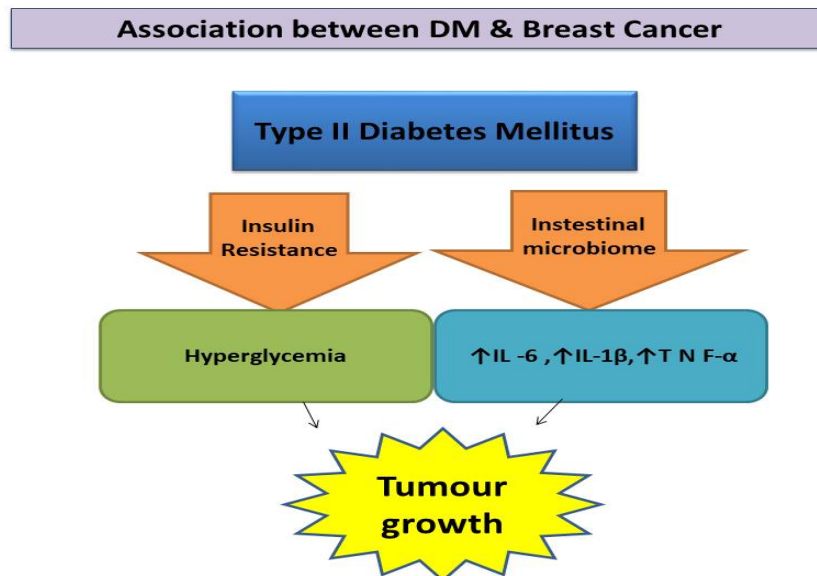


Figure 4: This figure shows the mechanism linking Type II Diabetic Mellitus and Breast cancer through the activation of a signaling pathway. [9]

Diabetes and Colorectal cancer: The risk of getting colorectal cancer for a diabetic patient is approximately 1.27%. The survival rate for colorectal cancer with diabetes mellitus got lowered by 18%. According to the reports of epidemiological data, colonoscopies done for 976

patients with diabetes have shown the presence of polyps and carcinoma. [5,12]

Figure 5 explains a cascade pathway where IGF from the liver and insulin from the pancreas acts on the intestine to release signaling factors responsible for breast cancer [13]

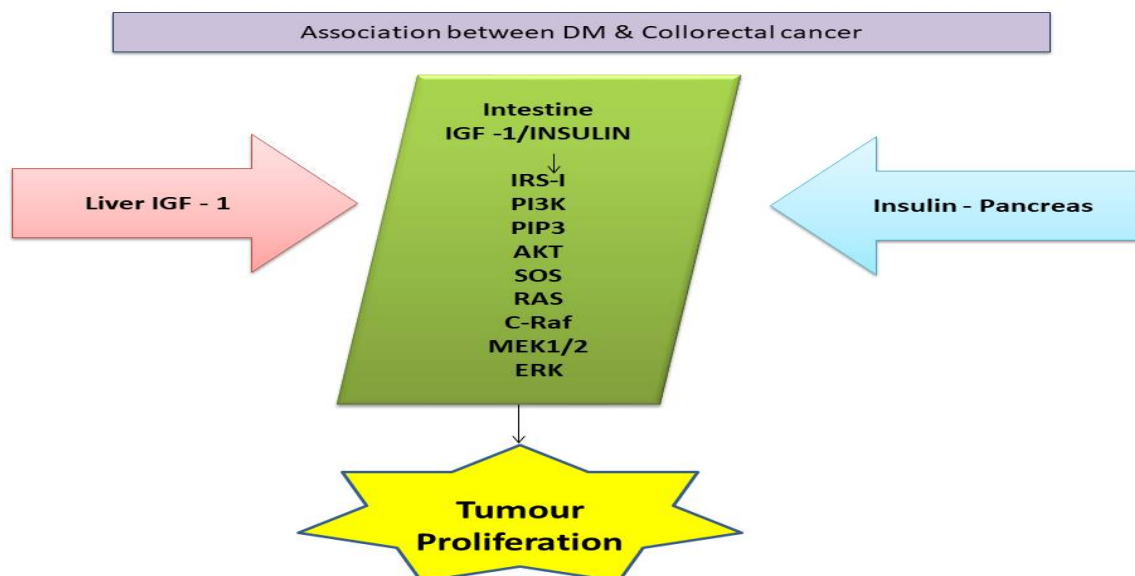


Figure 5: This figure explains the IGF-1 from the liver & Insulin from the pancreas and shows its action on the intestine to release Signal factors that are responsible for breast cancer. [13]

Diabetes and pancreatic cancer: Pancreatic cancer is the major cause of death across the globe. According to the survey pancreatic cancer is ranked in eighth place, with 227000 deaths/year. [14]

In addition Type II diabetes mellitus increase the rate of mortality for pancreatic cancer patient. The forecast of this study shows it may reach up to 700 million by 2045. [15].

Hence this prevalence of getting pancreatic cancer is high in diabetes and obese patients. [16]

Figure 6 shows the biological transformation that happened in the body due to the effect of pancreatic cancer will cause a new onset of diabetes mellitus.

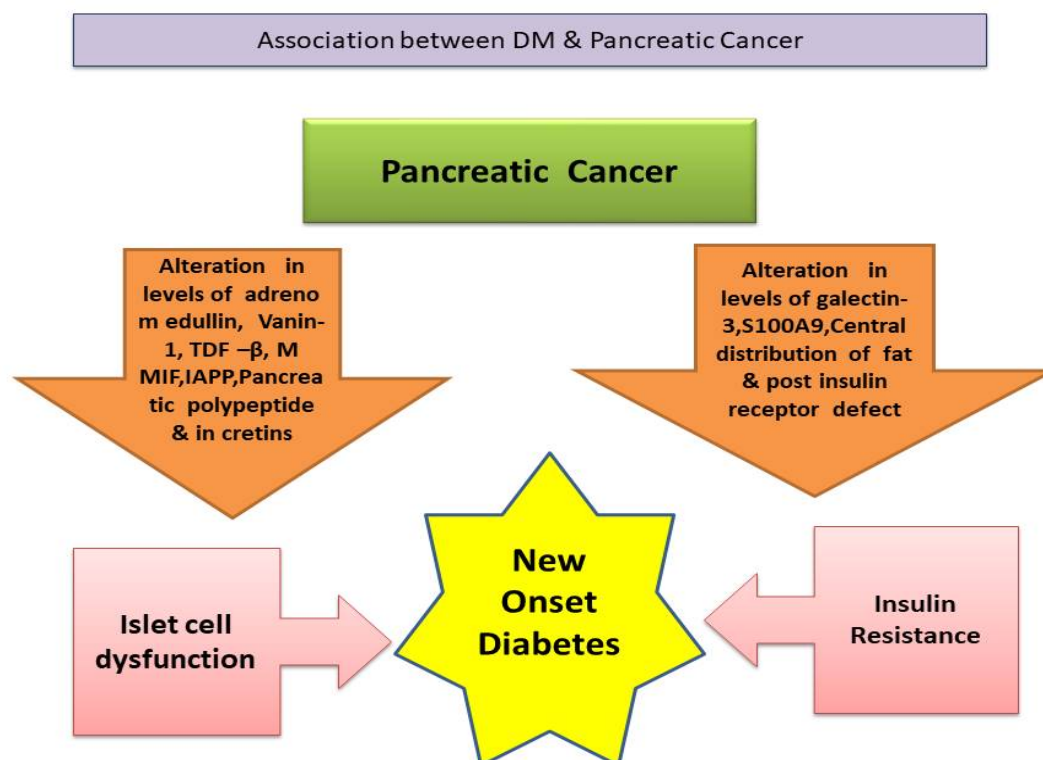


Figure 6: This mechanism explains the cause of the new onset of diabetes from pancreatic cancer. [15]

Related Drug inventions for Diabetes mellitus and cancer

Metformin: Metformin and thiazolidinediones (TZDs) are the two antidiabetic drugs that have a good effect on cancer treatment. [1] Metformin is the first drug given to a diabetic patient found to reduce the tumorigenesis of cancer cells. [8] In the study performed in mice with lung cancer tumor size got gradually decreased from 53-72%. Metformin has a special role in treating glucocorticoid-induced diabetes patients affected by Breast cancer, Lung Cancer, and melanoma. [1]

Studies show the inhibiting action of metformin on AMPK the TSC2/ mTOR/ S6 signaling factors to reduce the effect of cancer. [17] Metformin can perform G0/G1 cell cycle arrest, apoptosis, and autophagy, and brings a high AMPK phosphorylation effect.

Current studies have shown the suppression of the EMT process by speeding up the E-cadherin process and reducing the expression of mesenchymal markers such as N-cadherin,

vimentin, and fibronectin and EMT transcriptional pathways like Snail-1, Twist-1, and ZEB-1 thereby reduces the prevalence of getting EC cancer. [18]. Studies with proven results show the relationship between diabetes mellitus and breast cancer [19] Metformin activates the AMP-activated protein kinase and suppress the mammalian target of rapamycin (mTOR). It can also inhibit the azoxymethane-induced formation of colorectal aberrant crypt foci. [20]

Other drugs: CXCR4 inhibitor AMD3100 with HuR siRNA-nanotherapy inhibits the CXCR4/SDF signaling pathway thereby suppressing the lung cancer tumor formation [3] The risk of getting lung cancer can also be reduced by Metformin/Insulin treatment [12]. Sulfonylurea, Dipeptidylpeptidase-4 Inhibitors, α -Glucosidase inhibitors (AGIs) & Glucagon-like peptide-1 (GLP-1) receptor agonists, Sorafenib, Sunitinib, Brivanib, Linifanib, Tivantinib, etc, these drugs help to control diabetes by inhibiting the signaling pathway & biological mechanism which leads to the tumorigenesis. [1]

Carcinogenic activity of anti-diabetic drugs:

Recent studies have identified the risk of being affected by cancer using Anti-diabetic drugs. Insulin, Sulfonylureas, and GLP – I agonists can develop tumourigenesis through IGF -1, by inducing various signal cascade pathways which affect the cell metabolism [6] Thiazolidinediones drug and insulin have a higher risk of cancer cell proliferation.

Conclusion

Based on recent studies with proven results shows that diabetic patients are on the higher side of getting cancer. Hence the exact reason behind it is unclear. More studies need to be conducted shortly to get clarity to study the association between cancer and diabetes.

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