The primary function of insulin is viewed as a hormone that controls blood glucose level. However, there is growing evidence that aberrant insulin level and insulin-mediated signaling can lead to cancer development and progression. The insulin-cancer relationship has stemmed from various observational and epidemiological studies, which linked higher incidence of cancer with central obesity, type II diabetes and other conditions associated with increased levels of circulating insulin, insulin resistance and hyperinsulinemic states. Increased risk of developing a range of cancers is also seen with a certain treatment options used to lower blood glucose level in diabetic patients. While metformin monotherapy has the lowest risk of developing cancer, in comparison, treatment with insulin or insulin secretagogues shows more likelihood to develop solid cancers. Cellular signaling initiated by insulin provides a clue regarding these diverse cellular outcomes. This review discusses how the insulin enacts such diverse physiological effects and the insulin-cancer relationship, with focus on the role of insulin signaling in cancer.

Keywords: Insulin, Insulin-like growth factors, Insulin receptors, IGF-R, Insulin-like growth factor receptor, Insulin receptor substrate, PI3 kinase, Akt, GLUT4, mTOR

Introduction

In the fall of 1921, Fredrick Banting and Charles Best discovered that extract prepared from pancreas can dramatically lower the high blood sugar level in depancreatized, diabetic dogs. Following this discovery, both Banting and Best along with James Collip, all working in the laboratory of John Macleod, purified an active ingredient called insulin. In early 1922, a human clinical trial of insulin on patients with diabetes mellitus showed great success. The discovery of insulin was announced on May 3, 1922 by Macleod at a meeting of the Association of American Physicians. For their pioneering work on insulin, Banting and Macleod received the 1923 Nobel Prize in the area of Medicine/Physiology. In his Nobel Award accepting speech, Dr. Banting said “insulin is not a cure for diabetes, it is a treatment”. Interestingly, more than 90 years later, insulin still remains as a major treatment modality for diabetes. While the beneficial role of insulin in diabetes is well-recognized, enhanced level of insulin-mediated signaling could have deleterious consequences. A case in point is the harmful effect of insulin in cancer growth. Cellular function of insulin provides a clue for its harmful effect in cancer, where it is present at a higher level and highly active in mediating its function¹,².

How does insulin function?

Insulin allows most cells to absorb glucose from circulating blood and thereby it permits utilization of glucose for producing energy³. Physiological level of insulin is critical for maintaining adequate, not very high or very low levels of blood sugar. Insulin level rises on demand when blood sugar level is increased, following consumption of a meal. The signal of high glucose in the blood stream initiates insulin secretion from the pancreatic β cells, where it is synthesized and remains stored. By interacting with transmembrane insulin receptor (IR) proteins, insulin alters the permeability of cell membrane to glucose and promotes glucose adsorption. Insulin receptor is encoded by a single gene from which two isoforms of insulin receptor, IR-A and IR-B are generated via...
alternative splicing. In IR-A the exon 11, which codes for 12 amino acids is excluded and in IR-B, the exon 11 is included. Both, IR-A and IR-B proteins undergo further post-translational modifications and then assemble as homo- or hetero-dimer molecules to form the functional insulin receptor protein. When glucose enters the bloodstream, pancreas secretes insulin, which then binds to the dimerized insulin receptors and initiate intracellular signaling. Interaction of insulin with insulin receptor activates an intrinsic tyrosine protein kinase that is present in the intracellular domain of the IR. Activated insulin receptor kinase phosphorylates and activates a number of intracellular glucose transporter proteins, which upon assembly to the cell membrane open a channel, so that glucose can enter the cell. The glucose transporter proteins although are constitutively expressed and present in the cell, without the insulin-mediated signaling, these proteins remain entrapped within the intracellular cytoplasmic vesicles and cannot transport any glucose. The insulin-IR mediated signaling allows rapid movement of the cytoplasmic vesicles to the cell membrane, where the cytoplasmic vesicles fuse and allow entry of the glucose transporters into the cell membrane (Fig. 1). When blood glucose level declines, insulin no longer binds to the insulin receptors and the glucose transporters recycle back into the cytoplasm. Thus, the big picture is that insulin through its action of signal transduction controls the use of cellular fuel like sugar, for producing energy and imparts a profound effect on cellular homeostasis. Dysregulation of the insulin-signaling pathways, consequently would lead to widespread and devastating effects on many organs and tissues. In this review, we will focus the impact of insulin-signaling pathways in cancer.

Cancer cells utilize insulin to meet their high appetite for energy

From cohort studies, a direct link between high level of insulin and increased risk of breast cancer and cancers of the pancreas, colorectal, lung and colon became evident. Insulin has been shown to stimulate growth of breast cancer cells and in a non-obese mouse model of type II diabetes, it accelerates breast cancer development and progression. The mechanisms by which insulin promotes cancer are yet to be fully resolved, but it can be speculated that cancer cells which have much higher growth rate require higher level of energy source and high glucose uptake, which obviously could be met with increased supply of insulin and insulin receptors or both. Further information on the insulin-cancer relationship can be found in a recent review.

Role of insulin receptors in cancer

There is now clear evidence that in breast cancer cells, insulin promotes tumor growth and enhances tumor progression by acting through significantly over-expressed insulin receptors. Although insulin receptors are widely distributed, most normal cells contain very few of these proteins. The reason for low abundance of insulin receptor has been attributed to rapid turnover of this molecule. In normal human lymphocytes, insulin has been shown to accelerate degradation of insulin receptor proteins. Consistent with this finding, insulin treatment in diabetic rats is found to reduce the level of IR mRNA.
findings suggest that under normal condition, insulin down-regulates the level of insulin receptors and insulin most likely regulates IR gene expression by transcriptional, post-transcriptional, translational and/or post-translational regulatory processes, which alone or in combination are impaired in cancer cells. However, the results on the effect of insulin on IR mRNA level are ambiguous, probably due to the studies conducted in different cell types\textsuperscript{19-23}, including a recent observation rat hepatoma cells, indicating that although insulin reduces IR protein level, it is not involved in the inhibition of IR gene expression\textsuperscript{24}.

As mentioned earlier, concentrations of functional insulin receptors and insulin stimulated insulin receptor tyrosine kinase activity are markedly elevated in breast cancer tissues and cells\textsuperscript{15}. Pivotal role of insulin receptors in cancer is further supported by the finding that over-expression of the IRS in fibroblast and ovary cells induces a ligand-mediated transformed phenotype\textsuperscript{25}. Overexpression of IR has been found to be essential for virus-induced tumorigenesis of Kaposi’s sarcoma\textsuperscript{26}. Higher level of IR is found to be linked with poor prognosis in breast cancer\textsuperscript{27,28}. Although both IR-A and IR-B receptors participate in the insulin-mediated signaling, IR-A is more commonly over-expressed in cancer and thereby appears to play a higher role (reviewed earlier\textsuperscript{14}). The molecular mechanisms whereby insulin receptors promote cancer are still not clear, but studies have shown that breast cancer cells utilize insulin more efficiently due to an increased sensitivity of insulin receptors for the hormone\textsuperscript{29,30}. Such an increased sensitivity has been attributed to tumor-associated resistance to down-regulation of insulin receptor by insulin.

**Involvement of insulin-like growth factor and its receptor in cancer**

Insulin-like growth factors (IGFs) represent a group of proteins that have high sequence similarity to insulin and similar functional properties. IGFs contain two main members, IGF-1 and IGF-2. While insulin is synthesized by the pancreatic β cells, IGFs are mainly synthesized by the liver under the control of growth hormone (GH), but insulin is also one of the regulators of liver IGF-1 production. IGFs function through interaction with two IGF receptors (IGF-IR and IGF-IIR) and a group of IGF-binding proteins (IGFBPs). The type I IGF receptor (IGF-IR) is a tyrosine kinase, which is closely related to the insulin receptor (IR). IGF-IR can form heterodimer with insulin receptors, IR-A and IR-B and similar to IR, IGF-IR mediates its signal through p3K and Akt signaling pathway and regulates both metabolic and non-metabolic functions (reviewed earlier\textsuperscript{14}). In contrast to IGF-IR, the type II IGF receptor (IGF-IIR) lacks a tyrosine kinase activity and therefore does not transduce signals. One of the prominent functions of IGF-IIR is to remove IGF-2 from the cell surface and attenuate IGF-2 mediated cell signaling. After binding to IGF-2, the IGF-2/IGF-IIR complex gets accumulated in the vesicles, which then get internalized.

The bioavailability of IGF proteins is also regulated by the IGFBPs, which serve as carrier proteins for IGF-1. Almost all, about 98% of IGF-1 always remains bound to one of the six IGFBPs, but IGFBP-3 accounts for the most IGF-1 sequestration. Insulin, which promotes IGF-1 synthesis via growth hormone can also increase the quantity of bioavailable IGF-1 by decreasing the levels of IGFBP-3 and IGFBP-1. Lower levels of these IGFBPs result in more unbound IGF-1 that becomes free to interact with the IGF-1 receptor (IGF-IR). The IRs, IGFs, IGFRs and IGFBPs are part of an intricate regulatory system in insulin-signaling that is critical in the maintenance of cellular homeostasis and perturbation of the orchestrated interplay of these molecules can lead to abnormalities in both metabolic and non-metabolic functions\textsuperscript{14}.

Tumor cells are found to overexpress IGF-1 and dysregulation of IGF-mediated signaling pathways, plays a critical role in cancer. The role of IGF-1 in cancer has become increasingly clear from the studies in patients with the acromegaly syndrome that results in secretion of higher level of growth hormone (GH) and IGF-1 synthesis; these patients have exhibited increased risks of colon, thyroid, prostate and breast cancer\textsuperscript{31}. A strong link between higher circulating levels of IGF-1 and increased risks of breast and colorectal cancers is further supported from independent cohort studies\textsuperscript{32,33}. In correlation, serum level of IGF-IR is found to be significantly higher in those patients with short-time (less than 5 yrs) recurrence-free and overall low survival rates, as compared to those patients with low-level expression of IGF-IR\textsuperscript{34}. In animal models, overexpression of IGF-1 is shown to promote tumor growth\textsuperscript{35}, while IGF-1 deficiency decreases risk of mammary and colon cancers\textsuperscript{36,37}. Consistent with the implication of IGF-1 system as a risk factor, low level of IGF is shown to be linked with the reduced growth of cancer
Like IGF-1, IGF-2 is overexpressed in certain cancers and has an adverse effect in disease prognosis. In a cohort study of esophageal carcinoma, high level expression of IGF-2 is found to be associated with reduced disease-free survival.

Role of insulin-regulated mTOR signaling in cancer

The mammalian target of rapamycin (mTOR) is classified as a master regulator which integrates the signals from nutrient and energy sensors with cell growth and proliferation and thereby plays a central role in the regulation of cell growth, proliferation, differentiation, migration and survival. The mTOR protein is a serine threonine protein kinase, which itself gets activated by phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt/PKB). Thus, insulin, IGF receptors and other growth factors that can activate the PI3K/Akt signaling pathway are able to activate mTOR, formation of an active mTOR complex (mTORC1) and mTOR-mediated signaling (outlined in Fig. 2). Upon activation, mTOR phosphorylates at least two translational components, ribosomal S6 Kinase (S6K) and eIF-4E binding protein (eIF4EBP) and thereby promotes cellular protein synthesis. It is worthy of mention that the mechanisms by which nutrients and ATP activate mTOR are still not fully known.

Dysregulation of the mTOR signaling pathway, which can create a favorable environment for growth is reported in many human cancers. Additionally, changes in the level of the components of the mTOR signaling pathway have been reported in cancers of breast, prostate, pancreas, ovary, lung and lymphoma. In endometrial cancer, high level of the phosphorylated form of mTOR is reported. The evidences suggesting significant dysregulation of the mTOR signaling pathway in cancer have raised the possibility of using mTOR inhibitors for cancer therapy. Rapamycin and its derivatives are classical inhibitors of mTOR; these agents by successful inhibition of S6K and eIF4E can lead to cell growth inhibition and activation of apoptosis. A number of studies using inhibitors of the mTOR signaling pathway are currently underway and recent preclinical and clinical evidences suggest that reduction of mTOR function might be effective in anti-cancer therapy.

Conclusion

The association between type II diabetes, the choice of insulin therapy and the risk of cancer has hitherto attracted the attention on the role of insulin-mediated signaling in cancer development and progression. Many details of insulin-mediated signaling are still unknown, but it is clear that intricately complex cellular regulation mediated by insulin and its receptors, IGFs, IGF receptors and IGF binding proteins plays a critical role in maintaining normal homeostasis. Abnormal activity and/or aberrant expression of any of the key components of...
this pathway will create not only the risk of type II diabetes, but also cancer. Further understanding on insulin-mediated signaling and development of potential anti-cancer therapies by blocking this signaling pathway is a future clinical possibility.

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