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REVIEW

Insulin, insulin receptors, and cancer

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Abstract Insulin is a major regulator of cell metabolism but, in addition, is also a growth factor. Insulin effects in target cells are mediated by the insulin receptor (IR), a transmembrane protein with enzymatic (tyrosine kinase) activity. The insulin receptor, however, is represented by a heterogeneous family of proteins, including two different IR isoforms and also hybrid receptors resulting from the IR hemireceptor combination with a hemireceptor of the cognate IGF-1 receptor. These different receptors may bind insulin and its analogs with different affinity and produce different biologic effects. Since many years, it is known that many cancer cells require insulin for optimal in vitro growth. Recent data indicate that: (1) insulin stimulates growth mainly via its own receptor and not the IGF-1 receptor; (2) in many cancer cells, the IR is overexpressed and the A isoform, which has a predominant mitogenic effect, is more represented than the B isoform. These characteristics provide a selective growth advantage to malignant cells when exposed to insulin. For this reason, all conditions of hyperinsulinemia, both endogenous (prediabetes, metabolic syndrome, obesity, type 2 diabetes before pancreas exhaustion and polycystic ovary syndrome) and exogenous (type 1 diabetes) will increase the risk of cancer. Cancer-related mortality is also increased in patients exposed to hyperinsulinemia but other factors, related to the different diseases, may also contribute. The complexity of the diseases associated with hyperinsulinemia and their therapies does not allow a precise evaluation of the cancer-promoting effect of hyperinsulinemia, but its detrimental effect on cancer incidence and mortality is well documented.

Keywords Insulin · Insulin receptor · IR isoforms · Hybrid receptors · Diabetes and cancer

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The insulin receptor and its cognate receptors

Insulin, secreted from the beta cells of the pancreas, is the major regulator of the fasting-to-fed metabolic transition by altering substrate metabolism, promoting energy storage, and activating protein synthesis [1]. In addition to its glucoregulatory and other metabolic properties, insulin can also stimulate cell growth [1]. Insulin acts on various cells via the insulin receptor (IR) [2]. The IR is a transmembrane receptor that belongs to the large class of tyrosine kinase receptors [3] and is primarily activated by insulin, but can also be activated by different insulin analogs and by the insulin-related growth factors, IGF-1 and IGF-2 (especially the latter, v. i.). Metabolically, the insulin receptor plays a key role in the regulation of glucose homeostasis. Since the insulin receptor can stimulate cell growth, this functional process can, under certain conditions of hyperinsulinemia, result in pathological disorders including cancer and cardiovascular disease.

Biochemically, the insulin receptor is encoded by a single gene INSR, from which alternate splicing during transcription results in either IR-A or IR-B isoforms [4]. Downstream posttranslational events of either isoform

result in the formation of a proteolytically cleaved α and β subunits, which upon combination produce the tetrameric ≈320 kDa disulfide-linked transmembrane IR (Figs. 1, 2). The 12 amino acids derived from exon 11 are included in the longer IR isoform (IR-B), but not in the shorter isoform (IR-A). Both IR isoforms bind insulin at their alpha subunits, with the IR-B having a modestly higher affinity for insulin. In contrast to IR-B, the IR-A isoform can also bind and be activated by the growth factor IGF-2 at low-nanomolar concentration [5] (Fig. 2). The two IR isoforms are expressed at different proportion in insulin-responsive tissues; IR-A is predominantly expressed in embryo and fetal tissues [5, 6] and binds both Insulin and IGF-2 with high affinity (and also IGF-1 at a much lower affinity). However, postbinding effects of the two ligands are somewhat different: when activated by IGF-2, mitogenic effects and increased survival, motility, and invasiveness of cancer cells are more marked than when activated by insulin [7]. In contrast, IR-B is activated mainly by insulin and is mainly responsible for maintaining glucose homeostasis. The major functional difference between IR-A and IR-B, therefore, is represented by the different binding affinity with regard to IGF-2 and IGF-1. The affinity of IGF-I for IR-A is approximately tenfold higher than for IR-B, although 4- to 16-fold lower than that of IGF-2 [8, 9]. In vitro data suggest that IR-B can be considered the

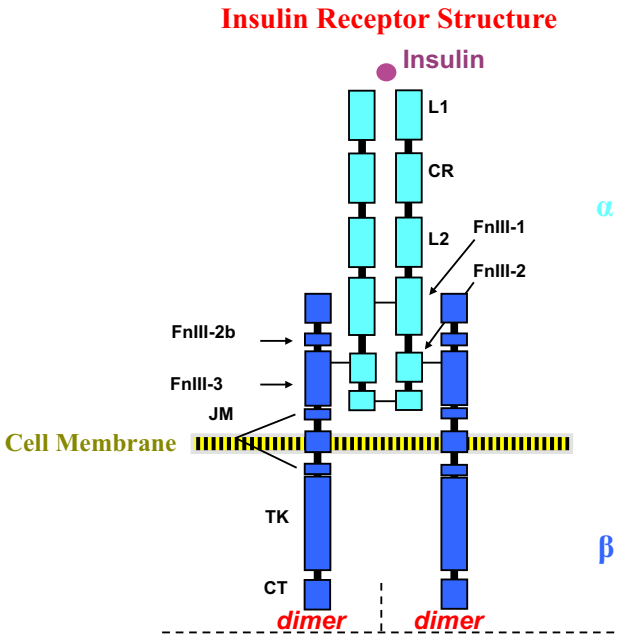

Fig. 1 Structure of the insulin receptor. The two α submits are extracellular and bind the ligands. The two β submits span the cell membrane and have enzymatic (tyrosine kinase) activity. *L1, L2* large domains, *CR* cysteine-rich domain, *FnIII* fibronectin type 3 domains, *JM* juxta-membrane domain, *TK* tyrosine kinase domain, *CT* carboxy-terminal

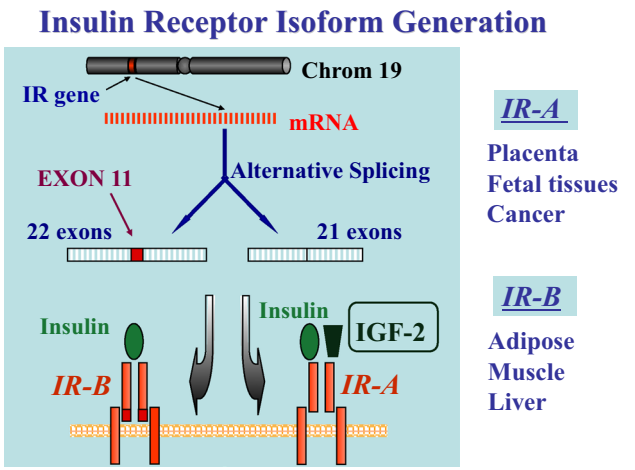

Fig. 2 Insulin receptor gene on chromosome 19 gives origin to a 22-exon mRNA transcript that during maturation may either include or not include exon 11. This alternative splicing produces two isoforms, IR-A and IR-B, differing for 12 amino acids at the COOH-terminal of the α-subunit. This difference causes different binding characteristics: the shorter isoform (IR-A) binds with high affinity not only insulin but also IGF-2

specific receptor of insulin that is predominantly implicated in metabolic effects, whereas IR-A is a less specific receptor that also binds IGFs and is now recognized as a high affinity receptor for IGF-2 (Fig. 2).

The insulin-like growth factor 1 receptor (IGF-1R) protein is highly homologous to the IR (45–65 % in its ligand binding domains, and 60–85 % in the tyrosine kinase and substrate recruitment domains), shares a nearly identical architecture, and is a potent stimulator of cell growth [10]. Both receptors derive from an ancestor gene, whose duplication has given rise to both the IR and the IGF-1R genes [4]. Moreover, the IGF-1R shares much of the same downstream signaling machinery with the IR and the resulting differences in signaling are a matter of degree, with the IGF-1R receptor being about tenfold more efficient at stimulating mitogenic actions than the IR [11]. Three protein ligands: insulin (and proinsulin), insulin-like growth factor 1 (IGF-1), and insulin-like growth factor 2 (IGF-2) are capable of binding and activating both the IR and the IGF-1R, albeit with different affinities and potencies [12–14] (Fig. 3).

The shared ligand and signaling structure between IR and IGF-1R plays a crucial role in embryonic development, where the IR acts as a functioning IGF-2 receptor and is required for full growth of the fetus. As a result of the shared ligand binding and signaling architecture between the IR and the more mitogenic IGF-1R receptors, there has been much concern about the potential of insulin and its therapeutic analogs to act as tumor-promoting mitogens [13, 15–17]. There is substantial support for the

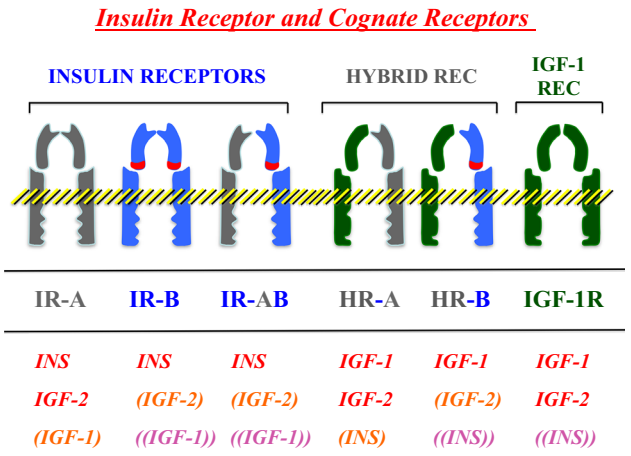

Fig. 3 Receptor family for insulin and IGFs include at least 6 receptors resulting from the combination of different hemireceptors. Each receptor binds different ligands with different affinity: *Ligands in brackets* have a binding affinity 10–100-fold lower than the one with the highest affinity; *double brackets* indicate even lower binding affinity

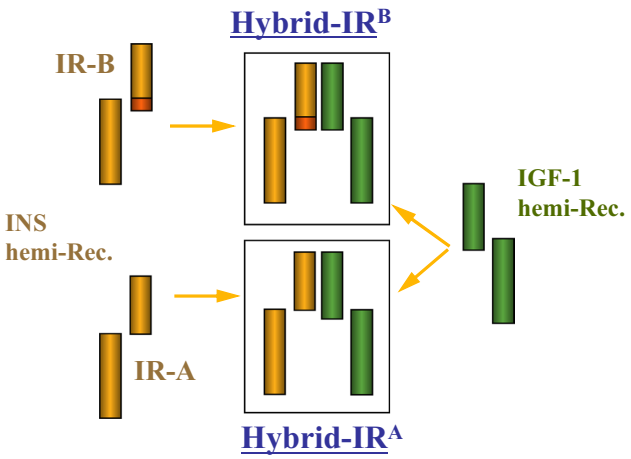

Fig. 4 Hybrid receptors IR/IGF-1R are formed by heterodimerization of one IR hemi-receptor and one IGF-1R hemireceptor. The IR can participate with the hemireceptor from either the *A* or the *B* isoforms, producing HR-A or HR-B hybrid receptors, respectively

notion that the hyperinsulinemia of T2DM plays an important role for increased rates of certain types of cancers, particularly pancreas, liver, endometrium, and breast [13, 18–20]. In cell models, it is clear that insulin can act as a mitogen similar to IGF-1, via both its own receptor (especially the A isoform) and also the IGF-1 receptor, but the latter effect often requires high insulin levels to bind to and activate IGF-1Rs since the affinity of this hormone for the IGF-1R is approximately 100-fold lower than for the IR [17].

Further complicating this relationship, IR and IGF-1R readily form heterodimeric hybrid receptors with each other (Fig. 3). The isoforms A and B of IR, which are co-expressed in most cells, can form homodimers (IR-A/IR-A or IR-B/IR-B) and heterodimers (IR-A/IR-B hybrids). Since IGF-1R is also expressed in most cells and the two receptors have a high grade of homology, several studies demonstrate that the dimers ($\alpha+\beta$ subunits) of the two receptors can form hybrid IR/IGF-1R (HR) receptors which include HR-A or HR-B depending on the IR isoform involved (Fig. 4). Because of the high homology between the two molecules, heterodimerization occurs with a similar efficiency as homodimerization. Therefore, the proportion of hybrids is related to the amount of each receptor in that cell. In tissues that express abundant levels of IGF-1R and IR, such as skeletal muscle, the hybrid receptor is the most abundant species [21]. These heterodimeric receptors can function as growth-promoting IGF receptors and demonstrate relatively poor activation by insulin although HR-A can also respond to marked hyperinsulinemia [15].

Insulin receptor signaling pathways

When activated by ligand binding [3], the IR undergoes tyrosine autophosphorylation at various sites. These phosphorylated tyrosines then interact with various intracellular proteins that generate inside the cell a complex network of biochemical signals that are responsible for the pleiotropic effects of the hormone. A simple way to classify these effects is to recognize its metabolic and mitogenic pathways. This is a simplistic representation of the very complex molecular interactions that characterize the biochemical perturbations induced by the IR activation; however, for the sake of clarity, we will follow this scheme.

The metabolic pathway stimulated by the activated IR to regulate glucose, protein, and lipid metabolism involves the PI3K/AKT pathway [22] (Fig. 5).

The binding of insulin to the IR results in the recruitment of PI3K to the plasma membrane. PI3K is then phosphorylated and activated by the IRS adaptor proteins and leads to increased production of phosphatidylinositol-3,4,5-triphosphate (PIP3), which, in turn, activates the 3-phosphoinositide-dependent protein kinase 1 (PDK1) and AKT. The PI3K/AKT pathway is negatively regulated by the lipid phosphatase PTEN (Phosphatase and TENsin homolog encoded on chromosome 10 gene) which dephosphorylates PIP3. AKT phosphorylates and activates other targets involved in several processes including glucose uptake and translocation of the glucose transporter GLUT4 to the plasma membrane cell (Rab-GTPase activating protein), glycogen synthesis (glycogen synthetase kinase 3, GSK3), gene transcription (Forkhead box O transcription factors, FoxO), and ribosome biogenesis (tuberous sclerosis complex, TSC1/TSC2 and mammalian target of rapamycin, mTOR).

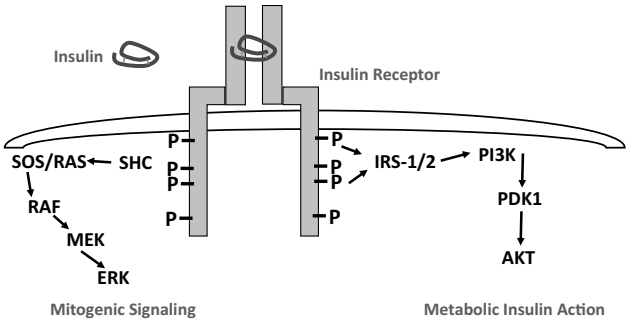

Fig. 5 Insulin receptor, under normal insulin stimulation, activates two major intracellular signaling cascades. The PI3K/AKT pathway has a predominant metabolic effect and is activated by the IR phosphorylation of IRS 1/2. The RAS/RAF/MEK/ERK pathway has predominant mitogenic effects and is activated by the IR phosphorylation of Shc. When the metabolic signaling pathway is partially impaired (insulin resistance), a compensatory increase of insulin occurs to maintain the metabolic homeostasis. Under this condition, the mitogenic pathway, which is not affected by specific impairment, is over stimulated

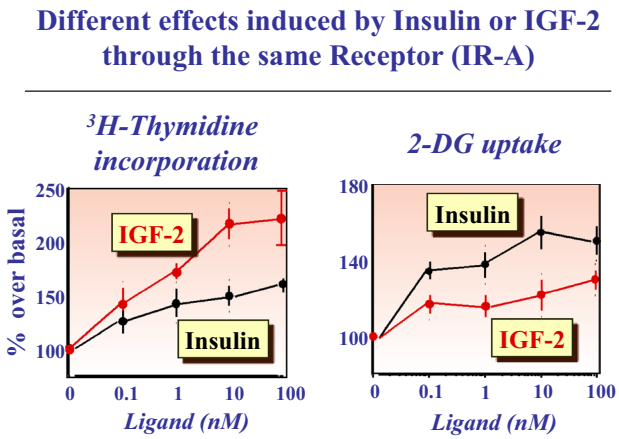

Fig. 6 Same receptor (IR-A) will trigger different biological effects when activated by different ligands. When stimulated by IGF-2, the mitogenic effect (^{3}H-Thymidine incorporation) is predominant. In contrast, when activated by insulin, the metabolic effect (2-D-Glucose uptake) prevails

The activated IR also stimulates the mitogenic pathway which causes cell proliferation. The RAS/RAF/MEK/ERK cascade of the IR is activated by insulin following the phosphorylation of Shc and the recruitment of the Grb/Sos complex. This complex, in turn, triggers the activation of GTPase Ras, and subsequently the RAF isoforms and their downstream signaling effectors MEK1/2 (MAPKKs) and ERK1/2 (MAPKs), a key enzyme in cell cycle entry and progression. Activated ERK1/2 phosphorylates cytosolic proteins that can translocate to the nucleus, where they regulate gene expression and cell growth [1, 3] (Fig. 5).

Although most phosphorylation and dephosphorylation reactions of the intracellular signaling pathways are shared by all receptors of the insulin/IGF receptor family, specificity is also present, based on the receptor involved and the type of ligand. On one hand, the same ligand (insulin) will cause different biological effects when binding to either the IR-A or IR-B [7]. On the other hand, the same receptor (IR-A) will activate the phosphorylation of intracellular substrates in response to insulin and IGF-2 with quantitative and temporal differences [7, 23] causing partially different biological effects (Fig. 6).

In conclusion, a network of cognate ligands and cognate receptors provides a spectrum of biological responses that are greatly variable in both quantity and quality.

The insulin receptor and cancer cells

It has been known for some time that several cancer cell lines require insulin for optimal cell growth. This effect had been attributed to the spillover of high insulin concentrations on the IGF-1R. Numerous in vitro and in vivo studies have now clearly established that insulin may affect tumor progression by acting through its own receptor and not by cross talk with the IGF-1R [24, 25]. The presence of insulin binding sites was reported in human breast cancers both in vitro [26, 27] and in vivo [28]. However, the possible implications of these findings for human cancer remained unclear for long time. Finally, analyses employing a specific IR ELISA indicated that approximately 80 % of breast cancers had a significantly higher IR content than the mean value for normal breast tissue; moreover, approximately 20 % of breast cancers had an IR content that was over tenfold higher than the mean value for normal breast tissue [28] (Fig. 7). Immunostaining indicated that IR was predominantly overexpressed in neoplastic cells and not in stromal adipocytes and inflammatory cells. It was then observed that IR overexpression was not specific to breast cancers but was a common phenomenon in various human cancers. Increased IR content was found in carcinomas of the colon, lung, ovary, and thyroid [5, 23, 29, 30].

IR overexpression in cancer cells is a possible consequence of increased HMGA1 protein [30, 31], a transcription factor that regulates gene expression and specifically inactivates p53, an oncogene suppressor. P53 suppresses the promoter activity of the IR and IGF-1R, and its inactivation increases the cellular content of the IR. Other mechanisms, frequently activated in cancer, can also contribute to IR overexpression in many malignant cells [32].

One relevant issue is to clarify whether insulin stimulates cancer cells by acting via its own receptor or by activating the IGF-1R. By employing blocking monoclonal antibodies specific to both the IR and IGF-1R, it was

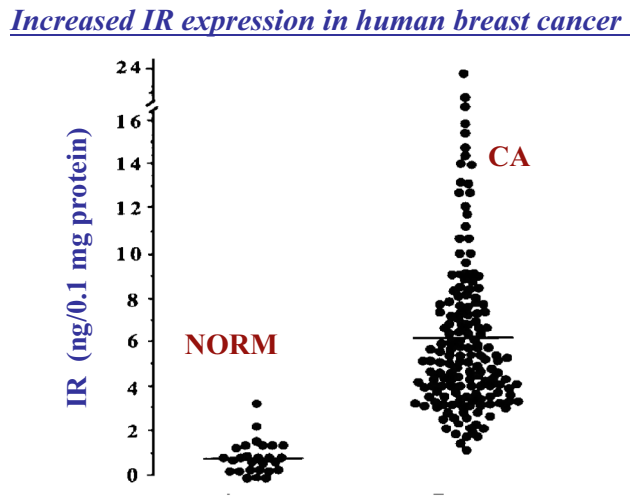

Fig. 7 IR expression is much higher in breast cancer ($n = 159$, mean value 6.2 ± 3.7 ng/0.1 mg protein) than in normal breast tissue ($n = 33$, 0.95 ± 0.7). Over 80 % of breast cancer cells have an IR content 2–20-fold higher than normal breast cells

demonstrated that the growth response to insulin of breast cancer cell lines could be specifically blocked by an anti-IR but not by the anti-IGF-IR blocking antibody [24]. These data demonstrated therefore that the mitogenic effect of insulin in breast cancer cells was due to insulin's binding to its own receptor and not to the IGF-1R. Cancer cells, therefore, are more responsive to insulin because they often express many more IRs, obtaining a selective advantage relative to nonmalignant cells.

Another insulin-dependent mechanism favors cancer cell growth. As already mentioned, most cells express both IR isoforms with the longer IR-B having predominant metabolic effects and being the predominant isoform in insulin target cells including liver, muscle, and adipose tissue. In contrast, cancer cells predominantly express IR-A the IR isoform typical of fetal, less differentiated cells. Many malignancies, including carcinomas of breast colon, lung, ovary, thyroid, and myosarcomas, were found to predominantly express IR-A rather than IR-B [5, 33–35]. This phenomenon, concomitant with the aforementioned IR overexpression, leads to the expression of very high levels of IR-A.

IR-A overexpression in cancer cells has deleterious consequences for two reasons. First, IR-A has an intrinsic capacity, when stimulated, to predominantly promote mitogenic rather than metabolic effects. Second, since IR-A is a high affinity receptor for IGF-2, locally (autocrine/paracrine) produced IGF-2 by both malignant and stromal cancer cells will sustain cell proliferation and invasiveness.

There is an additional cancer-promoting mechanism that involves the overexpression of IRs in cancer. IR and IGF-1R may heterodimerize, leading to the formation of hybrid IR/IGF-1Rs (HRs) [7, 8, 36, 37] (Figs. 3, 4).

Since cancer tissues express abnormally high levels of both IR and IGF-1R, their HR content is particularly elevated, as assessed by measurements performed in a variety of human cancer cells and tissues. In most tumors, HRs exceed IGF-1R content [38]. Therefore, HRs play an important role in mediating IGF-I effects in cancer cells. In cells expressing more HRs than IGF-1Rs, IGF-1 mitogenic effect is more strongly inhibited by anti-HR blocking antibodies than by an anti-IGF-1R antibody. Both IR-A and IR-B can form hybrids with IGF-1R with the same efficiency (HR-A and HR-B), in close accordance with the random assembly model [39]. Cancer cells, therefore, will mostly overexpress HR-A.

HR-A (at variance with HR-B) is a functional receptor for IGF-1, IGF-2 and, with much lower affinity, also for insulin [40]. As a consequence, cells expressing HR-A are more sensitive to biological effects of both IGFs and insulin, such as proliferation and migration, as compared to cells expressing mainly HR-B [39, 40]. The HR β-subunit moieties, belonging to both IR and IGF-1R, are phosphorylated in HRs. Insulin binding to HR-A, therefore, is able to activate the β-subunit of the IGF-1R moiety, and, as a consequence, both IGF-1 and also insulin are able to induce phosphorylation of specific substrates of the IGF-1R [40]. Therefore, insulin binding to HR-A hybrids may more effectively activate the growth-promoting signaling capability of IGF-1R as the insulin binding affinity for HR-A is higher than its affinity for the IGF-1R.

In conclusion, IR-A overexpression in cancer sensitizes cancer cells to autocrine IGF-2 and also to circulating insulin, especially when insulin levels are chronically high. At the same time, it leads to increased formation of HR-A, which seems to have unique binding and functional characteristics (Table 1). Therefore, IR-A overexpression in cancer has practical implications. One immediate practical consequence is that HRs should be taken into account by therapies designed to target IGF-1 effects in cancer. Another major consequence of the IR-A and HR-A overexpression in cancer cells is their potential role in sensitizing cancer cell growth in conditions of insulin resistance with compensatory hyperinsulinemia, such as type 2 diabetes mellitus. Hyperinsulinemia may both directly stimulate IR-A and HR-A, which are overexpressed, and also increase IGF-I bioavailability by suppressing the levels of IGF binding proteins 1 and 2 [41, 42].

Hyperinsulinemia may be worsened by the administration of insulin secretagogues (e.g., sulfonylureas) and also by exogenous insulin at high doses. While the risk of cancer may be increased by these treatments, this risk is decreased by treatment with metformin, an anti-diabetic

Table 1 Mechanisms of the Insulin Receptor's Role in cancer

IRs are overexpressed in many cancers
Therefore malignant cells are overstimulated by insulin
In cancer cells, the IR-A is the predominant IR isoform
This will cause three unfavorable consequences promoting cancer growth
(a) IR-A activates mitogenic effects more than IR-B
(b) IR-A binds IGF-2 with high affinity.
Therefore, the autocrine/paracrine produced IGF-2 will have a strong mitogenic effect on the tumor
(c) IR-A hemireceptors form hybrid receptors with IGF-1R hemireceptors
These hybrids stimulate cell growth not only in response to IGF-1, but also in response to IGF-2 and insulin

drug that is an insulin sensitizer that reduces insulin resistance and insulin levels [43–45].

In conclusion, cancer cells are very sensitive to the mitogenic effect of insulin via a variety of mechanisms. This has important implication in both primary and secondary cancer prevention. Measures to reduce hyperinsulinemia, and also selective treatment of patients that for either genetic or environmental factors are at increased risk of cancer, should be considered.

Clinical evidence for a role of insulin and the insulin receptor role in cancer

The role of insulin and its receptor in tumorigenesis is supported by clinical evidence indicating that diseases characterized by hyperinsulinemia are associated with an increased risk for cancer. The cancer-promoting effect of hyperinsulinemia is based on the knowledge that insulin is also a growth factor and that the IR is often overexpressed in cancer [27–29].

There is no firm evidence that insulin can promote the malignant transformation of target cells (cancer initiation or mutagenesis). However, in vitro and in a transgenic model, when the IR is overexpressed at a high level, this mutagenic effect occurs [46, 47]. Moreover, increased mutagenesis may be related to the well-known mitogenic effect of insulin, since excess DNA replication is a risk factor for copy errors.

If the effect of hyperinsulinemia on cancer initiation is questionable, there is much in vitro and in vivo data documenting its effect on cancer progression. Most cultured cancer cells increase their growth rate when exposed to insulin, even at low doses [47, 48]. Moreover, chemically induced breast cancer in rats undergoes regression when the animals are made diabetic (hyperglycemic) and insulinopenic with streptozotocin, while cancer growth is restored by the administration of exogenous insulin [49].

Hyperinsulinemia, in most cases, is associated with hyperglycemia. The role of increased glucose availability on cancer progression is still unclear since the two conditions, increase of insulin and also of glucose levels, are often associated making difficult to dissect the specific role of each one. Cancer cells have an abnormal metabolism and, in contrast to nonmalignant cells, mainly rely on aerobic glycolysis to generate the energy required for their accelerated growth (Warburg effect) [50, 51]. To satisfy the increased energy requirement, therefore, they need more glucose ("sugar fuels cancer"). Hyperglycemia, therefore, can reinforce the permissive role of sufficient energy substrate availability required by cancer cells. Many direct and indirect evidences support this possibility [52–54].

There is general consensus that hyperinsulinemia can promote the growth of latent, subclinical, and indolent cancers that, without the excessive IR stimulation, would have remained undiscovered and not harmful for the patient health and survival.

Since chronic hyperinsulinemia is recognized as an underlying cause of cancer, all diseases characterized by insulin resistance and the compensatory increase of insulin secretion are associated with increased cancer incidence. Also type I diabetes, characterized by endogenous insulin deficiency but treated with exogenous either insulin or insulin analogs, often at a dosage that exceeds the normal insulin levels, is associated with increased cancer risk [55].

Each one of these diseases is characterized by other, disease-specific, or site-specific risk factors for cancer. However, the role of hyperinsulinemia as a factor promoting cancer is well documented in humans provided that the circulating insulin levels are clearly increased and the exposure to hyperinsulinemia is chronic (many years).

Endogenous hyperinsulinemia

Prediabetes

Prediabetes represent a condition when plasma glucose is elevated above the normal range but below that of clinical diabetes. This condition includes both individuals with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The pathophysiology of prediabetes is based on the insulin resistance of peripheral tissues, with the mildly elevated plasma glucose levels triggering excessive insulin secretion.

Prediabetes is associated with increased risk of cancer. In a recent meta-analysis derived from 16 prospective cohort studies (891,426 participants), the overall increase of cancer was RR = 1.15 (95 % CI 1.06–1.23) with significant ($p < 0.05$) increases in liver, pancreas, breast,

endometrium, and stomach/colorectum cancers [56–58]. The duration of IFG exposure (>10 years) may be important to increase the cancer risk [58, 59].

Metabolic syndrome

The metabolic syndrome (MetS) is a cluster of disorders including insulin resistance and hyperinsulinemia, high blood pressure, dyslipidemia, and excess body weight with central obesity. Different components of the MetS are individually associated with an increased risk of cancer occurrence and mortality. It is difficult, therefore, to dissect the specific role of each factor because they can also work together to increase cancer risk beyond that of the individual component alone. Therefore, the specific role of hyperinsulinemia cannot be quantified. Quantitative data on the cancer risk level in patients with MetS are scarce and not well defined because of the great heterogeneity of the MetS patients, having phenotypes that can include the different MetS features at different levels of severity [60–63].

Obesity

Obesity has dramatically increased worldwide in the last 25 years. Therefore, even a small effect of obesity in promoting cancer will determine a large number of additional cancers.

Also obesity is a multifactorial syndrome, associated with many different metabolic, hormonal, and inflammatory components that can influence the risk of cancer. Obesity, therefore, is a heterogeneous syndrome is terms of different phenotypes that reflect the predominance of one or more of the multiple pathogenetic factors.

Both epidemiological and clinical studies provide clear evidence that obesity is associated with a higher incidence of many cancers and that this risk increases with increasing body weight excess [64].

Insulin resistance and hyperinsulinemia are typical metabolic abnormalities of most obese patients. The amount of body weight excess is not the only parameter determining hyperinsulinemia: the distribution of the extraweight and of adipose tissue is also a key variable. Central (or upper body or android) obesity, with predominant visceral adiposity, is the form of obesity where hyperinsulinemia is more accentuated and where the risk of cancer and its unfavorable outcome is more marked; the RR for cancer increases with increasing waist/hip ratio [65–67].

In addition, factors other than insulin, including diet, leptin, inflammatory cytokines, and increased estrogens derived from increased steroid aromatization in excessive adipose tissue contribute to the increased cancer risk in obese patients.

Since obesity is positively associated also with cancer mortality [68], it has been calculated that 14 % of cancer death in men and 20 % in women may be attributable to overweight and obesity [68]. The IR can contribute to this increase in mortality. Recently, 3 single-nucleotide polymorphisms (SNPs) of the IR gene were associated with the cancer main outcome [69].

Type 2 diabetes

Many epidemiological studies and meta-analyses have clearly established that cancer incidence and mortality are increased in diabetic patients. Thus, cancer could be considered a chronic complication of diabetes [18]. Most studies have combined patients with type 1 and type 2 diabetes although these are two different diseases with different characteristics. However, when not specifically indicated, the data generally refer to type 2 diabetic patients because of the much higher prevalence of this type of diabetes and because cancer is a disease of more advanced age.

In typical type 2 diabetic patients, hyperglycemia with compensatory hyperinsulinemia is present until the β-cell system exhaustion occurs; this loss of β-cell function then requires replacement with exogenous insulin. Type 2 diabetic patients, at variance with type 1 patients, have a long history of hyperinsulinemia during their prediabetes phase and are often obese (approximately 80 % of cases). Therefore, most type 2 diabetic patients are exposed for decades to increased insulin concentrations although the physiopathologic and therapeutic conditions may be very different in different individuals.

Several types of cancer are increased in diabetic patients with liver and pancreas cancer showing the maximal increase, followed by endometrium and most of other tumors, with the exception of prostate and lung. After adjusting for age, gender, smoking status, and body-mass index, the RR for death from cancer among persons with diabetes is 1.25 (95 % CI 1.19–1.31) as compared to individuals without diabetes (data from 820,900 people with 123,205 deaths) [70]. It should be considered that these type 2 diabetic patients often have organ dysfunctions that make them “fragile patients” and these dysfunctions can negatively affect both cancer treatment and survival to cancer.

Several confounding factors, having general (obesity, drugs) or site-specific relevance (infections such as hepatitis), make it difficult to accurately assess cancer risk in the individual diabetic patient. Moreover, drugs used to treat diabetes may also increase insulin secretion (such as sulphonylureas) or decrease it (like metformin): their effect on insulin levels parallels a similar effect on cancer incidence, another argument in support of a significant role of hyperinsulinemia.

Polycystic ovary syndrome (PCOS)

PCOS is characterized by oligo- or anovulation, biochemical and/or clinical manifestations of hyperandrogenemia and polycystic ovaries detected on ultrasound examination. Most of these patients are either overweight or obese. The prevalence of insulin resistance ranges 50–70 % in PCOS and may occur independently of obesity [71]. Although the presence of insulin resistance is not necessary to diagnose PCOS, hyperinsulinemia is recognized to be of great importance in PCOS so that metformin, an insulin sensitizer, has an important role in the treatment of these patients [72].

Insulin has a direct mitogenic and anti-apoptotic effect in endometrial cells. Endometrial cancer is 2–3 times more frequent in women with PCOS [73–75]. In spite of the frequent presence of additional risk factors for gynecological cancers such as obesity, hyperandrogenism, and unopposed estrogen stimulation, the insulin pro-cancer effect is considered well established in PCOS patients. The increased risk of other tumors in PCOS patients is not fully established because of the heterogeneity of the syndrome [75] and the still not well-defined consensus on the diagnostic criteria.

Exogenous hyperinsulinemia (type I diabetes)

Recent data from a very large series of T1D patients reported that also in these diabetic patients cancer incidence is increased [55]. In that study, linking nationwide diabetes registries from Australia, Denmark Finland, Scotland, and Sweden to national cancer registries, 9149 cancers were identified among persons with T1D. The overall HR for cancer was not increased in men (HR 1.01) and only slightly among women (HR 1.07), but important increases were observed for liver, pancreas, stomach, endometrium, and kidney cancers, resembling the cancer prevalence observed in type 2 diabetics [55]. Previous studies on much smaller series found a higher HR for cancer in T1D patients (HR 1.2) but a similar site-specific involvement [76].

Type I diabetic (T1D) patients have an absolute requirement for exogenous insulin since endogenous insulin is absent. Moreover, unlike type 2 diabetic patients, type 1 patients do not have a long prediabetes and diabetes history with compensatory endogenous hyperinsulinemia. Most T1D patients, however, are insulin-resistant and are treated with insulin doses that are greater than the normal pancreatic secretion. This exogenous hyperinsulinemia is worsened by the aberrant distribution of injected insulin. At variance with insulin secreted by the pancreas that is first distributed to the liver where approximately 80 % is retained and degraded, injected insulin goes to peripheral tissues that receive insulin at the same concentration as liver. This condition causes variable hyperinsulinemia in peripheral tissues depending on the dose and the type of insulin or insulin analog injected.

Insulin analogs

Insulin analogs are compounds with molecular structure similar to that of insulin and able to bind and activate the insulin receptor. They can mimic the metabolic effects of insulin with either a faster (short-acting) or a more prolonged (long-acting) effect. By this temporal mechanism, they may help to obtain a better metabolic control.

Because of the different structure, insulin analogs may interact with the insulin receptor and its cognate IGF-1 receptor in a slightly different way, thus altering postreceptor signaling and, consequently, biological effects. For instance B10Asp, a single amino-acid-substituted insulin analog, has increased affinity for both IR and IGF-1R and a longer residence on the receptor. These characteristics are associated with increased occurrence of mammary tumors in female rats [77–79].

Most data regarding short-acting insulin analogs indicate that their biological activity does not significantly differ from that of native insulin, except for the shorter duration. In contrast, long-acting analogs have been demonstrated to stimulate cancer cell proliferation in vitro more than native insulin [17]. This increased mitogenic effect occurs both because of a greater cross-reactivity with the IGF-IR and because of a predominant activation of the A isoform of the IR, with preferential activation of the MAP-ERK pathway [80].

These in vitro data, however, do not necessarily reflect in vivo data. A harsh debate on the possibility that insulin glargine, the most used and most studied long-acting insulin analog, might favor cancer in treated patients occurred in 2009. Retrospective cohort studies in Germany, Scotland, and Sweden (but not in the UK) found an increased risk of developing cancer in patients treated with glargine, even if data were partially discordant [81–84]. In an Italian series, this effect was associated with a higher dose of insulin glargine [85]. The above-mentioned studies were strongly criticized for both experimental procedures and conclusions [86, 87], and in the following years most retrospective studies found no difference in the risk of developing cancer in users of different insulins [88, 89]. Although retrospective observational studies can usefully detect unexpected drug effects, they may also favor biased conclusions. Moreover, all these studies did not meet the desirable scientific strength for many reasons including possible selection bias, retrospective design, heterogeneity of diabetes characteristics, associated drug interference, and insufficient (too short) follow-up. In 2012, a prospective study, aimed at evaluating the cardiovascular risk in 12,537 patients treated with glargine, measured also the risk of cancer in these patients and found no increase in the insulin glargine users [90]. The ORIGIN study was then taken as a strong demonstration for excluding the glargine-associated risk of cancer. However, also this study has severe weaknesses: the follow-up (6.2 years) was too short for the possible cancerogenic effect of the analog, 62 % of patients

discontinued glargine treatment temporarily or permanently, and the interference of drugs like metformin (that can reduce cancer risk) was not considered [91]. At present, therefore, the use of long-acting insulin analogs is recommended when required for better metabolic control but their potential effect on cancer requires further and better designed studies that are difficult to carry out because of the number of patients needed to be enrolled and the long period of observation needed.

Insulin receptors as prognostic markers in cancer

After the first observation that insulin receptors are often overexpressed in malignant cells [28], their role in cancer progression and their potential use as prognostic factors were given only limited attention. In breast cancer, a high level of IR expression is indicative of poor survival [92, 93]. Overexpression of IR predicts poor survival also in patients with nonsmall cell lung cancer [94]. The interpretation of these data is complicated because circulating insulin levels were not reported. A better understanding of the IR role in cancer may have important implications considering that clinical trials indicate that inhibitors specifically targeting the IGF-1R are not efficient for inhibiting cancer [95, 96] and one possible reason is that the mitogenic signal might be independently processed by the IR, even as compensation to the inhibition of the IGF-1R. Indeed, a recent experimental study has suggested a highly specific role of the IR in breast cancer progression [97].

Unfortunately, we know very little on the relative expression of the IR isoforms in those studies. Moreover, we have to consider that the role of the IR must be evaluated in a complex system like a malignant cell in which other factors are aberrantly activated to promote cancer growth. In vitro, insulin is a growth stimulator more potent that IGF-1 in some cancer cells but the malignant cell biological response to insulin cannot be predicted only on the basis of the insulin receptor content [98] (Fig. 8). In conclusion, the role and the prognostic value of the IR in the clinical setting of human malignancies are not yet defined and deserve further studies.

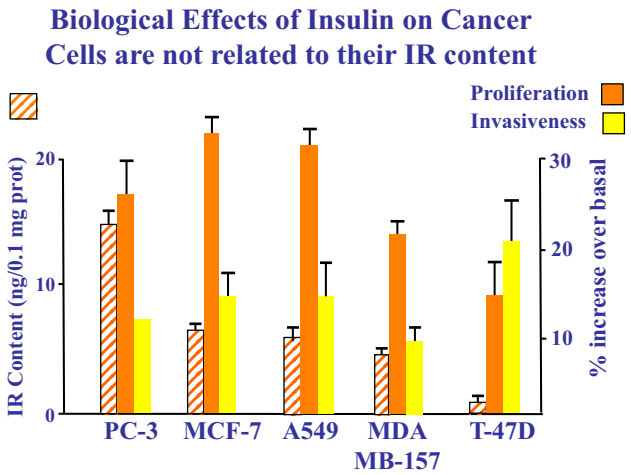

Fig. 8 In three human breast cancer cell lines (MCF-7, MDA-MB57 and T47D), one lung cancer (A549) and one prostate cancer cell line (PC-3), all expressing a different IR content (decreasing values from PC-3 to T-47D), the effect of insulin (5 nM) on cell proliferation and invasiveness was not correlated with the relative IR content. Moreover, the two biological effects were not correlated between them

Conclusion

The complexity of the conditions associated with hyperinsulinemia and the presence of confounding factors that can interfere with the host and the malignant cell responses to the growth-promoting effect of insulin prevent a precise assessment of the detrimental role of hyperinsulinemia on cancer biology. Based on the analysis of longitudinal data from the Third National Health and Nutrition Examination Survey (NHANES III; 1988–1994) [99], it was calculated age-adjusted risk of overall cancer death was higher among individuals with insulin resistance (HR 1.41; CI 1.07–1.87).

The IR definitely contributes to the unfavorable effect of hyperinsulinemia. A series of biological and molecular abnormalities of the IR family provide to cancer cells a selective growth advantage that has relevant clinical implications.

In conclusion, the pro-cancer effect of insulin excess has important consequences considering the large diffusion of the conditions characterized by hyperinsulinemia. The overall damage is of great relevance for health, social, and economic aspects. Therefore, hyperinsulinemia, which in most instances is a compensatory sequence of insulin resistance, should be identified and corrected not only for its well-recognized metabolic and cardiovascular adverse consequences but also as a significant risk factor for cancer.

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Compliance with ethical standards

Conflict of interest The authors have no potential conflict of interest.

Ethical approval For this type of study, ethical approval is not required.

Informed consent For this type of study, informed consent is not required.

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