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REVIEW

Obesity, diabetes and cancer: insight into the relationship from a cohort with growth hormone receptor deficiency

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Abstract Obesity with insulin-resistant diabetes and increased cancer risk is a global problem. We consider the alterations of metabolism attendant on the underlying pathogenic overnutrition and the role of the growth hormone (GH)–IGF-1 axis in this interaction. Obesity-induced insulin resistance is a determinant of diabetes. Excess glucose, and an elevated concentration of insulin acting through its own receptors along with complex interactions with the IGF-1 system, will add extra fuel and fuel signalling for malignant growth and induce anti-apoptotic activities, permitting proliferation of forbidden clones. In Ecuador there are ~100 living adults with lifelong IGF-1 deficiency caused by a GH receptor (GHR) mutation who, despite a high percentage of body fat, have markedly increased insulin sensitivity compared with age- and BMI-matched control relatives, and no instances of diabetes, which is present in 6% of unaffected relatives. Only 1 of 20 deceased individuals with GHR deficiency died of cancer vs 20% of ~1,500 relatives. Fewer DNA breaks and increased apoptosis occurred in cell cultures exposed to oxidant agents following addition of serum from GHR-deficient individuals vs serum from control relatives. These changes were reversible by adding IGF-1 to the serum from the GHR-deficient individuals. The reduction in central regulators of pro-ageing signalling thus appears to be the result of an absence of GHR function. The complex inter-relationship of obesity, diabetes and cancer risk is related to excess insulin and fuel supply, in the presence of heightened anti-apoptosis and uninhibited DNA damage when GHR function is normal.

Keywords Apoptosis · Cancer · Diabetes · Growth hormone receptor · IGF-1 · Insulin · Obesity · Review

Abbreviations

GH	Growth hormone
GHR	Growth hormone receptor
IGFBP	IGF-1-binding protein
MAPK	Mitogen-activated phosphokinase
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
TOR	Target of rapamycin

Persons who are naturally very fat are apt to die earlier than those who are slender.

Hippocrates (c.460–c.377 BC)

The replacement of infectious diseases as the main causes of mortality in advanced industrialised countries by cancer, cardiovascular disease, diabetes and chronic maladies associated with obesity, and the low incidence of these disorders in developing societies, led to the assumption that they were attributable to environmental factors characteristic of more industrial and urban communities [1–3]. The adoption of Western habits and nutritional patterns in developing areas, most importantly the increase in the consumption of carbohydrates, especially refined sugars, has consistently been followed by a dramatic increase in the frequency and severity of obesity and its comorbidities [4, 5].

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Summary points

- Nutritional transition of populations, especially greater consumption of refined carbohydrates, has consistently resulted in increased frequency and severity of obesity and its comorbidities.
- The recent recognition of the association of obesity with increased cancer risk suggests that concomitant hyperinsulinaemia, in concert with IGF-1, is enhancing mitogenesis, while associated hyperglycaemia provides an augmented energy source for malignant clonal proliferation.
- Individuals with growth hormone receptor deficiency in Ecuador do not have diabetes and are protected against cancer. Despite having increased body fat compared with control relatives, they have markedly enhanced insulin sensitivity.
- In vitro studies with serum from the Ecuadorian cohort with growth hormone receptor deficiency demonstrated enhanced apoptotic and anti-oxidant activities, resulting in greater disposal of damaged cells and fewer DNA breaks.
- Studies in the Ecuadorian population with growth hormone receptor deficiency have indicated that the association of obesity with increased risk for diabetes and cancer is dependent on intact growth hormone signalling.

Obesity and cancer

While a wide range of contaminants in the diet, water supply and air have been thought to act as carcinogens, the role of obesity and concomitant hyperinsulinaemia, typically accompanied by elevated circulating glucose levels, has more recently been recognised as contributing to the development of malignancy [6, 7].

The identification of singular environmental or genetic causality for cancer is not possible, as the causal factor will have a variable effect depending on the specific biology and circumstance of each individual. This is one of the reasons why present strategies preferentially include the search for common mechanisms by which potential carcinogens induce tumour formation and progression [8]. Among these systems, hormonal growth factors such as IGF-1 display anti-apoptotic characteristics, suggesting their involvement in the development of some malignancies [9]. Furthermore, the ability of insulin to activate some of the same mitogenic pathways would predict a comparable role for high insulin levels [10]. In the last few years, obesity-induced hyperinsulinaemia and, possibly, concomitant hyperglycaemia, have been identified as specific risk factors for either the development of cancer or its progression [11]. From this perspective, the quantity and especially the quality of nutrients could modulate the biological action of endogenous peptides that have been considered important for cancer development and progression [12].

Nutrition and cancer

Insulin and IGF-1 promote survival by regulating fat, protein, and carbohydrate metabolism. While insulin exerts its actions preferentially in metabolic pathways as a fuel regulator and main determinant of the assignment of energy to either immediate use or storage, IGF-1 has a more distinct role in growth and cell division [13]. Accretion and use of fat mass requires the dynamic interaction of the two hormones [14].

Experimental reduction of energy intake, including fasting in lower organisms and humans, is associated with a decreased incidence of tumour appearance and progression, as well as other protective effects. Furthermore, nutrient limitation has been associated with inhibition of tumour growth and extension of lifespan in various cell types, lower organisms, primates and humans [15]. Malignant cells induce alternative sources of energy to support their increased glucose uptake; most tumoural clones have a high rate of glucose consumption and several malignant cells express higher numbers of insulin receptors on their membranes [16, 17]. A considerable amount of cell growth is independent of the IGF-1 receptor and is thought to be mediated by RNA polymerase I, the ultimate controller of cell size. Cell proliferation is dependent upon both the cell cycle programme and cell size. It is possible that IRS1 transmits signals from both insulin and IGF-1 to intracellular pathways such as phosphatidylinositol 3-kinase (PI3K)/Akt and mitogen-activated phosphokinase (MAPK), thereby increasing the activity of RNA polymerase I and rRNA synthesis, thus regulating the cell cycle, and increasing cell size [18]. Taken together, these apparently independent events highlight the contribution of altered carbohydrate metabolism to the selective advantage of malignant clones [19]. Excess glucose consumption and concomitant hyperinsulinaemia, as a distorted fuel signalling mechanism, appear to contribute to an aberrant process that requires both higher energy use and larger amounts of nutrients for formation of rapidly proliferating cells [20].

A high intake of refined carbohydrates has been thought to be associated with an increased risk of cancer [21]. In addition, abnormal circulating concentrations of glucose, lipids, uric acid and other metabolic elements and components can be associated with overnutrition. Depending on the genetic endowment of each individual, and influenced by the accumulated load of cancer-inducing mutations, insulin might exert differential actions, not only as a discrete fuel regulator, but also as a growth and proliferation agent. Indeed, the normal process of ageing is associated with an unavoidable accumulation of cells with mutations that are eliminated by

the surveillance mechanisms of the healthy organism; however, if an increase in the pool of these cells is promoted by activation of the IGF-1 receptor, subsequent mutations that could lead to transformation and carcinogenesis might occur [22]. Also noteworthy is the increase in insulin binding to cultured fibroblasts with donor age [23], the association of familial longevity with insulin sensitivity [24] and observations that populations living in different environmental conditions and eating traditional diets frequently have a lower incidence of obesity, cancer and diabetes [25].

Caloric restriction in primates is associated with increased lifespan and a 50% reduction in cancer appearance [26]. One of the effects of the restriction is the reduction of circulating levels of IGF-1 that, in turn, slows cell growth, enhances apoptotic activities and reduces genomic instability via Ras- or PI3K-dependent mechanisms [27]. The metabolic and hormonal factors induced by the lower energy intake, with diminished glucose availability leading to enhancement of insulin sensitivity, may be an important mediator of these effects [28, 29]. Nonetheless, the reduction of total energy intake involving all nutrient groups is, by definition, a manoeuvre that exerts its effects mainly by providing less energy supply to all systems. In consequence, the discrete, independent and specific effects of single groups of nutrients, such as protein, fat or carbohydrate, will be obscured.

Among environmental influences, diet, especially excess fuel availability, might be an especially important contributor to cancer development. An increase in fuel consumption is associated with higher generation of free radicals and enhanced oxidative stress—a condition linked to more frequent DNA breaks [30]. In addition, glycation of proteins, a phenomenon that occurs normally in the body, is glycaemia dependent. Thus, elevated glucose concentrations augment glycation and accumulation of advanced glycated endproducts in cells and tissues. These alterations have been related, directly or indirectly, to the milieu in which malignant cells proliferate [31]. Furthermore, if increased availability of glucose as fuel is added to the enhanced growth and fuel signalling induced by higher circulating concentrations of IGF-1 and insulin, newly generated vicious cycles will create conditions appropriate for carcinogenic progression. The observed lifetime probability of developing cancer, ~45% for men and ~40% for women, appears then to coincide with overnutrition, concomitant hyperinsulinaemia and hyperglycaemia, and higher IGF-1 levels seen in obesity [15].

Ageing is associated with the accumulation of cancer-inducing mutations in all cell types of the body, and affected units might eventually become malignant. Rapidly dividing cells have evolutionary advantages over their normal counterparts, held in check by protective mechanisms such as apoptosis—programmed cell death—and promotion of genomic stability, resulting in the disposal of damaged cells and preservation of normal physiology [30–32].

IGF-1, insulin and cancer

IGF-1, the primary regulator of growth in humans, exerts its actions on a wide range of normal cellular processes. Chronic undernourishment and prolonged fasting induces an acquired form of growth hormone insensitivity, with elevated growth hormone (GH) and decreased IGF-1 serum concentrations; renourishment restores normal levels. Similarly, both acute and chronic food deprivation induce lowering of circulating insulin and glucose concentrations, which return to normal with refeeding [33]. In addition to the complex direct and indirect interplay between insulin and IGF-1, there are other interactions mediated by the IGF-1-binding proteins (IGFBPs). For example, free concentrations of IGF-1 appear to be partially regulated by IGFBP1, which is controlled by insulin and fed-fasting state and has also been related to some cancer events [34, 35].

In addition to metabolic functions reflecting long-term nutrient availability, IGF-1 has important actions in the biology of malignancy; higher concentrations of IGF-1 have been associated with various types of cancers [36]. Conversely, blockage of the IGF-1 receptor or anti-IGF-1 antibody administration is associated with tumour inhibition [37]. Along with increased numbers of insulin receptors, the membranes of malignant cells display greater numbers of specific binding sites for IGF-1 [38]. IGF-1 production is induced by GH in the liver, yielding endocrine IGF-1, and in a variety of other tissues, referred to as autocrine and paracrine IGF-1. The widespread production of the growth peptide provides the basis for a broad effect on pre-malignant and malignant cells, characteristics that, added to the MAPK-mediated IGF-1-dependent induction of cell proliferation and its increased anti-apoptotic PI3/Akt-mediated features, confer a central role for IGF-1 in the promotion of enhanced proliferation [9, 39].

The insulin molecule shares ~50% homology with IGF-1 and the beta subunits of their receptors are ~80% homologous [40–43]. In addition to potentiating their individual and discrete actions via promiscuous binding to individual sites, these peptides also share common intracellular mechanisms and pathways, potentially providing a powerful combination of fuel signalling with the growth-promoting activities necessary for cell proliferation. At the same time, IGF-1 acting on its own receptor promotes one of the most important anti-apoptotic effects in the body [44]. Apoptosis is a protective physiological mechanism that allows timely disposal of damaged cells, and inefficient apoptosis has been considered one of the hallmarks of cancer [45]. Higher levels of IGF-1 have been seen when uncontrolled malignant clones flourish and proliferate [46]. It is possible that in a similar fashion, excess amounts of insulin, characteristic of obesity, might induce anti-apoptotic activities [43]. Concomitantly, excess glucose and insulin, probably acting via the insulin receptor-A subtype [47], will add the necessary extra fuel and fuel signalling

needed for malignant growth. In agreement with this possibility, it has recently been shown that metformin, an insulin sensitiser, reduces prostate cancer deaths in type 2 diabetes, a hyperglycaemic hyperinsulinaemic state, along with decreasing the risk for all-cause mortality in the first 6 months after diagnosis [48]. Studies showing the benefits of metformin suggest that improving insulin sensitivity by lowering glucose levels in individuals with increased body fat content promotes the maintenance of homeostasis, thereby reducing cancer-related events [17, 49]. Understanding how this commonly prescribed drug acts upon the most universal biological fuel, glucose, is thus of great importance. It has recently been shown that metformin suppresses the endogenous production of glucose (gluconeogenesis) by inhibiting mitochondrial glycerophosphate dehydrogenase, with a concomitant increase in the cytosolic and decrease in the mitochondrial redox states, thereby providing possible explanations for the beneficial actions of metformin [50].

Animal models in which the GH receptor (GHR) has been inactivated display low concentrations of GH-induced molecules, including IGF-1. As expected, when these animals receive malignant transplants, the newly incorporated entities possess lower primary and secondary growth rates and the growth pattern is less aggressive; protective mechanisms, including apoptosis, appear to be enhanced and efficient [51, 52]. The protective effects of reducing pro-growth signalling mechanisms include those involved in cell cycle regulation, gene expression, cell motility and cell death. In addition, in normal cells, enhanced apoptosis determined by diminished growth signalling, the downregulation of specific genes such as those encoding Ras, protein kinase A (PKA) and target of rapamycin (TOR), and the upregulation of genes for superoxide dismutase (SOD) and similar proteins protects against carcinogens, delays the impact of deleterious mutations and enhances the disposal of damaged cells [9]. Observations in human centenarians with an over-representation of heterozygous mutations in the gene encoding the IGF-1 receptor, with higher IGF serum concentrations but reduced activity of the receptor, highlight the importance of growth signalling pathways in terms of the genesis of disease and lifespan [53].

Insights from individuals with GHR deficiency

GHR deficiency is a rare autosomal recessive condition affecting approximately 350 subjects worldwide. Nearly a third of affected individuals are native to a concentrated area of southern Ecuador, and all but two instances are caused by the homozygous state of a splice site mutation at codon 180 on exon 6 in the *GHR* gene [54, 55]. All other cases are from scattered populations worldwide and are the result of over 50 different mutations.

Thus, the Ecuadorian cohort is unique in that affected homozygous individuals can be compared with their heterozygous and non-carrier relatives with comparable environmental influences. We have studied 99 living individuals with the characteristic clinical phenotype (e.g. severe short stature, excess body fat), along with corresponding biochemical abnormalities (elevated serum GH concentrations, low levels of IGF-1, IGF-2 and IGFBP3). Morbidity and mortality data were also collected on ~1,500 unaffected relatives [56].

Considering that malignancy was the cause of death in 20% of the relatives, stomach tumours being the most common, the relative absence of cancer mortality in the Ecuadorian GHR-deficient population is surprising. We observed only one instance of death from malignant disease (an ovarian carcinoma). Prevalence studies in an international survey of individuals with congenital IGF-1 deficiency caused by GHR deficiency, isolated GH deficiency, GH-releasing hormone receptor deficiency or multiple pituitary hormone deficiency found no cases of malignancy among 230 individuals with GHR deficiency, compared with their 218 significantly older ($p<0001$) first-degree relatives who had a prevalence of 8.3%. For the other groups, the prevalence of malignancy was equal to or greater than that in the first-degree relatives [57]. That these groups with comparable IGF-I deficiency but intact GH receptors did not have a reduced cancer risk suggests a critical role for the GH receptor, as has been demonstrated in vitro [58, 59].

Diabetes was prevalent in 6% of the relatives of the Ecuadorian GHR-deficient individuals and the direct cause of 5% of their deaths. Nonetheless, there is no instance of diabetes in an individual with GHR deficiency, despite a higher prevalence of obesity, when compared with their age- and sex-matched relatives. Fasting insulin, 2 h blood glucose during an OGTT, very low-density lipoprotein and triacylglycerol levels were all significantly lower in individuals with GHR deficiency, which is indicative of insulin sensitivity. Indeed, the measure of insulin sensitivity, HOMA2%S, was greater, and the measure of insulin resistance, HOMA-IR, was lower in those with GHR deficiency [60]. Because GHR deficiency eliminates direct metabolic effects of GH, the most straightforward explanation for the dissociation of obesity and insulin resistance in individuals with GHR deficiency is the lack of the counter-regulatory effect of GH.

Among the Israeli GHR-deficient population, insulin resistance has been documented and two patients have developed diabetes with severe complications [61]. This is in contrast to our finding of enhanced insulin sensitivity and the absence of diabetes in Ecuadorian individuals with GHR deficiency. Brazilian individuals with lifelong isolated GH deficiency resulting from GH-releasing hormone receptor mutation have a high prevalence of diabetes (16%) and impaired glucose tolerance (38%) [62]. These differences from the Ecuadorian cohort remain unexplained. However, these populations are

undergoing different nutritional transitions that may play a role.

The cellular mechanisms associated with the clinical findings in GHR deficiency appear to largely depend on reduced activity of IGF-1 signalling pathways, activation of stress-resistant transcription factors and antioxidant enzymes, as well as lower glucose levels and, subsequently, enhanced insulin sensitivity. In fact, addition of GHR-deficient serum to cell cultures exposed to oxidant agents was associated with fewer DNA breaks when compared with cultures that received control serum from unaffected relatives, suggesting that the low concentration of IGF-1 in GHR-deficient serum protects from oxidative damage, independent of cell division [56]. In addition, indicators of increased apoptosis (greater cytotoxicity and a higher percentage of caspase-positive cells) were induced by the addition of the GHR-deficient serum. Microarray analysis of cells incubated with GHR-deficient serum showed that among 44 upregulated genes, four, including *SOD2*, were forkhead box, class O (FOXO) targets. Among other findings related to cell cycle regulation, gene expression, cell movement and death, ingenuity pathway analysis of global pathways of gene expression showed that, in cells incubated with GHR-deficient serum, apoptosis-related genes were upregulated, whereas *Ras*, *PKA* and *TOR*, whose expression is associated with increased superoxide production and age-dependent DNA mutation and damage, were downregulated. RT-PCR analysis confirmed higher levels of *SOD2* mRNA, the key mediator of cell protection against oxidative stress mechanisms, and a 70%, 50% and 20% reduction in the expression of the central regulators of pro-ageing signalling, N-Ras, PKA and TOR [56].

Conclusions

The complex inter-relationship among obesity, diabetes and cancer risk is related to excess insulin and fuel supply, in the presence of heightened anti-apoptosis and uninhibited DNA damage when GHR function is normal. The present pandemics of obesity and related morbidities are overtaxing health systems and seriously compromising national economies. Identification of actions to ameliorate this catastrophic situation is urgently needed. The aetiology of malignancy in a given individual is multifactorial and almost impossible to prevent; healthy IGF-1 concentrations are desired but lower blood glucose levels and subsequent enhancement of insulin sensitivity, as well as diminishment of body fat content are the only mechanistic determinants that can be monitored and modified at the population level. Because these alterations contribute directly to all the morbidities seen in these epidemic calamities, the decrease in the frequency of obesity is the most efficient public health measure.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement JG-A provided the initial draft, which was edited and finalised by both authors.

References

1. Burke-Gaffney H (1968) The history of medicine in African countries. Med Hist 12:31–412
2. Gohdes D, Kaufman S, Valway S (1993) Diabetes in American Indians. An overview. Diabetes Care 6:239–243
3. Steyn K, Fourie J, Bradshaw D (1992) The impact of chronic diseases of lifestyle and their major risk factors on mortality in South Africa. S Afr Med J 82:227–231
4. Reaven G (1988) Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes 37:1595–1607
5. Phillips C, Keese-Guoyot E, McManus R et al (2012) High dietary saturated fat intake accentuates obesity risk associated with the fat mass and obesity-associated gene in adults. J Nutr 142:824–831
6. Belpomme D, Irigaray P, Hardell R et al (2007) The multitude and diversity of environmental carcinogens. Environ Res 105:414–429
7. Wolin KY, Carson K, Colditz GA (2010) Obesity and cancer. Oncologist 15:556–565
8. Knudeson A (2001) Two genetic hits to cancer. Nat Rev Cancer 2: 157–162
9. Pollak M, Schernhammer E, Hankinson SE (2004) Insulin-like growth factors and neoplasia. Nat Rev Cancer 4:505–518
10. Hsu I, Kim S, Kabir M, Bergman R (2007) Metabolic syndrome, hyperinsulinaemia, and cancer. Am J Clin Nutr 86:867–871
11. Otake S, Takeda H, Suzuki Y et al (2005) Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res 11: 3642–3646
12. Thissen J, Ketelslegers H, Underwood L (1994) Nutritional regulation of the insulin like growth factors. Endocrinol Rev 15:80–101
13. Dupont J, Kahan J, Bao-He Q, Metzler P, Helman L, LeRoith D (2001) Insulin and IGF-I induce different patterns of expression in mouse fibroblast NIH-3T3 cells: identification by cDNA microarray analysis. Endocrinology 142:4969–4975
14. Guevara-Aguirre J, Al R, Guevara-Aguirre M, Saavedra J, Procel P (2013) Recommended IGF-I dosage causes greater fat accumulation and osseous maturation than lower dosage and may compromise long-term growth effects. J Clin Endocrinol Metab 98:839–845
15. Longo V, Fontana L (2010) Calorie restriction and cancer prevention: metabolic and molecular mechanisms. Trends Pharmacol Sci 31:89–98
16. Milazzo G, Giorgino F, Damante G et al (1992) Insulin receptor expression and function in human breast cancer cell lines. Cancer Res 52:3924–3930
17. Birsoy K, Possemato R, Lorbeer FK et al (2014) Metabolic determinants of cancer cell sensitivity to glucose limitation and biguanides. Nature 508:108–112
18. Baserga R, Peruzzi F, Krystof R (2003) The IGF-I receptor in cancer biology. Int J Cancer 107:873–877
19. Ferguson R, Novossyadlyy R, Fierz Y et al (2012) Hyperinsulinaemia enhances c-Myc-mediated mammary tumour development and advances metastatic progression to the lung in a mouse model of type 2 diabetes. Breast Cancer Res 14:R8
20. Klement R, Kämmerer U (2011) Is there a role for carbohydrate restriction in the treatment and prevention of cancer? Nutr Metab (Lond) 8:75

21. Drake I, Sonestedt D, Gulberg B et al (2012) Dietary intakes of carbohydrates in relation to prostate cancer risk: a prospective study in the Malmö diet and cancer cohort. Am J Nutr 96:1409–1418
22. Samani A, Yakar S, LeRoith D, Brodt P (2007) The role of the IGF-I system in cancer growth and metastasis: overview and recent insights. Endocr Rev 28:20–47
23. Rosenbloom A, Goldstein S, Yip CC (1976) Insulin binding to cultured human fibroblasts increases with normal and precocious aging. Science 193:412–415
24. Wijsman C, Rozing M, Streefland T, Leiden Longevity Study group et al (2011) Familial longevity is marked by enhanced insulin sensitivity. Aging Cell 10:114–121
25. Benetou B, Trichopoulou A, Orfanos P et al (2008) Conformity to traditional Mediterranean diet and cancer incidence: the Greek EPIC cohort. Brit J Cancer 99:191–195
26. Colman R, Anderson R, Johnson S et al (2009) Caloric restriction delays disease onset and mortality in rhesus monkeys. Science 325: 201–204
27. Fruman DA, Rommel C (2014) PI3K and cancer: lessons, challenges and opportunities. Nat Rev Drug Discov 13:140–156
28. Ikeno Y, Hubbard GB, Lee S et al (2009) Reduced incidence and delayed occurrence of fatal neoplastic diseases in growth hormone receptor/binding protein knockout mice. J Gerontol A Biol Sci Med Sci 64:522–529
29. Dossus L, Kaaks R (2004) Nutrition, metabolic factors and cancer risk. Nat Cancer Rev 4:579–591
30. Sancar A, Lindsey-Boltz L, Unsal-Kacmaz K, Linn S (2004) Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Ann Rev Biochem 73:39–85
31. van Heijst J, Niessen H, Hoekman K, Schalkwijk CG (2005) Advanced glycation end products in human cancer tissues: detection of N^{ε}-(carboxymethyl)lysine and argpyrimidine. Ann NY Acad Sci 1043:725–733
32. Dingli D, Chalub F, Santos F, van Segbroeck S, Pacheco J (2009) Cancer phenotype as the outcome of an evolutionary game between normal and malignant cells. Br J Cancer 101:1130–1138
33. Halberg H, Henriksen M, Soderhamn N et al (2005) Effect of intermittent fasting and re-feeding on insulin action in healthy men. J Appl Physiol 99:2128–2136
34. Lee P, Durham S, Martínez V, Vásconez O, Powell D, Guevara-Aguirre J (1997) Kinetics of insulin-like growth factor (IGF) and IGF-binding protein responses to a single dose of growth hormone. J Clin Endocrinol Metab 82:2266–2274
35. Wolpin B, Michaud D, Giovannucci E et al (2007) Circulating insulin-like growth factor binding protein-I and the risk of pancreatic cancer. Cancer Res 67:7923–7928
36. Wu Y, Yakar S, Hennighausen L, LeRoith D (2002) Circulating insulin-like growth factor-I levels regulate colon cancer growth and metastasis. Cancer Res 62:1030–1035
37. Kolb E, Gorlick R, Maris J et al (2012) Combination testing (Stage 2) of the anti-IGF-I receptor antibody IMC-A12 with rapamycin by the pediatric preclinical testing program. Pediatr Blood Cancer 58:729–735
38. MacEwen E, Pastor J, Kutzke J et al (2004) IGF-I receptor contributes to the malignant phenotype in human and canine osteosarcoma. J Cell Biochem 92:77–91
39. Chhabra Y, Waters J, Brokks A (2011) Role of the growth hormone/IGF-I axis in cancer. Expert Rev Endocrinol Metab 6:71–84
40. Belfioiri A, Frasca F, Pandini G, Sciacca L, Vigneri R (2009) Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev 30:586–623
41. Rinderknecht E, Humbel R (1978) The amino acid sequence of human insulin growth factor-I and its structural homology with proinsulin. J Biol Chem 253:2769–2776
42. Brzozowski A, Dodson E, Dodson G et al (2002) Structural origins of the functional divergence of human insulin growth factor-I and insulin. Biochemistry 41:9389–9397
43. Kim J, Accili D (2002) Signaling through IGF-I and insulin receptors: where is the specificity? Growth Horm IGF Res 12:84–90
44. Huo J, Xu S, Lin B, Chng WJ, Lam KP (2013) Fas apoptosis inhibitory molecule is upregulated by IGF-I signaling and modulates Akt activation and IRF4 expression in multiple myeloma. Leukemia 27:1165–1171
45. Hanahan D, Weinberg R (2000) The hallmarks of cancer. Cell 100: 57–70
46. Renehan A, Zwahalen M, Minder C, O'Dwyer S, Shalet M, Egger M (2004) Insulin-like growth factor (IGF)-I, IGF-binding protein-3, and cancer risk: systematic review and meta-regression analysis. Lancet 363:1346–1353
47. Huang J, Morehouse C, Streicher K et al (2011) Altered expression of insulin receptor isoforms in breast cancer. PLoS ONE 6:e26177
48. Margel D, Urbach D, Lipscombe L et al (2013) Metformin use and all-cause and prostate cancer-specific mortality among men with diabetes. J Clin Oncol 31:3069–3075
49. Currie C, Poole C, Jenkins-Jones S, Gale E, Johnson J, Morgan C (2012) Mortality after incident cancer in people with and without type 2 diabetes: impact of metformin in survival. Diabetes Care 35: 299–304
50. Madiraju AK, Erion DM, Rahimi Y et al (2014) Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 510:542–546
51. Yakar S, LeRoith D, Brodt P (2005) The role of growth hormone / insulin-like growth factor axis in tumour growth and progression: lessons from animal models. Cytokine Growth Factor Rev 16:407–420
52. Resnicoff M, Copolla D, Sell C et al (1994) Growth inhibition of human melanoma cells in nude mice by anti-sense strategies to the type-I insulin-like growth factor receptor. Cancer Res 54:4848–4850
53. Suh Y, Atzmon G, Cho M et al (2008) Functionally significant insulin-like growth factor-I receptor mutations in centenarians. Proc Natl Acad Sci 105:3438–3442
54. Guevara-Aguirre J, Rosenbloom A, Fielder PJ, Diamond FB Jr, Rosenfeld RG (1993) Growth hormone receptor deficiency in Ecuador: clinical and biochemical phenotype in two populations. J Clin Endocrinol Metab 76:417–423
55. Rosenbloom AL, Guevara-Aguirre J, Rosenfeld RG, Fielder PJ (1990) The little women of Loja: growth hormone receptor deficiency in an inbred population of Southern Ecuador. N Engl J Med 323: 1367–1374
56. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M et al (2011) Growth hormone receptor deficiency is associated with a major reduction in pro-aging signaling, cancer, and diabetes in humans. Sci Transl Med 3:70ra13
57. Steuerman R, Shivah O, Laron Z (2011) Congenital IGF-I deficiency tends to confer protection against postnatal development of malignancies. Eur J Endocrinol 164:485–489
58. Gebre-Medhin M, Kindblom LG, Wennbo H, Törnell J, Meis-Kindblom JM (2001) Growth hormone receptor is expressed in human breast cancer. Am J Pathol 158:1217–1222
59. Zhou D, Yang J, Huang WD, Wang J, Zhang Q (2013) siRNA-targeted inhibition of growth hormone receptor in human colon cancer SW480 cells. World J Gastroenterol 19:8108–8113
60. Guevara Aguirre J, Rosenbloom AL, Balasubramaniam P et al (2014) Enhanced insulin sensitivity in subjects with absent growth hormone receptor signaling despite increased body fat content. The Endocrine Society, Chicago, June 21-24, latebreaking abstract LB-OR02-1 (abstract)
61. Laron Z (2011) Insulin secretion and carbohydrate metabolism in patients with Laron syndrome: from hypoglycaemia to diabetes mellitus. In: Laron Z, Kopchick JJ (eds) Laron syndrome from man to mouse. Springer-Verlag, Berlin/Heidelberg, pp 259–272
62. Vicente TAR, Rocha IES, Salvatori R et al (2013) Lifetime congenital isolated GH deficiency does not protect from the development of diabetes. Endocr Connect 2:112–117