

Growth hormone, somatomedins and cancer risk

Hormon wzrostu, somatomedyna i ryzyko raka

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ABSTRACT

Growth hormone (GH) promotes growth and development in children and is the meaningful co-regulator of the metabolism in adulthood. GH may act directly, through its receptor (GHR), as well as via mediators – insulin-like growth factors: IGF-1, i.e. somatomedin C and IGF-2. Moreover, GH and two growth factors are involved in the mechanisms of cell proliferation, differentiation and survival, hence their oncogenic potential is propounded. Indeed, GH, somatomedins and their receptors are found abundantly in normal and cancer cells in several tissues. It has been shown in animal and human trials that polymorphisms and mutations that increase signal transmission from the GH and IGF-1 receptor are associated with more frequent tumors development and reduce life expectancy. Numerous epidemiological studies have confirmed a clear relationship between GH/IGF-1 level in circulation and a cancer-dependent morbidity and mortality. It dictates caution in case of treatment with use of growth hormone. Such replacement therapy is recommended in cases of GH deficiency. In the common opinion of scientific societies such treatment is generally safe, although in some cases unambiguous opinion in this field cannot be determined yet. On the other hand, on the basis of available evidence, GH cannot be recommended for use by the healthy elderly (anti-aging medicine), bearing in mind that GH decline with age may represent a beneficial adaptation to ageing. Understanding the molecular mechanisms by which GH and GH-dependent growth factors affect cell metabolism and proliferation will allow to use them in oncology in the future.

SŁOWA KLUCZOWE:

- hormon wzrostu
- somatomedyny
- czynniki wzrostowe
- rak

STRESZCZENIE

Hormon wzrostu (GH) odpowiada za wzrost dzieci i młodzieży, a także jest ważnym regulatorem metabolizmu dorosłych. Działa bezpośrednio przez swoisty receptor (GHR) albo za pośrednictwem mediatorów – insulinopodobnych czynników wzrostowych: IGF-1, czyli somatomedyny C i IGF-2. Zarówno GH, jak i czynniki wzrostowe uczestniczą w procesach proliferacji, różnicowania i przeżycia komórek, stąd uważa się, że mogą mieć udział w mechanizmach karcynogenezy. Istotnie, obecność GH, somatomedyn i ich receptorów wykazano w komórkach prawidłowych i nowotworowo zmienionych w wielu tkankach. Badania na zwierzętach i wśród ludzi ujawniły, że polimorfizmy i mutacje prowadzące do zwiększenia przesyłania sygnału z receptorów GH i somatomedyn, wiążą się ze wzrostem częstości występowania nowotworów i skróceniem życia. Wiele badań epidemiologicznych wykazało wyraźną zależność między stężeniem hormonów GH/IGF-1 w krążeniu a wskaźnikami zachorowalności i umieralności. Dane te nakazują ostrożność w trakcie leczenia z zastosowaniem hormonu wzrostu, a taka terapia rekomendowana jest w przypadkach niedoboru tego hormonu. W zgodnej opinii towarzystw naukowych leczenie substytucyjne hormonem wzrostu jest uważane za generalnie bezpieczne, choć w niektórych przypadkach nadal nie ma danych pozwalających na rozwianie wszelkich wątpliwości. Z drugiej strony, zgodnie z aktualną wiedzą nie zaleca się stosowania hormonu wzrostu osobom w podeszłym wieku w ramach tzw. medycyny przeciwstarzeniowej (anti-aging), uważając, że spadek wydzielania tego hormonu z wraz wiekiem stanowi mechanizm adaptacyjny w procesie starzenia. Zrozumienie molekularnych mechanizmów działania GH i czynników wzrostowych w procesach metabolicznych i proliferacyjnych komórek może umożliwić w przyszłości ich wykorzystanie w onkologii.

Growth hormone and somatomedins

Growth hormone is produced in the pituitary gland. It is mainly released at night, under control of the hypothalamic factors: stimulating – growth hormone releasing hormone (GHRH) and inhibiting – somatostatin. Also, ghrelin stimulates GH secretion, by activation of specific GH Secretagogues Receptors (GHSRs). In target organs growth hormone stimulates synthesis of insulin-like growth factors, in particular somatomedin C, that is, insulin-like growth factor 1 (IGF-1), which is a mediator of several actions of GH. In turn, IGF-1 by the negative feedback loop inhibits the release of growth hormone from the somatotrophic cells (1). Another somatomedin present in the circulation and some tissues, IGF-2 exhibits a much lower dependence on GH (2).

Growth hormone secretion decreases with weight gain (higher BMI), increases after intensive physical activity and falls after a longer acting effort. It is greater in women than in men and depends on age: since 35-40 year of age production of GH gradually decreases, so in the age of 70s it is reduced of 15-70% (3). Following this in the seventh decade of life IGF-1 levels are about 30-50% lower than in the age of 20-30 years (4).

Growth hormone acts in the target tissues directly, activating its receptors (GHR), as well as by mediation of growth factors. Somatomedin C (IGF-1) exerts its effects through specific receptor (IGF-R), and, if IGF-1 levels are high enough through insulin receptor as well. Moreover, hybrid receptors, composed of components of IGF-R and insulin receptor, if present, may be activated by somatomedins. There are also receptors for IGF-2 in peripheral tissues. However, these receptors, are called "blind", meaning that joining ligand do not pass the signal to the inside of the cell. It seems, that their role is to block the action of growth factors by sequestration them from the receptors for IGF-1 and insulin (5, 6).

Physiological role of growth hormone and somatomedin C

The effects of GH/IGF-1 are not limited only to stimulating growth in childhood and during adolescence. They also play an important role in the regulation of the metabolism of proteins (anabolic effect), carbohydrates (GH: antagonism to insulin, IGF-1: insulin-like activity) and lipids (lipolysis) (7). Hence, in the opinion of the experts of the Growth Hormone Research Society it "is not possible to achieve full development without continuing therapy" after puberty in children with short stature treated with recombinant human growth hormone (8).

Growth hormone, somatomedins and oncogenesis In vitro studies

Numerous in vitro studies have demonstrated growth hormone and its receptors expression in normal and tumor cells, including breast, prostate, brain, thyroid, pancreas, ovary, colon and kidney cells (9, 10). Over-expression of GH promotes cells proliferation and reduces apoptosis. Studies in human endometrial cancer and estrogen-dependent breast cancer cell lines demonstrated that GH may act also through an autocrine/paracrine manner (11, 12). Human endometrial cancer lines RL95-2 transfected with a plasmid designed to express human GH grow significantly faster during 14-day

observation and exhibited enhanced anchorage-independent growth in comparison to cells without genetically increased GH secretion (11). Local production of GH has been shown also in lung, stomach and prostate tumor-line cells. Such autocrine GH action dramatically increased breast cancer cell growth dependent on Janus Kinase 2 activity (13). Direct stimulation of cell growth by GH is also suggested by the observation that double knock-out of GH and IGF-1 genes results in a greater growth inhibition cells, than eliminating only one of these genes (14). Increased density of growth hormone receptors has been shown especially on cancer cells derived from treatment-resistant patients (15).

Growth hormone stimulates local production of IGF-1. Connection of somatomedin C to its receptor activates intracellular metabolic pathways associated with the Ras and Act proteins, leading to the subsequent phosphorylation of cyclin kinase system which regulates cell proliferation. The Act protein also plays a key role in inhibiting apoptosis by activation of specific intracellular factors, including NF κ B (16, 17). On this way IGF-1 inhibits action of the cell cycle suppressors, extending the cell longevity. In addition, it has been proved, that somatomedin C may stimulate angiogenesis and is able to promote metastases (18).

The effect of growth factors promoting oncogenesis can be modified by IGF-binding proteins (IGFBPs). The most important, IGFBP-3 can limit the bioactivity of somatomedin C then contributes to inhibition of tumor cell growth (19). However, due to the various effects of all six known IGFBPs on the bioavailability of growth factors, as well as due to their own activities summarized impact of these proteins on growth factors oncogenic properties is difficult to evaluate. Moreover, also intracellular signaling "crosstalk" between IGFs and other growth factors receptors (e.g. EGFR) has already been proved (10).

It has been shown that the increase in GH/IGF-1 gene expression in human "at risk cells" (damaged/transformed) stimulates their proliferation, inhibits apoptosis, and changes morphology increasing the pool of cells that are available for undergoing subsequent processes. However, it should be kept in mind that is not possible to initiate cancer development in this way in normal cells.

Studies in animals

The effects of GH/IGF-1 axis observed in vitro have been confirmed in animal studies. It has been demonstrated, that reduced activity of these hormones, usually as a result of genetic intervention leads to a decrease in the cancer risk. A lit/lit mice in which GHRH receptor is nonfunctional and GH as well as IGF-1 levels are less than 10% of wild-type counterparts exhibited marked retardation of human MCF-7 breast cancer xenograft growth compared to wild-type mice (20). In other study carcinogen nitrosomethylurea induced mammary tumors development in 4.8% of GH-deficient dwarf rats (dw/dw with 20% normal serum IGF-1) and GH-treatment increased tumor incidence to 100% (21). In rodents with natural, genetic origin GH and somatomedin C deficiency reduced incidence of mammary and other tumors has been observed (22). Mice with growth hormone resistance (Laron syndrome) are characterized by significantly lower cancer risk compared with individuals with normal GHR function (23). Deletion of the IGF-1 gene in the liver resulting in a 40-50% decline in serum levels of this hormone has been associated with the marked inhibition of breast and colorectal cancer in rodents (24).

On the other hand, transgenic mice overexpressing GH and exhibiting very high levels of this hormone in circulation have showed an increased incidence of spontaneous breast cancers (13). Also, local overexpression of IGF-1 in breast, pancreas and salivary glands has been associated with more frequent occurrence of tumors in these tissues in mice (25). In transgenic mice that expressed the activated IGF-1 receptor aberrant early development of the salivary and mammary adenocarcinomas has been shown (26). In individuals with high expression of IGF-2 marked increase in the incidence of several cancers: breast, liver, lung, thyroid, colon, as well as lymphomas and sarcomas has been demonstrated (27). Regarding IGF-BPs, the consistent correlation between these proteins overexpression and tumor grading or invasiveness could indicate their usefulness as a potential prognostic factor, which might predict outcome (28).

Involvement of GH/IGF-1 axis in carcinogenesis must obviously affect life expectancy. This assumption has been confirmed in numerous animal studies. It was noted already in 1961 that the life of mice with somatotrophic cells differentiation perturbations (Ames dwarfs) is increased by 30-70% (depending on the gender and nutrition) compared with wild individuals (29). Rodents with knock-out of GH-receptors and therefore with resistance to this hormone were characterized of life longer by 40-55% compared to the control group (30). Also, mutations resulting in a decrease in the number of IGF-1 receptors and bringing on partial resistance to somatomedin C extend the life of such animals significantly (31).

A summary of the mechanisms in which GH/IGF-1 axis affects the life span in animals shows the figure 1.

Human trials

The observations performed before decades pointed to the relationship between the growth rise and the cancer risk: the frequency of breast cancer in higher subjects was increased by 22%, prostate cancer by 20% and the colon cancer by 20-60%. Others described the correlations between growth increment during adolescence and later higher risk of various types of tumor, e.g. breast, prostate or colon. Nowadays, meta-analysis carried out already in 12 European countries showed an increase in the frequency of breast cancer in women with a higher levels of IGF-1, although only in estrogen receptor-positive tumors (high vs. low serum levels of IGF-1, OR: 1:28) (33). There has been also demonstrated a positive relationship between serum IGF-1 levels and mammographic breast density which may indicate a higher risk of breast cancer (34).

As part of a trial on extensive genetic studies (GWAS, Genome Wide Association Study) it was found that on 64 single polymorphisms predisposing to the development of lung cancer until 11 of them resulted in the increased activity of the GH/IGF-1 axis (35). Polymorphisms of similar importance were seen to be the third of the causes in over 1000 women with breast cancer (36).

With regard to the children there were published results from the large study that included 180 children with brain tumors, treated with radiotherapy and subsequently GH during 1965-1996, and 891 children also with brain tumors who received radiotherapy but not GH. 35 first recurrences occurred in the GH-treated children and 434 in the untreated subjects. The relative risk (RR) of first recurrence and RR

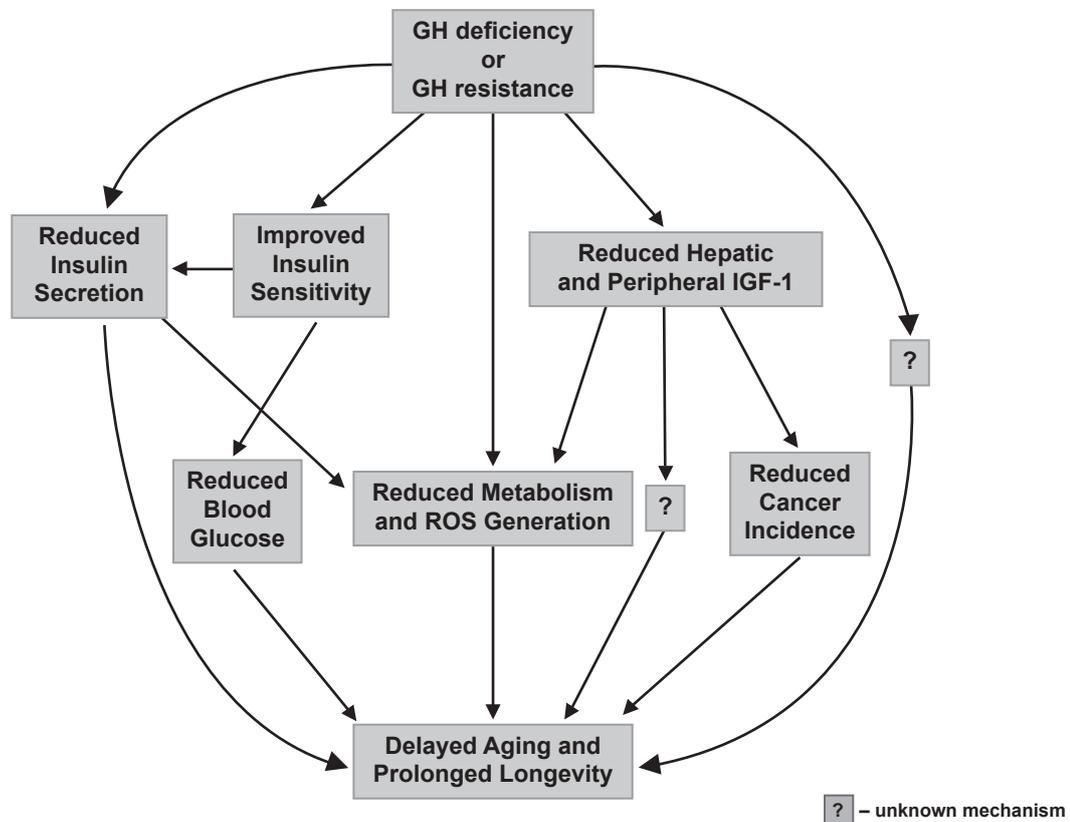


Fig 1. The proposed mechanisms of life extending in mice with the hypopituitarism, GH deficiency or resistance to this hormone (by Bartke A) (32).

of mortality in those treated with GH compared with untreated patients was lower: 0.6; 95% CI: 0.4-0.9, and 0.5; 95% CI: 0.3-0.8, respectively. However, the RR of mortality (not recurrence) increased gradually with time from the first GH treatment. These results suggest that GH does not increase the risk of recurrence of childhood brain tumors (37). Two big registers including total number of about 50,000 patients treated with growth hormone (a total of 200,000 patient-years): The National Cooperative Growth Study (NGCS) and Pfizer International Growth Database (KIGS) have demonstrated that a standardized incidence rate of cancer (SIR) in case of NGCS was 1.12 (CI: 0.75-1.61; table 1) and in case of KIGS was 1.26 (CI: 0.86-1.78) reflecting the insignificant, modest risk increase (38, 39).

SAGHE (Safety and Appropriateness of Growth Hormone Treatments in Europe) – long-term observation that involved about 30,000 patients treated with growth hormone in childhood in years 1980-90, conducted in 8 European countries demonstrated increased mortality among adults treated especially with high doses of GH during childhood in France, but with apparent no increase in the incidence of cancer (40). However, these disturbing results were not confirmed in observations from other countries. In Sweden, Belgium and the Netherlands (in total 46,556 patient-years) there was not a single death observed due to cardiovascular disease or cancer (41). On the other hand, the CCSS (Childhood Cancer Survivor Study) trial involving children with a previous successfully treated cancer who received

Table 1. New cases of cancer in children and adolescents treated with growth hormone with no risk factors.

New-onset malignancies without risk factors				
Age (yr)	Years of GH exposure	Expected rate per 100,000 yr of exposure	Observed cases	Expected cases
0-4	11,348	20.4	1	2.32
5-9	44,585	11.4	6	5.08
10-14	85,909	12.9	12	11.08
15-19	36,082	20.0	9	7.22
20-24	540	34.9	1	0.19
Total	178,464	14.5^a	29	25.88

SIR, 1.12; 95% CI, 0.75, 1.61.

^aAge-standardized expected rate.

Source: NGCS, by Bell J, et al. (38).

Table 2. Risk indicators (HR; hazard ratio) of death due to cancer. Observation of The Rancho Bernardo, California, 1988-2006.

Characteristics	Men (n = 633)		
	HR	95% CI	P value
IGF01 (1-SD increments)			0.048
<40	0.81	0.43-1.50	
40-79	1.01	0.66-1.53	
80-119	1.26	0.99-1.61	
120-159	1.58	1.27-1.96	
160-199	1.98	1.38-2.84	
200-239	2.48	1.41-4.34	
IGFBP-1 (ng/ml)	0.90	0.71-1.14	0.368
BMI (kg/m ²)	0.98	0.91-1.06	0.701
Waist-to-hip ratio	0.98	0.93-1.03	0.466
Alcohol (≥2 drinks/d)	1.17	0.73-1.87	0.516
Exercise (≥ times/week)	0.64	0.38-1.06	0.082
Current smoker	2.39	1.20-4.77	0.014
Previous cancer	1.95	1.14-3.34	0.015

IGFBP was log-transformed. The association of IGF-1 was modeled as a continuous (rather than categorical) predictor of cancer mortality. IGF-1 was centered to prevent collinearity with the quadratic term.

Source: Major JM, et al. (43).

growth hormone showed that the risk of tumor recurrence is 2.15 (1.33-3.47) compared to controls which should be considered as a significant risk increase (42).

Numerous trials were also carried out among adults, including elderly subjects. For example, in epidemiological study in which participated 633 middle-aged Caucasian men from the South California higher levels of IGF-1 were associated with an increased risk of death due to cancer, regardless of age, degree of obesity, lifestyle, and history of previous tumors (table 2). In the authors' opinion the results show the need for caution during GH-treatment leading to an increase in IGF-1, particularly in the elderly (43).

Contrarily, a meta-analysis of 2 retrospective and 7 prospective studies involving a total of 11,191 adults treated with growth hormone showed a reduced risk of malignancy in those treated compared to untreated GH-deficient subjects (relative risk 0.69; 95% CI: 0.59-0.82) (44). Other systematic review of 42 published studies concluded that raised circulating IGF-1 is associated with prostate cancer risk (inconclusive evidence for involvement of IGFBP-3) (45).

An increase in cancer risk have been also demonstrated in acromegaly. Retrospective analysis of patients with this disease revealed that 15-24% deaths were related to the cancer, particularly to the colorectal, and, to a lesser extent to breast, thyroid, prostate and other tumors (46). Also meta-analyses have confirmed a higher risk of colon cancer (relative risk [RR] 2.46; 95% CI: 1.79-3.38), thyroid cancer (RR 3.64; 95% CI: 1.63-8.11), and with high probability of lymphoma, multiple myeloma, lymphocytic leukemia, meningioma, melanoma and pheochromocytoma in patients with acromegaly (47).

Based on the data available so far Growth Hormone Research Society (GHRS) in its guidelines for the diagnosis and treatment of GH deficiency in adults published in 2007 says in agreement with the other scientific societies that "there is no evidence that hypothalamic or pituitary tumor recurrence is influenced by GH replacement therapy. Before GH replacement therapy is initiated, pituitary imaging should be performed. Good clinical practice predicates that patients with residual tumors should be monitored regularly; GH replacement therapy does not impose a need for intensifying follow-up. (...) There is no evidence that GH replacement in adults increases the risk of de novo malignancy or recurrence. GH treatment during childhood of survivors of cancer treatment increases slightly the relative risk of a second neoplasia, but there are no comparable data in adults. GH therapy should be halted in any patient with active malignancy until the underlying condition is controlled. Because GH replacement therapy has not been associated with an increase in cancer risk, current recommendations for cancer prevention and early detection

in the general population should be implemented" (8). A summary of the currently available knowledge in the field of oncological safety of growth hormone treatment in children and adults presents the joint opinion of The European Society of Pediatric Endocrinology, Growth Hormone Research Society and The Pediatric Endocrine Society published in 2016. Their Position Statement indicates that such proceedings are generally safe, although in some cases scientific data are insufficient to obtain unambiguous opinion. Therefore, there are remain doubts about possibility of recurrence of primary neoplasia in already oncological treated adults (no increased risk in children), occurrence of secondary tumors in survivors of cancer or the safety of GH in "high-risk" subjects (table 3) (48).

Similarly to animals, mutations and polymorphisms leading to increased activity of GH and somatomedin C contribute to the life shortening in humans. For example, the aforementioned GWAS study revealed that increasing expression of FOXO gene associated with the insulin/IGF-1 receptor signal transmission pathway, which triggers growth factors dependent cell maturation and proliferation reduces life span (49). A similar effect is observed in other cases of increased GH expression leading to higher IGF-1 production (50).

Growth hormone deficiency during aging

Growth hormone secretion gradually decreases with age and in consequence decline in circulating levels of IGF-1 is also observed. As a result, changes in body composition: fall of lean body mass (sarcopenia and osteopenia) and muscle strength concomitant with increase in fat mass (abdominal obesity) that leads to atherogenic blood lipid profile and to increase rate of cardiovascular diseases occur (51). As these symptoms resemble to a large extend cardinal signs of aging the attempts to treat them with growth hormone replacement therapy were carried out since the end of the last century (52). Also, currently growth hormone is one of the most important products offered in anti-ageing medicine (53). It is calculated that over 100,000 people per year only in the US use GH as an anti-ageing drug. The estimated annual growth hormone sales value over the world is 1.5-2.0 billion dollars, including approx. 30% of the "off-label" prescriptions for GH. It is so, although (a few, in fact) observations performed in accordance with the rules of evidence-based medicine have not confirmed the initial promising results. In the light of the current knowledge such therapy is therefore considered unjustified and even potentially damaging, particularly in relation to the increased oncological threat in older subjects (54).

Tab. 3. Majority view of the effect of GH treatment for approved indications on cancer risk in children and adults (including those with a childhood-onset of GH deficiency).

Age at onset of GH treatment	New primary cancer	Recurrence of the primary cancer in survivors	Second or subsequent neoplasm in survivors
Child	No evidence for GH treatment effect Level: robust	No evidence for GH treatment effect Level: robust	Risk present but diminishes with time from onset of GH treatment Level: robust
Adult	No evidence for GH treatment effect Level: suggestive	Insufficient data available	Insufficient data available

Source: Allen DB, et. al (48).

GH/IGFs axis as a potential target in the cancer treatment

Awareness of impact of GH and somatomedins on cell growth and proliferation as well of the potential role of these hormones in carcinogenesis order caution during growth hormone treatment. However, it seems that if such therapy is carried out in accordance with actual guidelines it is generally safe and should not be give up in patients who require it. On the other hand, understanding the molecular mechanisms by which GH and GH-dependent growth factors affect cell metabolism and proliferation will allow to use them in oncology in the future. For example, already the ability to implement gene therapy (nonsensical oligonucleotides, antisense RNA), use of monoclonal antibodies, protein kinase inhibitors, or growth hormone antagonists are under investigation. These first attempts have yielded first results. Monoclonal antibodies against IGF-R inhibited breast cancer cells proliferation in vitro and blocked the mitogenic effects of exogenous somatomedin C (55). Similar blockade inhibited growth of estrogen-independent breast cancer cells in vivo. Antisense RNA directed against IGF-R inhibited colon cancer growth in study in vitro (56). Block of IGF-I signaling with IGF-R antibody in combination with docetaxel on human androgen-independent prostate tumor has showed, that such block resulted in enhancing of the therapeutic effect of docetaxel on prostate cancer (57). However, a phase II randomized clinical trial in chemotherapy-naïve men with progressing castration-resistant prostate cancer treated with figitumumab (a human IgG2 monoclonal antibody targeting IGF-IR) did not corroborate these preliminary findings. Also, other studies on single agents of IGF-1R inhibitors (ganitumab, dalotuzumab, cixutumumab, teprotumumab and figitumumab) alone or combination with other therapies in solid tumor did not make significant differences in these tumor prognosis. On the contrary, pessimistic effects were shown in the dalotuzumab, breast cancer, colorectal cancer and prostate cancer subgroups (58).

Moreover, it should be mentioned, that in majority of such treated patients development of diabetes was observed. In animal models of metastatic colon cancer, pegvisomant – GH antagonist, in combination with conventional chemotherapy, virtually abolishes metastatic disease (59, 60).

Summary

Growth hormone with its mediators somatomedins through the several molecular mechanisms stimulate cells proliferation and differentiation, as well prolongs their life span. In vitro studies and animal models show that increased gene expression resulting in increased GH/IGF-1 axis activity contribute to the stimulation of growth, inhibition of apoptosis, and facilitate malignant transformation and cancer progression. Numerous clinical observations and epidemiological studies performed in animals and in humans have shown that disruption of GH/IGF-1 signaling leads to a clear decrease in cancer risk, while overexpression of these hormones causes a higher incidence of various types of tumors.

These are only the first attempts to use knowledge about the GH/IGF-1 and their binding proteins system in oncological care. Further research is needed, taking into account the histologic diagnosis, the progress of the disease but also the type of disturbances in signal transmission, and the ability to individualize cancer treatment.

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