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Hyperinsulinism Gateway Between Diabetes and Cancer: New Roles for Bifunctional Antidiabetic - Anticancer Active Somatostatins, IGF - 1 Inhibitors and Insulin Sensitizers

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Abstract

Hyperinsulinism refers to a condition of abnormally high concentration of circulating insulin in the body commonly seen in obese and type 2 diabetic patients due to insulin resistance. Elevated circulating insulin is the main factor linking obesity, diabetes and cancer and an important mechanism of cancer therapeutic resistance and failure.

The insulin receptor subfamily which is made up of the insulin receptor (IR), the type 1 IGF receptor (IGF-1) which binds insulin-like growth factors I and II, and the orphan insulin receptor-related receptor (IRRR) have been identified and linked to the process of carcinogenesis, as cancer cells require insulin for growth. IR receptors are overexpressed in various cancers and insulin activates growth mostly through these receptors and their interplays through mainly the PI3K/AKT/mTOR, MAPK and RAS signal transduction pathways.

Estrogens and androgens synergistic effects worsen hyperinsulinism and accelerates its carcinogenesis properties while progesterone and Sex Hormone Binding Globulins exert modulatory effects.

This review examined the various factor interplays in hyperinsulinism that links diabetes with cancer and the biomarkers involved. It equally identified the potentials and therapeutic roles for Somatostatins, IGF – 1 inhibitors and Insulin sensitizing antidiabetics in preventing and reversing the cancer linked trends.

Introduction

The association between diabetes and cancer has been known for long, with several epidemiological studies establishing link between obesity and diabetes and the risk of various types of cancers.

Patients with type 2 diabetes have been observed to have poorer response to cancer chemotherapy with more complications and worse prognosis than cancer patients without diabetes [1]. High levels of insulin and proinsulin are seen in obese and type 2 diabetic patients as a result of insulin resistance due to little or no response of the metabolic tissues to insulin stimulation. This elevated circulating insulin is the main factor linking obesity, diabetes and cancer and an important mechanism of cancer therapeutic resistance and failure [2]. Insulin resistance and hyperinsulinemia contribute to hyperglycemia, dyslipidemia and changes in the levels of circulating estrogens [3].

Insulin is both a metabolic hormone and growth factor and has mitogenic effects on all cells, especially in cancer cells which usually overexpresses the insulin receptor. Hence, the incidence, progression and mortality associated with various cancers are more in patients who has metabolic diseases marked by hyperinsulinemia [4]. Morvan et al proved that when human melanocytes are cultured at two times the standard glucose and insulin concentration, they were associated with carcinogenesis, marked by increased mitosis, DNA content, chromosomal abnormalities, p-Akt and c-Myc [5].

Insulin like growth factor 1 (IGF-1) stimulates and promotes growth in most cells of the body. It is structurally and functionally related to insulin and its production in the liver is regulated by the growth hormone. Insulin and IGF-1 stimulate anabolic signals and processes which promote tumor formation by inhibiting apoptosis and by activating cell proliferation. Epidemiological studies link the risk of colon, pancreas, endometrium, breast and prostate cancers to increase levels of insulin, IGF-1, or both [6]. Researchers from the International Agency for Research on Cancer (IARC) and partners carried out observational and Mendelian randomization analysis with approximately 430,000 women which showed that higher IGF-1 concentration were associated with a greater risk of breast cancer [7].

Insulin, IGF-1, Cholesterol, their receptors, signal transductions and links with estrogens and androgens play a significant part in the formation, growth and progression of various cancers. These factors are the major link between individuals with diabetes, obesity, metabolic syndrome and the risk of associated various cancers [3].

The main aim of this review is to identify these risk factors, genes, receptors and pathways linking hyperinsulinism and insulin resistance to cancer. This review, will equally proffer appropriate preventive, therapeutic and intervention measures and advances in managing these disorders.

Therapeutic roles will equally be identified for growth hormone inhibitory hormone (GHIH) somatostatin, insulin sensitizers and IGF-1 inhibitors interventions in the management and control of hyperinsulinism and insulin resistance.

Insulin and IGF-1 Receptors Link to Cancer

Insulin receptors are transmembrane signaling proteins made up of 2 subunits α and β subunits and are present in almost all cells of the body mainly in the liver and fat cells. The receptor (IR) is a member of the ligand-activated receptor and tyrosine kinase family that functions primarily in regulating cell differentiation, growth and metabolism [8]. The insulin receptor subfamily is made up of the insulin receptor, the type 1 IGF receptor (IGF-1) which binds insulin-like growth factors I and II, and the orphan insulin receptor-related receptor (IRRR) [9].

The insulin receptors are encoded by a gene located on chromosome 19 with 22 exons and 21 introns. The short exon 11 encodes a 12-amino acid sequence which is spliced in to 2 receptor isoforms A and B. The receptors are synthesized as single chain proreceptors, but in cells that expresses both insulin and IGF-1 receptors, hybrid receptors are formed made up of 50% of each [9].

Many cancer cells require insulin for growth and insulin activates growth mostly through its own receptor and not the IGF-1 receptor. In various cancer cells, the IR is overexpressed and the A isoform that is mainly mitogenic is represented more than the B isoform [10, 11]. This is the reason most diseases associated with hyperinsulinemia like prediabetic, diabetes, obesity, metabolic syndrome and polycystic ovary syndrome increase the risk and related mortality of cancer [11].

Insulin receptor isoform A (IR-A) in conjunction with autocrine production of its ligand IGF2 is linked cancer stem cell proliferation and characteristics of many malignant tissues. Activation of IR-A / IGF autocrine loop is an important mechanism of resistance to cancer therapies and IR-A signaling target will be an important pathway for future anticancer therapies [12].

Genes and Pathways Link Between Hyperinsulinism and Cancer

Insulin gene primary translation product is preproinsulin, a 110 amino acid peptide that is converted to proinsulin in β-cells of pancreas and finally to c-peptide and insulin. Proinsulin concentration is a biomarker of type 2 diabetes and a very specific marker for insulin resistance. Gene mediated hyperinsulinism linked to loss of β-cell functions leads to failure of insulin secretion to correct for tissue resistance [13].

PI3K/AKT/Mtor

When insulin binds to its receptor, it initiates phosphorylation cascade that activates the catalytic activity of phosphoinositides 3-kinase (PI3K), a lipid kinase which regulates uptake and use of glucose, and mTOR, a kinase downstream of PI3K that activates transcription and translation. PI3K chronic activation can drive malignant transformation [14]. PI3K/AKT/mTOR pathway is commonly activated in many human cancers and majority of the positive regulators of this pathway has oncogenic abilities. This pathway induces malignant transformation by activating upstream oncoproteins including tyrosine kinases and RAS and enhance proliferation, survival, metabolic reprogramming, invasion/metastasis, suppression of autophagy and senescence [15]. Patrick Hu et al showed that TRAP- α a protein regulating the PI3K/Akt pathway is completely required for the synthesis, processing and secretion of insulin. TRAP- α was deleted from rat beta cells and the deletion caused 90% insulin reduction in total insulin inside cells with the degradation and accumulation of preproinsulin and proinsulin elements and triggering of the unfolded protein response [16, 17].

Mapk

Mitogen – activated protein kinases (MAPK) are serine threonine specific kinases that regulate many cell processes like cell differentiation, proliferation, mitosis, metabolism and apoptosis. MAPK pathway are cascade of 3 kinases which include ERK a mitogen activated and JNK and p38 which are stress activated MAPKS. MAPK/ERK pathway are involved in the regulation of cellular insulin responsiveness. Persistent MAPK/ERK pathway inhibition leads to insulin-like receptor gene expression downregulation and insulin resistance [18]. Prolonged activation of the ERK pathway in adipocytes was linked to type 2 diabetes and targeted inhibition of this pathway showed potential efficacy in treatment of insulin resistance and type 2 diabetes [19].

IGF

Circulating IGF-1 and IGF-2 bind to IGF-1 receptor (IGF-1R) and activate a signal transduction cascade culminating in enhanced growth and survival of IGF-responsive cells. The proliferative activity of IGF-1R is mediated through the Ras and AKT pathways. Also, IGF-1R activation downregulates cell cycle suppressor [20].

RAS

RAS genes are oncogenes whose mutation leads to dysregulated growth and carcinogenesis. Insulin is one of the important activators of RAS signaling pathway. Insulin is involved in the activation, farnesylation and translocation of p21Ras to the plasma membrane where they are activated by other growth-promoting agents [21]. High fat (HF)- induced diabetic mice were treated with 5-fluoro-farnesylthiosalicylic acid (F-FTS) which is a small molecule Ras inhibitor. This resulted in increased glucose

uptake, reduction in hyperglycemia and serum levels of insulin [22].

MYC

Genetic ablation of Mycl led to a decrease in the growth of pancreatic endocrine cells in neonatal mice but the expression Mycl in adult mice activated the growth of both β and α cells [23]. After MYC activation in adult β-cells in vivo, apoptosis was preceded by hyperglycemia, decreased insulin secretion and loss of β-cell differentiation suggesting glucotoxicity could enhance Myc – induced apoptosis. Glucose reduction measures did not prevent loss of β-cells. Hence Myc can induce diabetes by direct effects on β-cell apoptosis [24]. Curcumin a bioactive compound found in root of turmeric is known to possess anticancer activity due to its inhibition of migration and metastasis of cancer cells. Curcumin significantly reduced insulin and IGF-1 receptors in addition to MYC expression in resistant SW480 cells treated with 5-FU. The downregulation of insulin and IGF-1 receptors was correlated to much reduction in the growth and migration of chemoresistant colorectal cancer cells [25].

p53

Point mutation of p53 is a very important factor in cancer development and progression. Breast and Prostate cancer cells with mutant p53 (mutp53) respond to insulin stimulation by increasing mitosis and invasiveness and this response depends on the presence of p53. Mutant p53 enhances insulin – induced AKT1 activation by binding and inhibiting the tumor suppressor DAB2IP [26]. P53 inhibits IGF-IR, IGF-II and PAPP-A expression. Inhibited IGF maintain cellular homeostasis when the DNA is damaged. Mutations in p53 stimulate IGF-IR, IGF-II and PAPP-A expression. Increased IGF signaling enhances proliferation of tumor cells [27].

HIF-1

Hypoxia inducible factor 1 is a transcription factor implicated in several disease conditions. It consists of two subunits HIF-1α and HIF-1β. Insulin activates HIF-1 through the PI3K/mTOR target of rapamycin pathway leading to enhanced VEGF expression [28]. Insulin upregulated pyruvate kinase M2(PKM2) expression through the PI3K/mTOR mediated HIF1α induction leading to enhanced aerobic glycolysis and cancer metabolism [29].

Biomarkers Linking Hyperinsulinism to Cancer.

Insulin Like Growth Factor 1 (IGF-1) and IGF Binding Proteins (IGFBP 1 - 7): IGF-1 and IGFBPs are associated with the risk of various types of cancers. Pre-treatment Serum levels of IGF-1 and IGFBP 1 - 7 were assessed in 100 non-small cell Lung cancer (NSCLC) patients using immunobead assays, IGFBP 5 and IGFBP 7 showed value as biomarkers for identifying NSCLC progression and patient outcome Serum IGFBP-1 showed significantly elevated levels in upper gastrointestinal tumors compared with normal controls, but dropped significantly after surgical resection of the primary tumours [30, 31]. IGFBP 2 an important oncogene is significantly increased in serum or tissues of patients with cancer, serving as a biomarker and it is involved in tumor cellular growth, migration, angiogenesis and epithelial-to-mesenchymal transition [32]. Serum IGFBP2 levels were found to be raised in advanced Lung cancer patients with severe malnutrition with 73.3% sensitivity and 70.5% specificity [33]. IGFBP-4 transports and regulates the activity of IGFs. Serum level of IGFBP-4 was found to be significantly higher than control in lung cancer [34].

Proinsulin, C – Peptide and Insulin

Proinsulin and C-peptide responses during 75g of oral glucose tolerance test (OGTT) were investigated in 32 patients with pancreatic cancer and 32 controls. The pancreatic cancer patients had greater proinsulin and lower C-peptide levels than the control in both non-diabetic and diabetic groups, due to impaired proinsulin conversion [35]. Insulin, C-peptide and proinsulin levels were investigated in 33 patients with endogenous hyperinsulinism and in 67 controls to find out the most appropriate threshold and biomarker to diagnose endogenous hyperinsulinism. Proinsulin levels above 5pmol/l with blood glucose levels below 2.5mmol/l were the best parameters to diagnose endogenous hyperinsulinism with 100% sensitivity and specificity [36]. The gold standard for measuring insulin resistance in human is the hyperinsulinemic-euglycemic clamp. Developed by DeFronzo et al, it assumes that at high doses of insulin infusion (>80mU/m2.min), the hyperinsulinemic state is enough to completely inhibit hepatic glucose formation [37].

Adipokines or Adipocytokines (leptin, IL-6, IL- 8, IL-10, A-AFABP, vaspin, MCP-1, CTRP-4, Apelin, Neuregulin-4, TNFα, IFN-ϒ, Visfatin, Adiponectin, Resistin, Omentin, Chemerin, Progranulin, PAI-1, IP-10)

These are any of the various cytokines secreted from the human adipose tissues. While many are inflammatory mediators, others have homeostasis, metabolic, insulin – sensitizing and angiogenesis properties. The Adipokines have shown potentials as biomarkers of insulin sensitivity because they play important roles in determining insulin sensitivity [38]. Circulating levels of adipokines are used as biomarkers for diabetes mellitus progression and therapeutic targets [39].

The first adipocytokine to be discovered was leptin, a hormone whose level is increased in obesity and associated with the development of breast cancer. Leptin enhances the growth, migration and invasion of breast cancer cells through ACAT2 up-regulation via the PI3K/AKT/SREBP2 signaling pathways. The leptin /ACAT2 pathway is a potential therapeutic target for breast cancer [40]. Visafatin an adipokine also known as nicotinamide phosphoribosyltransferase (NAMPT) have insulin mimicking properties and its serum concentration correlated strongly with biomarkers of liver, renal dysfunctions. Adiponectin is a potential biomarker for type 2 DM or insulin resistance and neuregulin 4 levels associated with metabolic syndrome in newly diagnosed type 2DM [41]. Novel adipokines (chimerin, plasminogen activator inhibitor -1) concentration were higher with greater sensitivity and specificity than classic adipokines (leptin, adiponectin) in patients with NSCLC [42]. Systemic chemerin and tumor produced chemerin enhance tumor growth by direct effect on growth, proliferation, angiogenesis, migration, inva-

sion and metastases. These effects are mediated via signaling through CMKLR1 (chemerin1), GPR1(chemerin2) and CCLR2 on target cells [43].

Myokines (Interleukins, Osteonectin, Decorin, Irisin, Myostatin, Oncostatin M, PGC-1, Brain-Derived Neurotrophic Factor)

These are cytokines and peptides secreted when muscles contract. They are involved in muscle growth and metabolism. Myokines significantly counteract insulin resistance and metabolic disturbances of obesity and type 2DM [44]. Novel myokine irisin is known to induce a white to brown shift in adipocytes, is a potential therapeutic target [45]. Irisin, IL-13, follistatin-related protein- 1 (FSTL-1) levels were decreased in diabetic group compared to normal and prediabetic groups, while fractalkine showed a progressive increase from normal to diabetic, in a cross-sectional study of the circulating myokine concentrations in various stages of glucose intolerance [46]. Irisin was found to significantly inhibit cell proliferation, migration, invasion, epithelial-to-mesenchymal transition of cancer cells and also inhibit the PI3K/AKT pathway [47].

Hepatokines (Fetuin – A, Fetuin – B, RBP4, FGF21, Selenoprotein P)

Hepatokines are proteins secreted by hepatocytes and are linked to induction of metabolic dysfunctions and serve as link between hepatic steatosis and insulin resistance [48]. Hepatokines are known to play important roles in the pathogenesis of metabolic syndrome, nonalcoholic fatty liver disease, type 2DM, and CVDs [49]. Fetuin – A deficient mice showed improved insulin sensitivity; high level of fetuin – A are predictable markers for the incidence of Type 2DM. FGF21 improved insulin sensitivity and ameliorated steatosis in diet-induced obesity mice. Selenoprotein P is important in the transport of selenium. Selenoprotein P inhibited insulin signaling and glucose metabolism in liver and skeletal muscle and impairs angiogenesis. Selenoprotein deficient rats showed improved insulin resistance and glucose tolerance [49]. Angiopoietin-like protein 4 (ANGPTLA4) reduced blood glucose levels and reduced glucose tolerance to balance glucose homeostasis. ANGPTL4 levels were lower in Type 2DM patients than normal controls, showing that reduced ANGPTL4 is causative factor for Type 2DM. Leukocyte cell-derived chemotaxin 2 (LECT2) impairs insulin signaling via the JNK pathway in muscle cells. LECT2 deficiency in mice enhances insulin sensitivity in skeletal muscles by activation of Akt phosphorylation [49].

Hormonal Pathways Linking Hyperinsulinism and Cancer

Estrogen

A link exist between sex hormone homeostasis and metabolic processes. Insulin is an important modulator of human sex hormone production and control their signals at receptor level. Insulin resistance and overproduction enhance hypoandrogenism and estrogen deficiency in females leading to anovulation, cardiovascular diseases and cancer. Knowing the cancer risk of insulin resistance and estrogen deficiency entails potentials for primary cancer prevention and adjuvant therapy treatment of hormonal and metabolic changes for patients with cancer [50].

Male Wistar rats fed on high – fat diet come down with insulin resistance, but females do not have much induction. Men are more likely to develop metabolic syndrome than premenopausal women. But, this protection in women is very much reduced when the level of estrogen reduces especially following menopause. Research showed that the risk of developing insulin resistance and metabolic syndrome rises following surgically induced menopause [51].

Estrogen and Insulin has been shown to be synergistic in Endometrial carcinogenesis (EC) by activating Insulin receptor-β (InsR-β) and estrogen receptor-α (ER-α), mutually enhancing crosstalk and leading to activation of PI3K/Akt and MAPK/ERK signaling pathways [52]. EC cells treated with both estradiol and insulin showed more stimulation than those treated with each alone. Estradiol very much activated phosphorylation of InsR-β and IRZS – 1, while insulin very much induced phosphorylation ER-α. Concomitant treatment with insulin and estradiol significantly enhanced the expression and phosphorylation of Akt, MAPK and ERK. Insulin and Estradiol solely and synergistically enhanced EC xenograft growth in mice [52]. Estradiol response in MCF-7 breast cancer was studied solely and in addition to chronic exposure to insulin. It was shown that insulin priming is important and specific for estradiol-induced tumor cell growth. Treatment with ERK or Akt specific inhibitors suppressed estradiol-induced growth [53]. Estradiol significantly enhances expression of cyclin A and B, and reduces p21 and p27 in insulin-primed cells. Also, estradiol activates metabolic genes in pentose phosphate and serine biosynthesis pathways in insulin-primed cells, but insulin priming reduces metabolic gene expression linked with glucose catabolism in breast cancer cells [53].

Progesterone: progesterone is a C-21 steroid sex hormone synthesized mainly from cholesterol and plays important role in the regulation of female menstrual cycle and pregnancy. This hormone equally exerts significant effect on carbohydrate, lipid and protein metabolism. Parenteral injection of progesterone induces hyperinsulinism, gluconeogenesis, pancreatic islet hypertrophy and excess insulin secretion in vitro in response to glucose [54]. Maternal insulin resistance through elevated placental hormones, is necessary for effective delivery of glucose to the fetus.

Progesterone at 10^{-4} M but not 10-5 M decreases the amount of IRS-1. Consequently, insulin-induced phosphorylation of IRS-1, association of IRS-1 with p85α, and subsequent phosphorylation of Akt1 and Akt2 and insulin-induced translocation of GLUT4 to plasma membrane were reduced by 10^{-4} M progesterone [55]. Ovariectomized rats were treated with various doses of progesterone and/or 17beta-estradiol so as to mimic the plasma concentrations in normal pregnant rats. At 6th and 11th days, Vehicle (V) and progesterone (P) treated groups were more insulin resistant than 17beta-estradiol (E) and 17beta-estradiol+progesterone (EP) – treated groups. But, at 16th day, the V, EP and E groups were more insulin resistant than the P group. The V, EP and E were more resistant to insulin at day 16 than at day 6, while the P

group was more resistant to insulin at day 6 than at day 16. This study showed that the role of estrogen in pregnancy is to regulate the effect of progesterone on insulin in dose related manner [56].

Anovulatory cycles, obesity and insulin resistance are important risk factors for Endometrial Carcinoma (EC). Progestogens are used to prevent or treat hyperplasia and well-differentiated EC. Progestogens protect the endometrium against the mitotic effects of estrogens in women with uterus during menstrual hormone therapy. Studies showed that micronized progesterone (MP) is safer for breast but less effective than synthetic progestin on endometrium [57].

Androgens

Hyperandrogenism is linked to hyperinsulinemia and insulin resistance in women. Adult female Wistar rats implanted with dihydrotestosterone or placebo were investigated after 10 weeks. DHT exposure raised plasma DHT levels by 2-fold comparable to that seen in polycystic ovary syndrome in women [58]. DHT treatment induced hyperinsulinemia with raised HOMA-IR index in fasting state and glucose intolerance and increased insulin responses after glucose tolerance test. Insulin gene (Ins) expression was increased in DHT islets. In vitro incubation of control islets with DHT stimulated Ins1 transcription in dose dependent manner [58]. The most dramatic clinical expression of link between hyperinsulinemia and hyperandrogenism is the HAIR-AN (Hyperandrogenism Insulin resistance Acanthosis Nigricans) syndrome where grave insulin resistance leads to compensatory hyperinsulinemia that activates ovarian androgen production and Acanthosis nigricans, a dermatologic external complication of severe insulin resistance [59].

510 Patients with type 1 EC and 510 controls were investigated for the effect of androgen and insulin, (sole and combined effects) in the development of endometrial carcinoma. High C-peptide and testosterone levels, diabetes and hypertension were independent risk factors. Raised serum total testosterone and insulin levels were positively correlated EC risk in total, premenopausal and postmenopausal women [60]. 25 men with locally advanced or recurrent prostate cancer, with no radiographic evidence of metastases, no evidence nor history of DM were treated with leuprolide depot and bicalutamide. Short-term treatment markedly raised fat mass and reduced insulin sensitivity in men with prostate cancer [61].

Sex-Hormone Binding Globulin (SHBG)

Investigation of sex hormones and binding proteins in premenopausal and postmenopausal women showed that raised free testosterone and reduced SHBG is associated with increased glucose and insulin concentrations. Increased insulin resistance is equally linked with reduced SHBG concentration [62]. SHBG has been reported, apart from regulating estrogen free fraction, to directly act on breast cancer cells, interacting with these cells and activating intracellular transduction pathways that results into cross-talk with estradiol-regulated pathways leading to inhibition of various effects of estradiol on breast cancer cells [63].

Roles of Somatostatins, Insulin Sensitizers and IGF – 1 Inhibitors in Regulating Hyperinsulinemia-Diabetes-Cancer Link

Somatostatin (Growth Hormone Inhibitory Hormone)

Somatostatin (SST) is a peptide hormone produced mainly in the nervous and GIT systems (δ-cells of pancreas) and is principally involved in regulating the secretion of other hormones, neurotransmission and cell proliferation through interaction with G protein – coupled somatostatin receptors. The half – life of SST is about 1 – 3 min as a result of rapid breakdown by peptidases in plasma and tissues. Hence, requiring direct continuous intravenous or subcutaneous infusion to get therapeutic effect. These problems led to the development of SST analogues [64].

Five somatostatin receptor subtypes have been identified (SSTR1 – SSTR5), and the SSTR2 subtype has two variants (SSTR2A and SSTR2B). The first synthetic SST analog (SSA) is octapeptide octreotide marketed as sandostatin and it inhibits rapid growth of cells expressing SSTR2 gene by activating tyrosine phosphatase pathway. Other analogues include lanreotide approved for acromegaly and carcinoid syndrome treatment and pasireotide a novel SSA [65].

Somatostatin analogues are extremely valuable in the treatment of various neuroendocrine tumors, other endocrine diseases like congenital hyperinsulinism, diabetic retinopathy, diabetic macula edema, and non -endocrine tumors like breast, colon, prostate, lung and hepatocellular [65]. Somatostatin significantly inhibits insulin and glucagon secretion from pancreatic islet cells. Glucagon secretion inhibition in mouse islets is mainly through SSTR2, but insulin release inhibition is mainly through SSTR5 [66].

IGF – 1 Inhibitors

The expression of IGF-IR has been shown to be important for the malignant transformation in pre-clinal models. IGF – 1 deficient mice have inhibited tumor proliferation ability. IGF expression in breast cancer is almost 90% compared to HER2+ breast cancer which is about 20 – 25% of all breast cancers [67].

Since most tumors appear to rely on the IGF systems for rapid growth and resistance to cancer therapies, targeting the various IGF systems and signaling like proliferative signaling and pro-survival signaling, appears to be a very important step in development of effective cancer targeted therapy and control.

Other Steps Include Targeting

IGF – 1R, IR-IGF-IR hybrids, IR-A receptors with biomolecules and monoclonal antibodies

Receptor – ligand interaction, Receptor tyrosine kinase activity, ligand bioavailability.

Resistance to cancer therapeutics like cytotoxics, hormonal, HER/erbB receptor therapy [67].

Insulin Sensitizers

Researches have shown that the various antidiabetic drugs and their regimens can modify cancer risk. Most findings showed

that metformin reduces, while the insulin secretagogues slightly elevates the risk of some kinds of cancers in type 2DM patients. Metformin reduces rapid cell division and growth and equally induces apoptosis in cancer cells. But endogenous and exogenous hyperinsulinemia may be mitogenic and elevates the risk of cancer in type 2DM [68]. Studies have shown that metformin can inhibit xenograft growth of MCF – 7 and MDAMB231 breast cancer cells and phenformin is more potent than metformin in inhibiting these cancer cell lines growth without murine toxicity [69].

Conclusion

Several epidemiological studies have established association between obesity, diabetes and the risk of various types of cancers. Hyperinsulinism caused mainly by insulin resistance is the major linking factor.

Insulin, IGF-1, their receptors, signal transductions and links with estrogens and androgens play a significant part in the formation, growth and progression of various cancers. These factors are the major link between individuals with diabetes, obesity, metabolic syndrome and the risk of associated various cancers.

This review examined the various factor interplays in hyperinsulinism that links diabetes with cancer and the biomarkers involved.

It equally identified the potentials and therapeutic roles for Somatostatins, IGF – 1 inhibitors and Insulin sensitizing antidiabetics in preventing and reversing the cancer linked risks.

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