Insulin Signaling Linking Metabolism and Malignancy

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Contents

Abstract

Dysregulation of insulin/insulin-like growth factor (IGF) pathways is a major feature of both the metabolic syndrome (MetS) and cancer. This chapter explains the molecular events linking MetS to carcinogenesis, thereby focusing on the insulin/IGF signaling. Specific differences in receptor expression, ligand affinity, and substrate activation enabling differential signaling of insulin and IGFs are summarized.

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4.1 Introduction

Both the metabolic syndrome (MetS) and cancer constitute a growing health problem worldwide. In the last decades, MetS as a risk factor for cancer has become apparent [1]. The MetS is a cluster of risk factors for both cardiovascular disease and type 2 diabetes and includes glucose intolerance or insulin resistance together with two or more of the following components: raised arterial pressure, raised plasma triglyceride and/or low HDL-C, central obesity, and microalbuminuria. Jaggers and colleagues demonstrated in a study with more than 30,000 patients that the MetS is associated with an increased risk of all-cause cancer mortality in men [2]. Also other studies reported that the individual components of the MetS independently increase the risk for the development of certain cancer types [3–5]. For example, MetS was described to be associated with increased incidences of colorectal and prostate cancer, and with the recurrence of breast cancer [6–8]. A meta-analysis reported an association of MetS with liver, colorectal, bladder, endometrial, pancreatic, and breast cancers [9].

The mechanisms linking MetS and cancer risk are not completely understood. MetS may be only concomitant with other cancer risk factors, such as decreased physical activity, consumption of high calorie foods, high dietary fat intake, low-fiber intake, and oxidative stress [9]. Still, adiposity, in particular visceral obesity, results in a chronic inflammatory state, in which adipocytes and infiltrating immune cells create a pro-tumorigenic environment by producing inflammatory cytokines and chemokines [10]. The obesity-driven altered balance between proinflammatory and antiinflammatory cytokines influences insulin sensitivity [11]. Increased concentrations of inflammatory cytokines suppress insulin signal transduction, which, in turn, promotes inflammation [12, 13]. Chronic inflammation is commonly known to promote tumorigenesis [14].

Also other symptoms of MetS have been linked to insulin resistance and type 2 diabetes, i.e., high blood pressure and hypertriglyceridemia [15]. Insulin resistance can predict microalbuminuria [16].

This chapter focuses on the link between type 2 diabetes and cancer, thereby omitting other symptoms of MetS. Especially alterations in the insulin metabolism seem to increase cancer risk [17–19]. Patients with type 2 diabetes were reported to show increased cancer risk, which may be caused by hyperinsulinemia, elevated IGF1, or potentially both factors [20]. While normal cells often show little responsiveness toward insulin and IGF-dependent growth stimulation, tumor cells highly express both insulin and IGF1 receptors [20] (Fig. 4.1). Insulin resistance is characterized by a defective classical metabolic signaling. At the same time, altered signaling is induced due to increased levels of insulin, IGFs, and other factors as discussed below. Low insulin, IGF1, and IGF2 levels appear to protect from tumorigenesis [21].

Noteworthy, insulin induces the generation of reactive oxygen species (ROS) [22] (Fig. 4.1). Also hyperglycemia is known to increase oxidative stress [23], leading to increased DNA damage in diabetic individuals compared to healthy subjects [24] (Fig. 4.1). ROS can lead to downregulation of the tumor suppressor phosphatase and tensin homolog (PTEN) [25], a process known to promote insulin

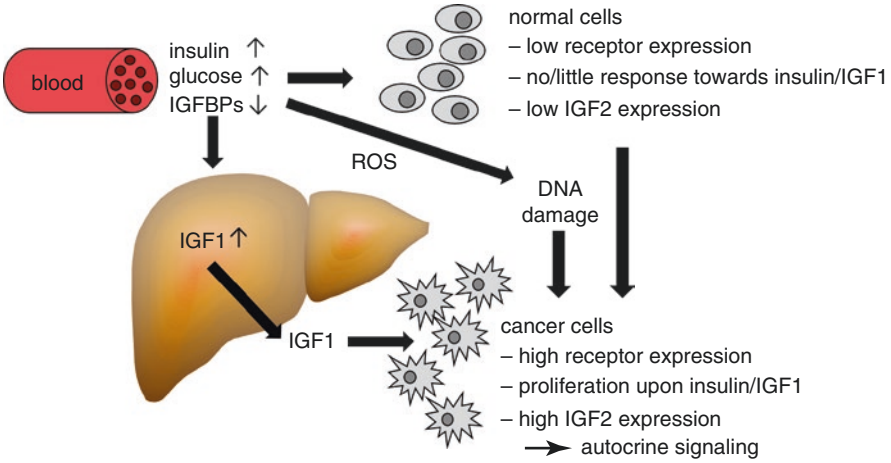

Fig. 4.1 Cancer promoting insulin/IGF signaling during insulin resistance. In normal cells of insulin target tissues, high glucose and insulin levels lead to glucose uptake and metabolic actions such as glucogen synthesis and lipid synthesis. Nonclassical insulin target tissues lack mechanisms which regulate mitogenic actions of insulin. In insulin resistance, increased systemic levels of insulin and glucose induce hepatic IGF1 production, which can lead to tumorigenesis due to the growth and survival-promoting effects of IGF1, especially in nonclassical insulin target organs. Elevated insulin and glucose levels can elicit an elevated generation of reactive oxygen species (ROS), which induce DNA damage, thereby facilitating tumor initiation

signaling. ROS generation, in general, is regarded as a hallmark of inflammation and can lead to carcinogenesis due to DNA damage [26].

Insulin/insulin-like growth factor (IGF) signaling is mediated by binding of insulin or IGFs to insulin and/or IGF receptors. IGF levels can be regulated by IGF-binding proteins (IGFBPs), which can inhibit and potentiate IGF actions by ligand binding. High circulating insulin levels decrease levels of IGFBP1 and IGFBP2, thereby increasing the bioavailability of IGF1 and concomitant changes in the cellular environment facilitating tumor formation (Fig. 4.1). In insulin resistance, nonclassical insulin target tissues which express insulin receptors are exposed to the elevated plasma levels of insulin, triglycerides, free fatty acids, and glucose [27] (Fig. 4.1). In contrast to classical insulin target tissues, such as skeletal muscle, adipose tissue, and liver, these tissues may lack a specific mechanism regulating the mitogenic actions of insulin [27]. Additional changes in signaling pathways may be induced by the increased availability of energy substrates, such as glucose, triglycerides, and free fatty acids, which also ensure energy substrates for already transformed cells [27]. High insulin levels as found in insulin resistance enhance growth hormone (GH) receptor signaling and hepatic IGF1 production [28], both of which can contribute to carcinogenesis. Concordantly, in vitro, animal, and human epidemiological studies demonstrate that despite suppressed classical metabolic insulin signaling, high concentrations of insulin and insulin-like growth factors (IGFs) promote cancer development by acting through the insulin/IGF axis [29] (Fig. 4.1).

4.2 IGF1 in Cancer

IGF1, i.e., circulating IGF1, is produced throughout life mainly in the liver under GH stimulation. A small amount of autocrine IGF1 is also produced in peripheral tissues and can be controlled by other factors released from surrounding cells. Cancer epidemiological studies have focused mainly on circulating total IGF1 and its major binding protein, IGFBP3. Circulating IGF1 is associated positively with the risk of breast, colorectal, prostate, and lung cancer, whereas total IGFBP3 concentrations are negatively associated with cancer risk [30–32]. In acromegaly patients, typically showing hypersecretion of GH, elevated levels of total IGF1, and hyperinsulinemia, the risk of colorectal cancer was increased [33]. In the healthy state, 99% of circulating IGF1 is bound by IGFBPs [34]. It is believed that free circulating IGF1 levels better reflect IGF1 bioactivity than total IGF1 levels [35]. Free circulating IGF1 has also been correlated to an increased risk of breast cancer, but independent of total IGF1 levels. In contrast to total IGF1 levels, free IGF1 was not related to tumor development in prostate cancer [36]. In addition to a hyperinsulinemia-induced increase in circulating levels of IGF1, prostate cancer cells in rodents were suggested to upregulate their intrinsic IGF1 production, thereby enabling independence from growth-promoting, circulating IGF1 [37]. In contrast, knockout mice with liver-specific IGF1 deficiency had decreased growth and metastasis of transplanted colonic adenocarcinomas and mammary tumors [38–40]. Administration of IGF1 abrogated the protective effect of IGF1 deficiency on tumor progression and resulted in neovascularization due to vascular endothelial growth factor (VEGF) induction [38, 40]. Angiogenesis is further promoted by IGF1-induced expression of hypoxia-inducible factor 1α (HIF1α) [41, 42]. Moreover, IGF1-induced metastatic tumor spread was suggested to be related to the relocation of integrins to the edge of migrating cells and the extension of lamellipodia [43, 44].

4.3 IGF2 in Cancer

IGF2 is expressed in the embryonic and neonatal state and its expression strongly drops after birth. IGF2 was reported to be reexpressed in several cancer types [45–51], defining IGF2 as an oncofetal protein [52]. Tumors take advantage of the proliferative [53, 54] and antiapoptotic properties of IGF2 by increasing IGF2 expression in tumor cells [55]. IGF2 expression was associated with the tumor grade in hepatocellular carcinoma [56, 57]. Furthermore, IGF2 expression was observed to correlate with tumor grade and lymph node metastasis in breast cancer [58]. In adrenocortical carcinoma and osteosarcoma, IGF2 expression was described to correlate with microvessel density [59, 60], to influence taxol resistance, and to be linked to a shortened disease-free survival [61]. *Igf2* transgenic mice are more susceptible to diverse malignancies [62]. Mouse models of colon cancer showing overexpression of IGF2 had a doubled tumor incidence in the presence of the adenomatous polyposis coli gene mutation [63]. Also enhanced sensitivity to IGF2 signaling led to elevated expression of proliferation-related genes and enhanced tumor development [64].

4.4 Insulin and IGF Signaling and Its Implication in Carcinogenesis

The insulin/IGF signaling network impresses through its complexity. In the following section, we point out important links between insulin/IGF signaling and carcinogenesis.

4.4.1 Insulin Receptors, IGF Receptors, and Hybrid Receptors

The three ligands insulin, IGF1, and IGF2 can act via five different receptors, namely, insulin receptors (IR) A and B, IGF1 receptor (IGF1R), and two hybrid receptors IRA/IGF1R and IRB/IGF1R. Insulin displays highest affinity for the two IRs, whereas IGF1 and 2 rather bind to the IGF1R and the hybrid receptors. IRB/IGF1R is exclusively bound by IGF1 but not by IGF2 (Fig. 4.2). The activation of the respective receptor by the different ligands can induce distinct downstream effects. Interestingly, binding of IGF2 to IRA results in a different gene expression pattern compared to binding of insulin [65], which is of relevance for tumors showing elevated IGF2 expression. However, the exact mechanisms of the different consequences of ligand binding to the insulin/IGF receptors are still unknown.

The different receptors mediate their effects through recruitment, phosphorylation, and finally activation of insulin receptor substrates (IRS), Src homology 2 domain containing transforming protein (SHC), and Janus kinase (JAK) 1/2,

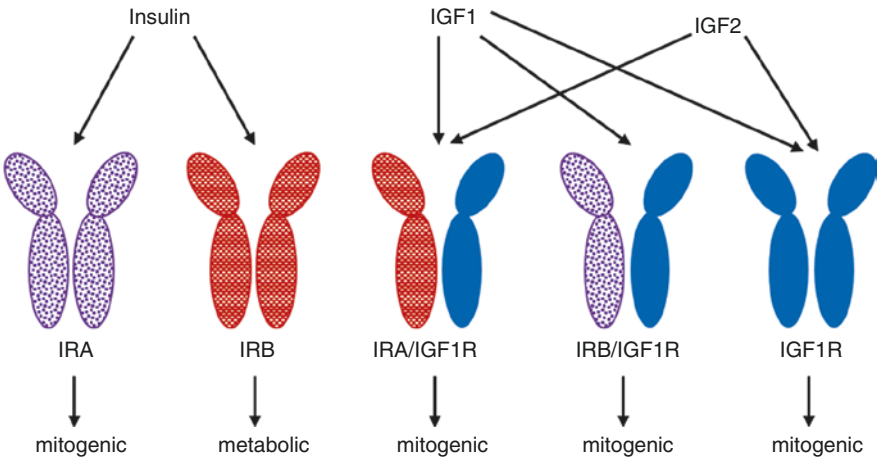

Fig. 4.2 Binding affinities of IR and IGF1R receptor ligands. Insulin preferentially binds to insulin receptors IRA and IRB. IGF1 rather activates the hybrid receptors and IGF1R. IGF1R and the hybrid receptor variant IRA/IGF1R are also bound by IGF2. IRA, the hybrid receptors, and IGF1R tend to a more mitogenic signaling, whereas IRB rather activates metabolic pathways. In cancer IRA, IGF1R, and the hybrid receptors are overexpressed, resulting in a mitogenic signaling

leading to an activation of phosphoinositide 3-kinase (PI3K), protein kinase B (PKB/AKT), and mammalian target of rapamycin (mTOR), mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK), or JAK/signal transducer and activator of transcription (STAT). Although all five receptors share the same signaling pathways, it is known that IRA and IGF1R favor mitogenic actions, whereas IRB rather induces metabolic effects (Fig. 4.2) [66–68]. Insulin resistance is caused by defects in the metabolic signaling pathways, favoring a mitogenic and growth-promoting signaling [27]. Concordantly, insulin induces transcription of a set of genes involved in metabolism, whereas insulin-like ligands increase expression of mitogenic genes [69]. Thus, differential expression of the respective receptors or their ligands in cancer, as well as in development, can implicate distinct consequences, i.e., metabolic and/or mitogenic or growth-related signaling. For example, overexpression of IGF2 in tumor cells also leads to increased mitogenic signaling via IRA [70].

IGF2 can also interact with a sixth receptor, IGF2R, which degrades IGF2 protein and therefore decreases IGF2 bioavailability. Thus, inhibitory IGF2R is often mutated or downregulated in cancer [71, 72].

4.4.2 Insulin Receptor Substrates

Autophosphorylation of the five signaling receptors mentioned above leads to the recruitment of different proteins, mainly IRS1, IRS2, and SHC, resulting in PI3K or MAPK pathway activation. Although IRS1 and IRS2 share biological effects, they exert tissue-specific roles [73]. PI3K can be activated by both IRS1 and IRS2. Besides antiapoptotic signaling, the PI3K/AKT pathway regulates metabolic pathways in tumors which promote aerobic glycolysis, a hallmark of cancer [74, 75]. Cancer cells depend rather on glycolysis than oxidative phosphorylation for energy production, even in high oxygen states, a phenomenon called the “Warburg” effect [76]. IRS2 signaling preferentially regulates tumor cell metabolism, i.e., aerobic glycolysis by inhibition of GSK-3β [77]. In line with this finding, aerobic glycolysis is diminished in IRS2 knockout cells compared to IRS1 knockout cells. Moreover, IRS2 may be required for glucose transporter (GLUT) 1 to localize to the cell surface where it can facilitate glucose uptake [78].

MAPK signaling seems to be preferentially induced by IRS1 (Fig. 4.3) [79]. Indeed, several studies suggest that IRS1 distinctly mediates the insulin/IGF1-induced mitogenic effects, whereas IRS2 appears to be more involved in generating the metabolic responses of insulin [80–83] and the migration-promoting potential of IGF1 (Fig. 4.3) [84]. However, metabolic stress induces specific phosphorylations of IRS1, which aggravate insulin resistance [85]. Specific responses were suggested to be altered by integrins differentially regulating IRS1 and IRS2 expression (Fig. 4.3) [86]. While IRS2 promotes aggressive tumor behavior, IRS1 may negatively regulate tumor progression, although IRS1 and IRS2 may play redundant roles in tumor initiation and primary tumor growth [78]. However, IRS1 was described to elevate growth and migration in breast cancer cells [87]. Different

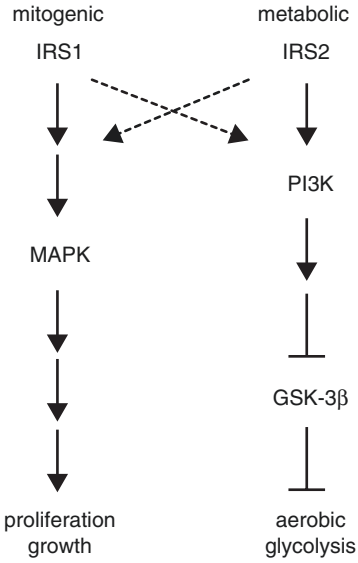

Fig. 4.3 Preferential signaling of the two insulin receptor substrates supporting tumorigenesis. IRS1 preferentially activates MAPK signaling, leading to a mitogenic signaling, thereby increasing proliferation and growth. IRS2 inhibits GSK-3βs by PI3K phosphorylation, leading to an increased aerobic glycolysis, which is essential in tumor metabolism

activation of and by IRS1 and IRS2 may be also due to the structural differences, since they share only 14 conserved sites of 21 and 23 phosphorylation sites of IRS1 and IRS2, respectively [88].

4.4.3 PI3K-Related Signaling

The PI3K/AKT pathway is the major signaling network involved in insulin/IGF signaling (Fig. 4.4). PI3K plays a central role in cancer promoting cancer cell growth, survival, motility, and metabolism [89]. By induction of several activating factors, as well as by repression of different inhibitory factors, a constitutively activated pro-survival signaling is achieved. One of these inhibitory factors is PTEN, which usually counters cell growth and cell cycle progression by inhibiting PI3K-induced PIP_3 phosphorylation. PTEN displays one of the most commonly mutated tumor suppressor genes in human cancer. Loss of PTEN results in increased signaling of IGF2 through IGF1R and IRA in breast cancer cells [90]. PIP_3 activates AKT, resulting in activation of the key metabolic regulator mTOR and thereby initiating ribosomal protein synthesis and mitosis through 4E–BP1 (Fig. 4.4). Deletion of the mTOR target S6K1 in mice was shown to result in hyperinsulinemia and glucose intolerance [91]. These mTOR-induced mechanisms all favor tumor growth; thus, dysregulated mTOR signaling has been linked to numerous human cancers [92–94]. Loss of PTEN leads to constitutively activated mTOR [95]. mTOR regulation is controlled not only by PTEN but also by the tumor suppressor gene products tuberous sclerosis (TSC) 1, TSC2, and AMP-activated protein kinase (AMPK). AMPK interacts with both TSC2 and mTOR and thus directly and indirectly inhibits the activation of mTOR (Fig. 4.4) [96]. In colorectal cancer, frameshift mutations in the

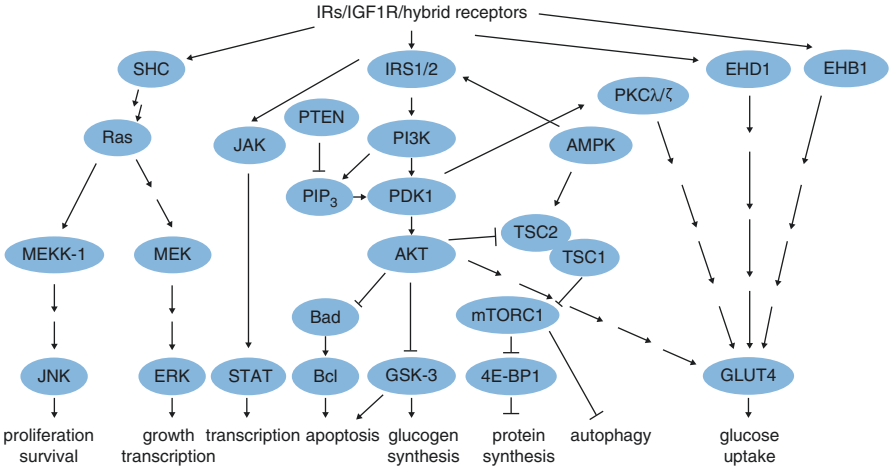

Fig. 4.4 Overview of the insulin/IGF signaling network. Central factors of the insulin/IGF signaling pathways are shown. For details see text

AMPK-encoding gene were observed [97]. mTOR itself was also shown to be mutated in several types of cancer [98–100].

Antiapoptotic insulin/IGF signaling via AKT is realized by initiating phosphorylation of the Bcl-2 family member BAD, followed by Bcl-XL leading to inhibition of apoptosis (Fig. 4.4). Moreover, multiple transcription factors, such as cAMP response element-binding protein (CREB), nuclear factor (NF)-κB, and p53, which are involved in the transcription of genes encoding apoptotic mediators, are regulated by IGFs [101]. Akt hyperactivation in cancer not only contributes to the inhibition of apoptosis but is also coupled with metabolic alterations in cancer cells, including aerobic glycolysis [102].

4.4.4 MAPK-Related Signaling

Besides PI3K activation, insulin or IGF stimulation has been shown to increase interaction with SHC [103]. SHC initiates the MAPK pathway, which represents a key promoter of cell proliferation, tumor development, tumor growth [104], as well as in the maintenance and progression of several tumors [105, 106]. The MAPK pathway involves activation of Ras, which can activate both JNK and MEK/ERK pathways (Fig. 4.4). The Ras/Raf cascade is frequently elevated in cancer, either growth factor dependently or independently, e.g., due to mutations [107, 108].

Noteworthy, ERK signaling is also implicated in metabolic alterations, such as insulin resistance. Chronic activation of ERK induces severe insulin resistance by inhibiting expressions of both GLUT4 and insulin-signaling proteins [109]. Targeting the MEK/ERK cascade normalized hyperglycemia and hyperlipidemia

and improved insulin sensitivity, as well as glucose tolerance in diabetic mice [110]. Thus, the MAPK pathway displays a second important insulin/IGF-mediated pathway linking insulin resistance to cancer.

Conclusion

Insulin/IGF signaling is of particular importance in carcinogenesis, especially when tumor development is the consequence of chronic metabolic diseases. Insulin/IGF signaling mediates its effects through different signaling cascades. Not surprisingly, tumor cells activate multiple signaling pathways at once to achieve growth, protection against apoptosis, metastasis, metabolic alterations, and other features being a characteristic for cancer. Here, the activation of the insulin/IGF axis offers the advantage of activating several pathways at once for tumor development and progression. As a result from the extensive basic research, several therapeutic approaches targeting the insulin/IGF axis in cancer are currently under investigation and reviewed in detail elsewhere [111–113].

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