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Literature Review

GLP-1 Receptor Agonists and Cancers

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Abstract

Diabetes mellitus is associated with various types of cancers and presence of diabetes as a co-morbidity worsens the prognosis of cancer [1]. Glucagon-like peptide-1 receptor agonist (GLP-1RA) is a class of drug, which is used as a treatment of type 2 diabetes. Studies linking GLP-1RAs with cancers have found that GLP-1 RAs are associated with increased risks of pancreatic and thyroid cancers and decreased risks of breast, prostate, endometrial, colon, ovarian cancers and various other cancers. This review discusses the impact of GLP-1RAs on different cancers and pathways involved in carcinogenic and anti-carcinogenic effects of GLP-1RAs. GLP-1RAs exerts their carcinogenic and anti-carcinogenic effects by attenuating various pathways including mTOR, ERK ½, and MAPK. Studying and understanding core pathways of GLP-1RAs directs more research on GLP-1RAs and guides the future management of diabetes mellitus.

Keywords: Diabetes Mellitus; Pancreatitis; Glucagon-like receptor agonists (GLP-RAs); Pancreatitis; Insulin; Pancreatic Cancer; Breast Cancer; Prostate Cancer; Endometrial Cancer; Ovarian Cancer; Thyroid Cancer; Exenatide; Liraglutide; Exendin -4; MAPK; mTOR; Akt; Apoptosis; Carcinogenic; Anti-carcinogenic

Abbreviations

GLP -1: Glucagon Like Peptide; GLP-1R A: Glucagon Like Peptide -1 Receptor Agonist; GLP-1 R: Glucagon Like Peptide -1 Receptor; FDA: Food and Drug Administration; EASD: European Association of the Study of Diabetes; ADA: American Diabetes Association; PI3K: Phosphoinositide-3 Kinase; mTOR: Mammalian Target of Rapamycin; MAPK: Mitogen Activated Protein Kinase; NF-κB: Nuclear Factor Kappa Light Chain Enhancer of Activated B cells; MMP: Metalloproteinase; cAMP: Cyclic Adenosine Monophosphate; CREB: cAMP Response Element-Binding Protein; CRE: cAMP Response Elements; T2DM: Type 2 Diabetes Mellitus; Ex-4: Exendin-4; ERK: Extracellular Signal–Regulated Kinase; NSAID: Non-Steroidal Anti-inflammatory Drug; AMPKa2: AMP-Activated Protein Kinase Catalytic Subunit a2; GPCR: G-Protein Coupled Receptors; ICAM: Intracellular Adhesion Molecule; VCAM: Vascular Cell Adhesion Molecule; IRS: Insulin Receptor Substrate; TNF: Tumor Necrosis Factor; IL: Interleukin; VEGF: Vascular Endothelial Growth Factor; HBA1c: Hemoglobin A1c

Introduction

GLP-1 receptor agonists, include exenatide and liraglutide, is a class of drug which is approved by the FDA in 2005 [2,3]. According to guidelines of American Diabetes Association (ADA) and National Institute of Clinical Excellence (NICE), GLP-1RAs are currently prescribed as a dual or triple therapy for the treatment of type 2 diabetes [3,4]. GLP-1RAs are analogues of natural hormone, incretin, which is secreted by L- cells of the intestine. GLP-1RAs control blood sugar through increasing glucose dependent insulin secretion [5], suppressing fasting and post-prandial elevated glucagon level and delaying gastric emptying [6,7]. GLP-1RAs not only control blood sugar level but they also have beneficial effects on weight, blood pressure, pancreatic β cell function and cholesterol levels which make this class of drug extremely valuable for the treatment of diabetes as hypertension, obesity and hypercholesterolemia are frequent comorbidities of diabetes [8]. However, several preclinical and clinical studies have linked GLP-1 RAs to different cancer, which unveils new problems in the use of this drug.

GLP-1 receptors have been found in CNS regions (hypothalamus, brainstem), pituitary, thyroid (C-cells) [9], lungs, heart, stomach, pancreas (α, β, γ, δ) intestine, kidney, skin and several other organs. Besides these regions, GLP-1 receptors are also found in endometrial cells (cancerous and non – cancerous) [9], breast cancer cells [11], colon cancer cells [12] and prostate cancer cells [13]. The presence of GLP-1 receptors in cancer tissues and normal tissues depicts the pleiotropic effects of GLP-1RAs on cancer and other tissues and demands special attention during their prescription to type 2 diabetic patients because diabetes mellitus is already known to play an important role in the occurrence of breast, endometrial, liver, pancreases, colorectal, and bladder cancers [14-17].

This review gives an overview of the association of GLP-1RAs with different cancers so that safety of the drug can be determined, and future research can be conducted in the light of knowledge presented here.

GLP-1 Receptor Agonists and Pancreatic Cancer

With the report of cases of pancreatitis due to exenatide, concerns for pancreatic cancer have increased because of the link between pancreatitis and cancer [18]. Pancreatitis as an adverse event of GLP-1RAs is significant because acute pancreatitis, if recurrent turns into chronic pancreatitis that causes stenosis of the pancreatic duct leading to an increase in intra-ductal pressure and the development of pancreatic carcinoma over the years [19].

Studies on mice demonstrated that GLP-1 administration doubled the pancreatic β cell mass, which is due to the trophic effects of GLP-1RA on pancreatic cells. GLP-1RAs preserve β cells by increasing proliferation, inhibiting apoptosis, and promoting differentiation of ductal stem cells of the pancreases into β cells. GLP-1RAs also protect β cells from an unfavorable metabolic environment due to diabetes by normalizing blood glucose and decreasing free fatty acids [20,21]. Xu., *et al*. demonstrated the increase in β cells mass of partial pancreatectomy rats after administration of exendin-4. The increase in β cells mass were seen to be due to β cells proliferation as well as differentiation of ductal progenitor cells

(neogenesis) into β cells. In patients with type 2 diabetes, 60% of beta cell mass is lost, which makes trophic properties of GLP-1RA beneficial in diabetic patients. This increase in β cell mass is considered as potentially causative of pancreatic cancer [22].

The mechanism by which GLP-1RAs exert their proliferative effect is that GLP-1RAs bind to GLP-1R, which are G-protein coupled receptors. The downstream signaling pathways involved in the proliferative activity of GLP-1, are PI3-K, AKt, MAPK, protein kinase C and MEK/ERK1/2 pathways [20]. Kennedy., *et al.* found activation of PI3K/AKT/mTOR due to a PTEN mutation. PTEN is the negative regulator of PI3K/Akt/mTOR pathway and mutation of PTEN promotes accelerated progression of pancreatic cancer and poor survival rate [23].

Several studies have found direct and indirect links of Exendin -4 with pancreatic cancer. Exendin -4 indirectly triggers cancer development by increasing the release of insulin which itself causes both the development and metastasis of cancer. Insulin encourages the growth of tumors by supplying nutrients, increasing sex hormones e.g. estrogen that also play roles in tumor development, and via activating insulin and IGF receptors. Insulin through its receptors also up regulates insulin response substrates (IRS-1), which downstream activate MAP kinase and PI3K/AKT pathways [10,24].

A study of human pancrease obtained from organ donors concluded that incretin therapy supports pancreatic mass with proliferation and dysplasia of pancreatic exocrine cell and hyperplasia of endocrine α cells that can grow into neuroendocrine tumors [25]. Although this study has several conflicts yet it directs our attention towards carcinogenic effects of GLP-1RAs and raises the need of more research.

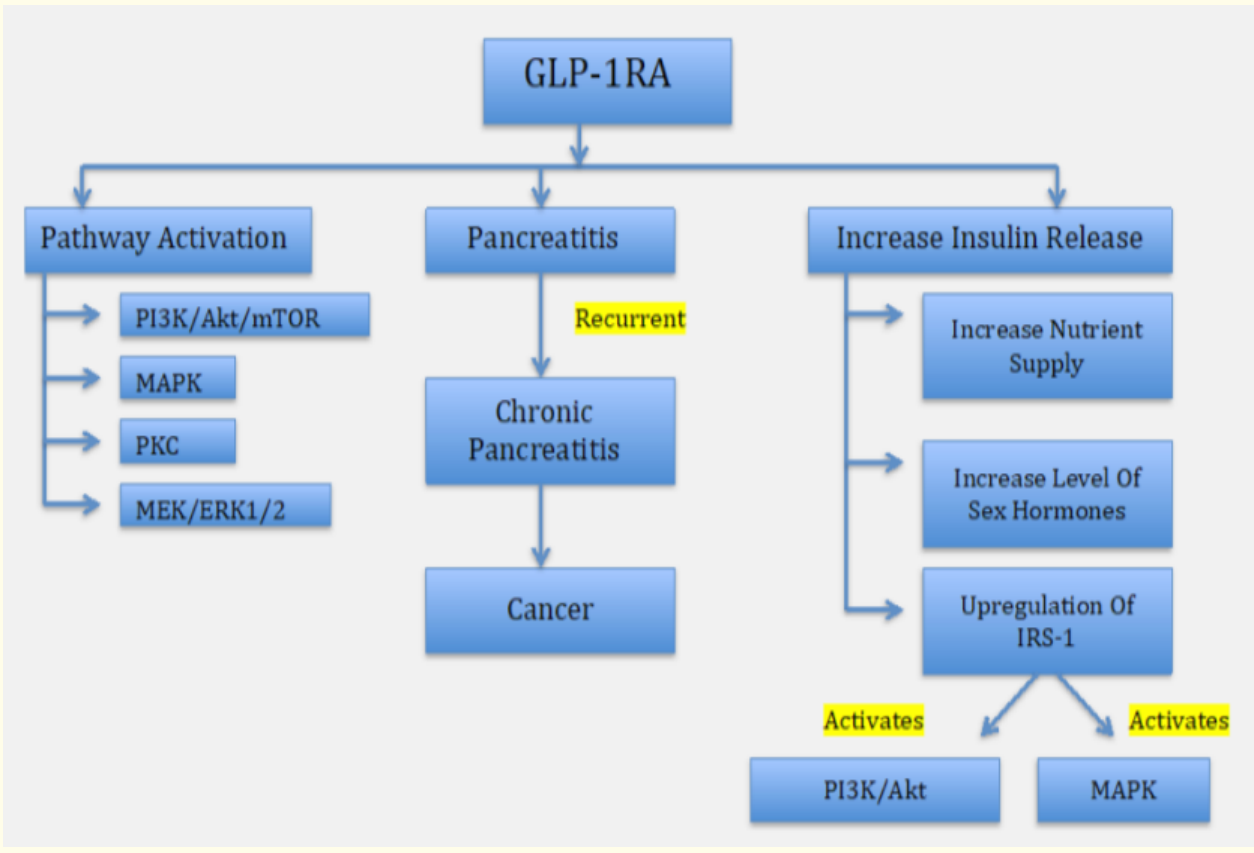

Figure 1: Depicts different mechanisms involved in development of pancreatic cancer by GLP-1RAs. GLP-1RA: Glucagon Like-Peptide Receptor Agonists; PI3K: Phosphoinositide-3 Kinase Pathways; m TOR: Mammalian Target of Rapamycin; MAPK: Mitogen Activated Protein Kinase; ERK-1: Extracellular Signal Regulated Kinase; PKC: Protein Kinase C; IRS-1: Insulin Receptor Substrate-1.

GLP-1 Receptor Agonists and Thyroid Cancer

Cancer of thyroid is rare as compared to other cancer, however the incidence of being diagnosed with thyroid cancer has increased 3 fold in the past 30 years [26]. A large prospective study revealed 25% increased risk of thyroid cancer in patients with diabetes [27]. Furthermore, analysis of FDA data exhibited a significant link between thyroid cancer and GLP-1RA use [19,28].

GLP-1RAs come with the black box warning from the FDA, which prohibits the use of these drugs in patients with thyroid cancer or multiple endocrine neoplasia [29]. GLP-1 receptor activation increases the transcription of calcitonin gene [30,31]. Elevated calcitonin blood levels, is an indicator of C cell hyperplasia, medullary thyroid cancer, C – cell proliferation and activation. The mechanism behind thyroid cancer formation by GLP-1RAs is that GLP-1RAs bind with G- protein coupled receptor and increases. The levels of cAMP in the cells that in turn activates mTOR pathway. mTOR pathway promotes protein synthesis, cell cycle progression and block apoptosis [32].

In clinical trials and in many other human studies, no association has been seen between GLP-1RAs and thyroid cancer [33]. However, the FDA AERS database shows increase risk of thyroid cancer with exenatide [28].

Examination of human thyroid tissue obtained from surgery revealed the expression of GLP-1 receptors on medullary thyroid cancer, C- cell hyperplasia and papillary thyroid cancer. Presence of these receptors indicates GLP-1RAs a potential cause of thyroid cancer in humans [34].

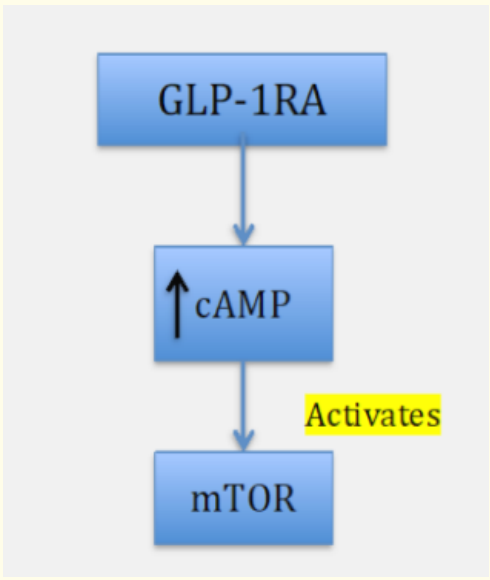

Figure 2: Represents mechanism of thyroid cancer development by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; cAMP: Cyclic Adenosine Monophosphate; mTOR: mammalian Target of Rapamycin.

GLP-1 Receptor Agonists And Breast Cancer

The risks of breast cancer in diabetic patients are 2 fold higher than non- diabetic patients and prognosis of breast cancer is worse in women with diabetes. Exenatide has been seen to be associated with anti-breast cancer effects via inhibiting the proliferation of breast cancer cells both *in vitro* and *in vivo*. Iawaya*., et al.* and colleagues demonstrated anti-breast cancer effect of exenatide. They found that exenatide mediates its anti-proliferative effects on breast cancer cells via inhibiting the translocation of nuclear factor- κB into nucleus and suppressing gene expression [35]. NF-κB is an important transcription factor in inflammatory and metabolic diseases such as T2DM [36]. Additionally, NF-κB is also found to be a key regulator of vascular complication of diabetes [37]. Type 2 diabetes is also considered as inflammatory disease, which fosters the infiltration of macrophages and T – cells into adipose tissue. Salsalate, which is a NSAIDS, has been reported to improve insulin sensitivity [38] and insulin secretion [39]. Thus, exenatide improves glucose level of blood not only by increasing insulin release and decreasing glucagon release but also works as anti-inflammatory drug which points towards the beneficial effects of exenatide on diabetes, breast cancer as well as various other inflammatory diseases.

Exenatide also exerts its anti-breast cancer effects by inducing apoptosis of breast cancer cells. Exenatide suppresses the expression of caspase-9, and MMP2 in breast cancer cells [40]. Exenatide is also studied to induce apoptosis by increasing the level of cAMP cells. Increase cAMP levels in cells activate CREB and promote CRE promoter transcription [11].

Liraglutide, another GLP-1RA also demonstrated anti-breast cancer properties as exenatide. A study conducted on MCF-7 breast cancer cells, showed that Liraglutide inhibits proliferation and promote apoptosis by preventing the expression of miR-27 [41]. miR-27a is a micro RNA, which are reported to be highly expressed in breast, gastric, pancreatic and colon cancer. micro RNA regulates cell growth, cell differentiation, drug resistance and promotes metastasis through induction of epithelial-mesenchyme transition. It is involved in cell apoptosis, cell cycle checkpoints and metabolism [42]. The reduced expression of micro RNA increases the expression of AMPKa2. AMPK is an important protein, which regulates various pathways involved in cell cycle and apoptosis.

Studies have shown that activation of AMPK by Liraglutide, translocates GLUT-4 to the muscle cell membrane, which causes increase entry of glucose into muscles and decrease demand of insulin [43]. AMPK activation also increases proliferation of β cell of pancrease, prevents from fatty liver [44,45], inhibits proliferation and promotes apoptosis of MCF-7 breast cancer cells.

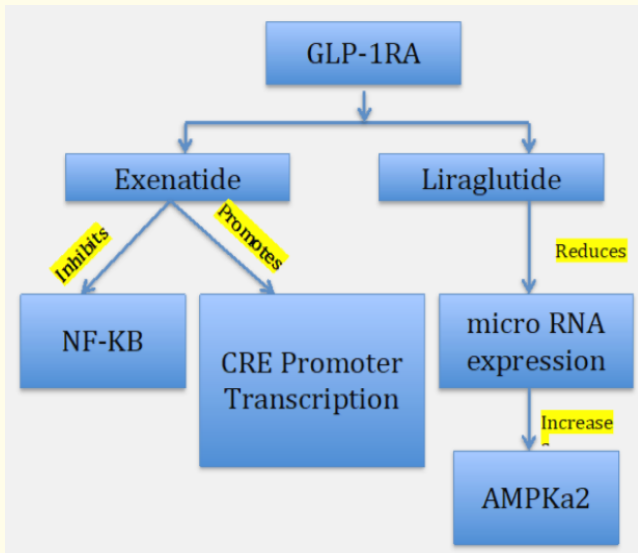

Figure 3: Depicts Mechanisms of Breast Cancer Prevention by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; NF-KB: Nuclear Factor Kappa Light Chain Enhancer of Activated B Cells; CRE: Camp Response Elements; AMPKa2: AMP-Activated Protein Kinase Catalytic Subunit A2; micro RNA: Micro Ribonucleic Acid.

GLP-1 Receptor Agonists and Prostate Cancer

In the United States, prostate cancer is the 3rd leading cause of cancer related deaths in men. Type 2 diabetes is also associated with prostate cancer. A meta-analysis inferred poor prognosis of prostate cancer for men with diabetes [46]. Li., *et al.* concluded in his study on prostate cancer cells that both exenatide and liraglutide inhibit proliferation and increase apoptosis of prostate cancer cells in a dose dependent manner. These drugs bind with GLP-1receptors, which increase the ratio of Bax/Bcl-2 and activate p38 MAPK pathways [47]. Depending upon specific cell and stimulus type, p38 MAPK pathway participates in both cell survival and cell death [48].

Tsutsumi., *et al.* demonstrated in his study that Ex-4 inhibited human prostate cancer growth via inhibition of extracellular signal-regulated kinase-mitogen-activated protein kinase (ERK-MAPK) pathways. He also found the additive effect of metformin on exenatide in tumor size reduction. Metformin exerts its anticancer effects via activating AMPK which inhibits m-TOR pathways and through improving insulin sensitivity and reducing insulin

levels [48]. This anti-cancer mechanism of metformin is similar to anti- breast cancer effect of liraglutide decribed above which gives the idea of anti-breast cancer effect of metformin and warrants more studies on the combine effect of metformin and liraglutide.

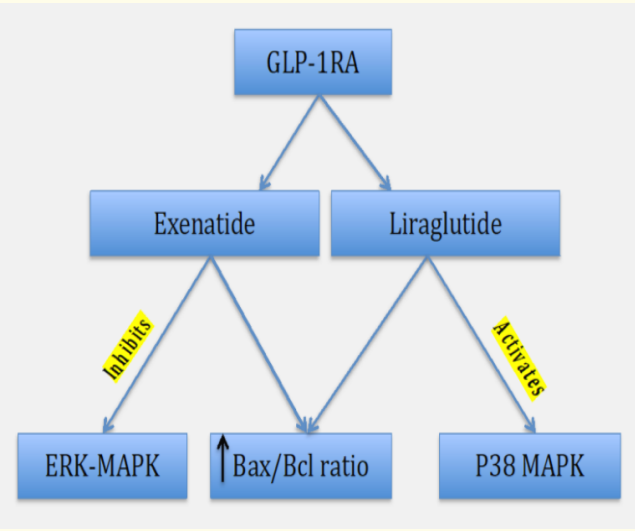

Figure 4: Depicts Mechanisms of Prostate Cancer Prevention by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; ERK-MAPK: Extracellular Signal-Regulated Kinase-Mitogen-Activated Protein Kinase; MAPK: Mitogen Activated Protein Kinase.

GLP-1 Receptor Agonists and Colon Cancer

Colon cancer is the 2nd leading cause of cancer deaths and 4th most common cancer diagnosed in United States [50]. Diabetes as a risk factor of colon cancer demands the use of drugs, which not only normalizes blood sugar but also help prevent cancer development. Recent studies on GLP-RAs have shown that exendin-4 reduces growth and survival of colon cancer cells by increasing intracellular cAMP levels. Increase cAMP levels inhibit signaling kinase glycogen synthase kinase 3 and ERK1/2 [12]. A recent study on human colon cancer cells has shown no association between Ex-4 and growth of colon cancer cells. No association between Ex-4 and colon cancer makes Ex-4 safe for patients having high risk of colon cancer especially diabetic patients above 50.

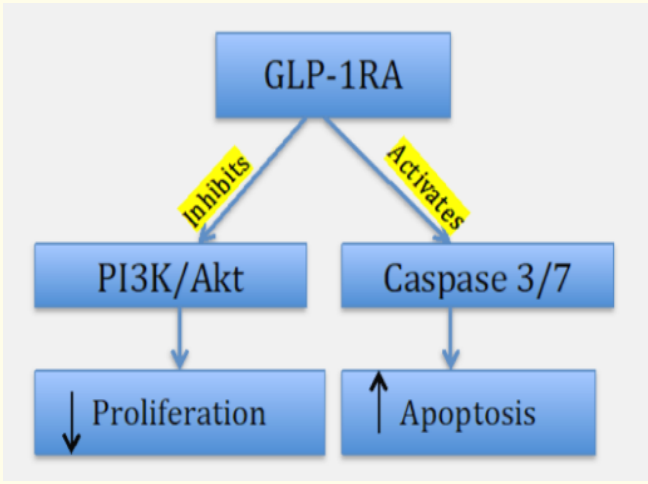

Figure 5: Depicts Mechanisms of Colon Cancer Prevention by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; PI3K: Phosphoinositide -3 Kinase Pathways.

GLP-1 Receptor Agonists and Endometrial Cancer

Endometrial cancer is the 4th most common cancer of the women in the United States [51]. The risk of endometrial cancer is double in diabetics than in non –diabetics and the prognosis of endometrial cancer in diabetics is worse than non –diabetics. Obesity, along with low physical activity and diabetes further increase the risk of endometrial cancer [52]. A study on the effects of exenatide on endometrial cancer cells and on mice revealed that exenatide protects from endometrial cancer via deactivating mTOR pathways. Phosphorylation of AMPK decreases phosphorylation of mTOR protein [10]. This study directs our attention towards protective effects of GLP-1RA on endometrial cancer, more research should be conducted to signify this effect.

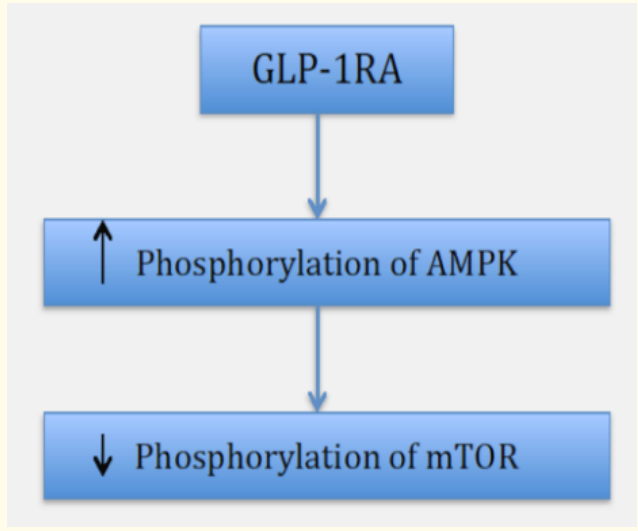

Figure 6: Depicts mechanisms of endometrial cancer prevention by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; AMPKa2: Adenosine Monophosphate-Activated Protein Kinase Catalytic Subunit a2; mTOR: Mammalian Target of Rapamycin.

GLP-1 Receptor Agonists and Ovarian Cancer

Diabetic women have higher risk of ovarian cancer than non-diabetic women [53,54]. The use of GLP-1 receptor agonists especially exendin-4 as the treatment of diabetes is beneficial in women because studies have shown that exendin-4 reduces proliferation, augments apoptosis, attenuates dissemination potential and response to chemotherapy of ovarian cancer cells. Generally, the mortality rate of ovarian cancer is high because it is metastasized mostly at the time of diagnosis and the higher risk of ovarian cancers in diabetic women as compare to non- diabetics makes exendin-4 extremely advantageous for women with diabetes.

Exendin-4 binds with GLP-1receptors on ovarian cancer cells and encourages apoptosis by activating caspase 3/7 and inhibits proliferation via inhibiting PI3K/AKT pathway [55,56].

Exenatide hinders the dissemination of breast cancer cells via following mechanisms

1. Exenatide inhibits the expression of MMP2 and MMP-9, which breaks down extracellular matrix and encourages metastasis of ovarian cancer cells.
2. Exenatide reduces the production VEGF proteins levels that commence neovascularization.

3. Exenatide decreases pro-inflammatory cytokines TNF-a and IL-6, which are responsible for the production of MMP2 and MMP9.

4. Exenatide prevents IKB phosphorylation and prevents translocation of NF-κB, leading to decreased transcription of genes associated with metastasis, proliferation, and angiogenesis

5. Exenatide inhibits expression of adhesion molecules VCAM-1 and ICAM -1 in endothelial cells and obstructs the transmission of tumor cells from primary site to secondary site [57].

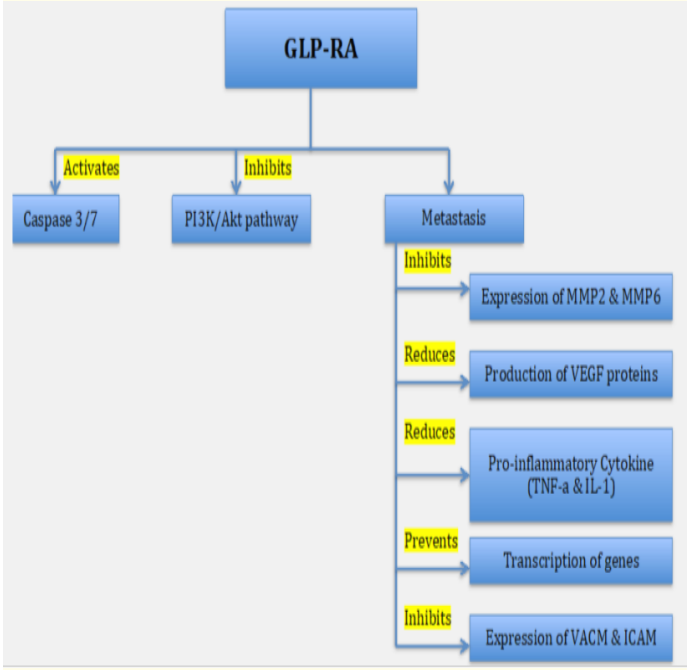

Figure 7: Depicts mechanisms involved in ovarian cancer prevention by GLP-1RAs.

GLP-1RA: Glucagon Like-Peptide Receptor Agonists; PI3K: Phosphoinositide-3 Kinase Pathways; MMP: Metalloproteinase; VEGF: Vascular Endothelial Growth Factor; TNF: Tumor Necrosis Factor; IL: Interleukin; VCAM: Vascular Cell Adhesion Molecule; ICAM: Intracellular Adhesion Molecule.

Discussion

GLP-1 receptor agonists, the analogue of incretin hormones, have been used to treat diabetes mellitus for over a decade. GLP-1 receptor agonists have become the integral part of guidelines for the treatment of type 2 diabetes. Besides normalizing blood sugar level, these drugs have advantageous effects on hypertension, hyperlipidemia, obesity and cardiovascular diseases. These beneficial effects make GLP-1RAs ideal for the management of diabetes. Concerns regarding the safety of these drugs are on rise because of the recent approval of these drugs and evidence of thyroid and pancreatic cancer in laboratory animals. Diabetes Mellitus that is associated with various comorbidities have been found to be significantly high risk factor for cancer and GLP-1RAs link with cancers complicate the use of GLP-1RAs as the treatment of type 2 DM.

Preclinical and clinical studies have linked GLP-1RAs to pancreatic, thyroid, breast, prostate, ovarian, endometrial, colon and other cancers. Studies show GLP-1RAs are positively associated with the development of pancreatic and thyroid cancers and negatively associated with breast, prostate, colon, ovarian and endometrial cancers. The association between GLP-1RAs and different types of cancer is controversial because of recent approval of this class of drugs and lack of sufficient studies. GLP-1RAs exerts their carcinogenic and anti-carcinogenic effects by stimulating GLP-1receptors and attenuating proliferation, apoptosis and differentiation of normal and cancer cells. Pathways that are involved in carcinogenic and anti-carcinogenic effects of GLP-1RAs are pro-survival pathways e.g. mTOR, MAPK, ERK, Akt and pro-apoptotic proteins e.g. caspase, Bax/Bal. The study of pathways gives us clue that GLP-1RAs can be used in other diseases besides diabetes and cancer, which involve the pathways attenuated by GLP-1RAs e.g. inhibition of mTOR pathway decreases the severity of neurodegenerative diseases, such as Parkinson disease, Alzheimer disease, Huntington disease, amyotrophic lateral sclerosis, and frontotemporal dementia [11].

Review of literature lead us to following questions

1. Do GLP-1 RAs have beneficial effects on patients having risk factors for breast, endometrial, prostate and ovarian cancer?

2. Could GLP-1RAs be provided to non- diabetic cancer patients to prevent various cancers describe above?

3. Are GLP-1RAs really the cause of thyroid and pancreatic cancer?

4. Can GLP-1RAs decrease the demand of insulin in type-1 diabetics as they work by delaying gastric emptying and decreasing pre-prandial and postprandial glucagon level?

5. What would be the risk of cancer occurrence if GLP-1RAs combined with other carcinogenic anti- diabetic medications e.g. sulfonylureas, insulin etc.?

6. What would be the combine effect of GLP-1RAs and anti-diabetic drugs on cancers, which are studied to have anti-cancer actions e.g. Metformin etc.?

7. What would be the effect of GLP-1RAs in combination with NSAIDS, which are reported to improve insulin sensitivity [33]?

8. Should the dose of anti-diabetic drugs be reduced in patients taking NSAIDS for a long time e.g. rheumatoid arthritis?

Conclusion

Review of the literature on pre-clinical and clinical studies linking GLP-1RAs to cancers gives the idea that so far there is no significant link of cancers with GLP-1RAs and more long term should be conducted to get better results.

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Volume 2 Issue 3 April 2018