Why are People with Laron Syndrome Immune to Cancer?

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Abstract

Laron syndrome is a congenital autosomal recessive disorder that is caused by a mutation in the growth hormone receptor. People with this syndrome have an insensitivity to growth hormone. Insulin-like growth factor 1 is produced by the liver in response to GH stimulus. It is responsible for systemic GH activities. If there is something wrong with the growth hormone receptor there will be decreased levels of IGF-1. Low IGF-1 levels cause physical deformities notable short stature. Additionally, people with low levels of IGF-1 have a natural resistance to cancer. This article discusses the ways that the decreased levels of IGF-1 in Laron subjects protect the body from cancer.

Introduction

Laron Syndrome, eponymously named after the scientist Zvi Laron who first discovered the syndrome, is a growth hormone insensitivity syndrome. People with Laron Syndrome have a genetic mutation in the growth hormone receptor. These patients have a normal level of growth hormone but a reduced level of Insulin-like Growth Factor 1 (IGF-1) and are characterized by dwarfism and other physical deformities. Remarkably, patients with this condition have been proven to be immune to cancer. Through research on Laron Syndrome scientist have found a link between a key growth hormone and resistance to cancer.

Methods and Materials

Information was compiled from various articles that were obtained through Touro College's library database and Pubmed. The information was narrowed down to those directly related to the topic. The information extracted and synthesized was used to hypothesize why Laron Syndrome patients are immune to cancer.

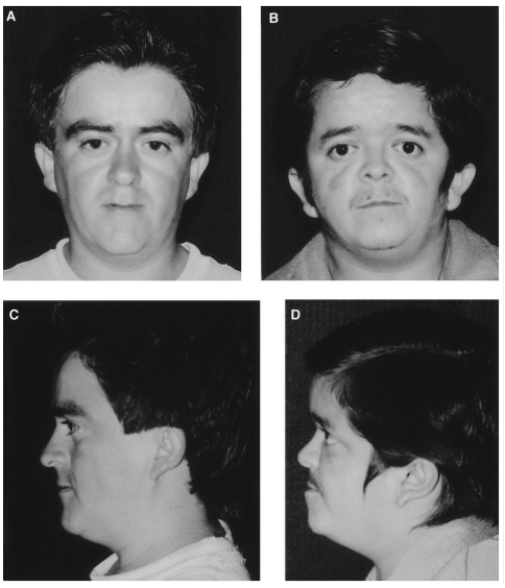
Background information

Data shows that Laron Syndrome (LS) patients have normal levels of, and a normal, GH molecule, but a defect in the Growth Hormone Receptor gene (GHR). Patients with LS have either a gene deletion or a point mutation in this gene (Wood & Savage, 1996).

Mutations in the growth hormone receptor interrupts the JAK-STAT signaling pathway which stimulates the production of IGF-1. The JAK-STAT signaling pathway brings information from chemical signals outside the cell, through the cell membrane, and into the cell where gene promoters on the DNA in the cell nucleus can causes DNA transcription and activity in the cell. The mutation in the Growth Hormone Receptor, leads to an inability of the extracellular domain to bind growth hormone and stimulate the production of IGF-1 (Gastier et al., 2000).

Cited from Rosenbloom and Guevara-Aguirre that in 1966, Laron, Pertzelan and Mannheimer did research on the high levels of growth hormones in patients with clinical and laboratory signs of growth hormone deficiency (Rosenbloom and Guevare-Aguirre, 1998). There are ~251 reported people with this syndrome. One hundred and forty eight are known to have Semitic origin. One third of the people with this syndrome live in Loja, Ecuador which is where most of the genetic studies take place. The people in Loja, Ecuador are said to have ancestors who converted to Christianity during the Spanish Inquisition (Wood & Savage, 1996).

Laron syndrome is a congenital autosomal recessive disorder. The parents of an individual with Laron syndrome must each have a copy of the mutated gene while displaying no signs of the syndrome. People with Laron Syndrome have postnatal growth failure; it begins with "subnormal birth length, retarded brain growth, acromicria, also of the facial bone, defective and crowded teeth, sparse hair, small gonads and genitalia, obesity, retarded skeletal maturation, delayed puberty, hypoglycemia. As these patients get older they have obesity, muscle underdevelopment and weakness, osteoporosis, hypercholesterolemia, hyperinsulinemia, and various degrees of glucose intolerance (Yamamoto et al, 2007)." There is wide phenotypic variability among patients with this syndrome. With that said, there is uncanny similarity between patients with LS even with variability in genotype and even if they are from different places. In the image below of two men with



Laron Syndrome, it is evident that there is a similarity in physical features.

The man in figure A and C is 21 years old with a height of 126.6 cm. The man in B and D is 28 years old and has a height of 115 cm. Analysis of the faces indicate different craniofacial phenotype, but still both men with Laron Syndrome have an uncanny resemblance (Rosenbloom and Guevare-Aguirre, 1998).

Patients with LS have extremely low levels of insulin-like growth factors, below the 0.1st percentile for age, such as IGF-I which is the major hormone responsible for growth and it is under the control of GH. Patients with GHD also have a low level of IGF-I but those patients responded well to exogenously administered GH, whereas patients with LS did not which is a characteristic of LS. This is the primary difference between GHD and GHRD. LS patients also have extremely low levels of Insulin-like growth factor binding proteins (IGFBPs). Specifically, IGFBP-3 levels are decreased in LS patients (Wood & Savage, 1996).

Insulin-like growth factor 1 (IGF-1)

IGF-1 is a 70 amino acid polypeptide hormone involved in endocrine, paracrine, and autocrine functions. An original name for this hormone was somatomedin C because it was under the control and mediates the effect of the growth hormone. The name was changed to Insulin-like because it shared a similarity to proinsulin. Also, it mimics insulin activity such as stimulating glucose uptake in the cells. Additionally, IGF-1 has mitogenic capabilities (Puche & Castille-Cortazar, 2012).

Synthesis and Circulation

Growth hormone is secreted by the pituitary gland and it stimulates the production of IGF-1 by acting on the liver where it is made. The pituitary gland releases GH and it works together with the liver in a negative feedback mechanism to stimulate the secretion of IGF-1; increased levels of IGF-1 cause a decrease in production of GH which stimulates the production of less IGF-1 (Puche & Castille-Cortazar, 2012).

Recent research by Puche and Castille-Cortazar is uncovering IGF-1 as an independent and self-sufficient peptide, separate from GH. IGF-1 is produced mainly by the liver in response to the endocrine GH stimulus, but it is also secreted by multiple tissues for autocrine and paracrine purposes. In tissues throughout the body it is evident that IGF-1 expression is regulated and stimulated by other factors besides GH, such as estrogen in the uterus (Puche & Castille-Cortazar, 2012).

The stimulatory role of IGF-1 on intrauterine growth is GH-independent. Regardless of the levels of GH, IGF-1 deficiency is the main determinant of a reduced birth size. (Puche & Castille-Cortazar, 2012).

Research done on the effects of GH to stimulate skeletal growth has proven that GH directly stimulates bone growth. Additionally, GH stimulates the production of IGF-1 which will then promote bone growth. This proves, along with other findings, that IGF-1 and GH work independently and synergistically to promote postnatal body growth (Puche & Castille-Cortazar, 2012).

Central nervous system development

IGF-1 binds to IGF-1R a cell surface receptor. When IGF-1 binds to the receptor intracellular signaling is initiated. The AKT signaling pathway, which is a stimulator of cell growth and proliferation, and a potent inhibitor of programmed cell death, is activated.

IGF-1 production coincides with periods of neuron progenitor proliferation and differentiation. The role of IGF-1 in the brain is not only neuronal produced IGF-1. Systemic IGFs (mainly produced by the liver) can cross the blood-brain-barrier and are also involved in these processes. Labeled IGFs were placed in the carotid arteries of rats and were later on detected in the choroid plexus, median eminence, brain arterioles, and parenchyma. This coincides with the data that confirmed the presence of IGF-1 receptors in the brain capillary endothelial cells which constitutes the BBB, and the role in internalizing IGFs from circulation to the CNS. There is evidence that growth factors, GH, basic fibroblast growth factor; nutrition; and injury influence and regulate IGF-1 expression in the brain. All of the growth abnormalities that are attributed to LS patients (see above), indicate that IGF-1 plays a critical role on brain development and function.

Current therapeutic options and limitations

In 1980, Recombinant Human IGF-1 (rhIGF-1), Mecasermin became available for experimental therapy for people with severe primary IGF-1 deficiency. An average of 8.5 cm in height was grown the first year. Besides for an increase in height, patients with rhIGF-1 treatment had an increase in testosterone levels, testicular size and stretched penile length. This shows the effect of IGF-1 on sex hormones and organs in male patients (Puche & Castile-Cortazar, 2012).

Another treatment that the FDA approved was a combination of IGF-1 and IGFBP-3, Mecasermin Rinfabate. This was thought to have been a smarter alternative to Recombinant human insulin growth factor 1 (rhigf-1) because it was supposed to extend the duration of IGF-1 in the body. Interestingly enough, when the combination of IGF-1 and IGFBP-3 were used to

treat patients compared to a control group who only were treated with IGF-1, those treated with IGF-1 alone had better results (Puche & Castile-Cortazar, 2012).

Dosing guidelines for rhIGF-1 are still being debated. The international Congress of Endocrinology has stated that both one and two injections of rhIGF-1 is safe and efficient. One or two injections regimen have the same growth velocity. By carefully monitoring the IGF-1 serum levels the negative side effects can be avoided. Long-term rhIGF-1 has reported negative side effects. These side-effects, namely tachycardia were easily managed without treatment discontinuation (Puche & Castile-Cortazar, 2012).

A novel and efficient method for hormone replacement therapy is being developed using Sertoli cells. Sertoli cells are originally from the male testis, and they can ameliorate development and survival and function of different cell types. In the "Laron mouse" it was successfully reported that pre-pubertal sertoli cells in microcapsules can successfully promote growth. There was a significant increase in body weight and body length compared with the control "Laron mouse" treated with empty capsules. IGF-1 serum levels were noticeably increased in mice treated with Sertoli cells microcapsules. The reduction in side effects, the increase in growth, and the fact that sertoli cells do not require intramuscular daily injections are all reasons that sertoli cell treatment is preferred over rhigf-1 treatment (Kinam Park, 2012).

Puche and Castille-Cortazar cite a study done by Steuerman R, Shevah O, Laron Z. on the prevalence of cancer in people with Laron Syndrome compared to their family members. This study proved that IGF-1 deficiency provides protection against cancer. Interestingly, this study reported that Laron Syndrome patients are protected against future cancer development, even when treated with rhIGF-1. (Puche & Castile-Cortazar, 2012).

The positive results of exogenously administered IGF-1 in subjects without IGF-1 deficiency, to use its anti-inflammatory, hematopoietic, antioxidant, metabolic or anabolic properties, is not clearly determined (Puche & Castile-Cortazar, 2012).

Discussion

Studies have shown that patients with overexpression of IGF-1 are more susceptible to tumors. Laron set out to determine if patients with IGF-1 deficiency (LS) are less likely to develop cancer. Two hundred and twenty eight patients with IGF-1 deficiency and 338 of first and second degree family members were surveyed. Cancer was not a cause of death in GHRD patients of any age. Ten to twenty four percent of the family members had a history of malignancies. Only one GHRD subject monitored had cancer, papillary serous epithelial tumor in the ovary. The table below shows the prevalence of the malignancies in patients and family members. Because of the results of this and further studies, IGF-1 receptor blockers are being developed as drugs for cancer therapy (Shevah & Laron, 2006)

Prevalence of malignancy in the surveyed subjects				
Diagnosis	Patients	Malignacy	Relatives	Malignacy
Israeli Cohort				
Laron syndrom	n=40a	0	n=99	n=24(24.2%)
M:F	18:22	2:49:00	15:08	
Age Range	3–75	19–91	42–81	
Mean age	32.3	55.4	51	
Other diagnosis	n=22	0	n=83	n=7(10%)
M:F	13:09	19:40:00	3:04	
Age Range	3–56	5–93	32–80	
Mean Age	27	51.4	64.8	
Other Countries				
Laron syndrom	n=129	0	n=151	n=17(11.2%)
M:F	59:70	78:73	8:09	
Age Range	6–78	27–68	45–85	
Mean Age	16	50	68	
Other diagnosis	n=31	0	n=5	n=3
M:F	19:12	3:02	2:01	
Age Range	2.5–50	40–80	68–80	
Mean Age	16.8	60	65	

(Laron & Shevah, 2006)

What is the link between GH and cancer?

Data suggest that the GH/IGF-1 axis shows an important role in cancer.

Growth Hormone does not have the ability to induce cancer, but it has cancer-enhancing properties. There are many different factors that influence the different effects of the IGF-1. The powerful effects of IGF-1 on the stages of cancer development and behavior include "cellular proliferation and apoptosis, angiogenesis and metastasis…" Additionally, IGF-1 is a powerful antiapoptotic agent. These opposing effects relate strongly to cancer. Firstly, there is increased proliferation causing epithelial cell turnover within tissues. Secondly, there is an imbalance in the control between proliferation and cell death because of the anti-apoptotic effects which leads to hyperproliferation. This is the first stage of development of many cancers. Thirdly, this imbalance between cell proliferation and cell death causes the favoring of cell survival even in damaged cells. This could

accelerate carcinogenesis. Both the second and third point are ways that cancer is accelerated not initiated (Puche & Castile-Cortazar, 2012).

Research in epidemiological studies have shown a correlation between the role of GH and carcinogenesis. People with more growth hormone are naturally taller. The Boyd-Orr study showed an SD of 1 inch height to be linked with a 42% higher risk of cancer later in life in boys. High birth weight, high stature at 14, low body mass index, and peak growth at early age were independent risk factors for breast cancer. (Jenkins et. al., 2005) Epidemiological date found a correlation between adult height and cancer. An increase in breast cancer by 22 % was noted with increased height. These studies suggest that the GH/IGF-1 axis plays an important role in cancer development and behavior (Jenkins et. al., 2005). Many pharmaceutical companies are creating drugs that inhibit the IGF-1 signaling to inhibit breast cancer proliferation and block the mitogenic effects of exogenous IGF-1. They are also experimenting with Inhibitors of the IGF-IR as a chemotherapeutic (Jenkins et. al., 2005).

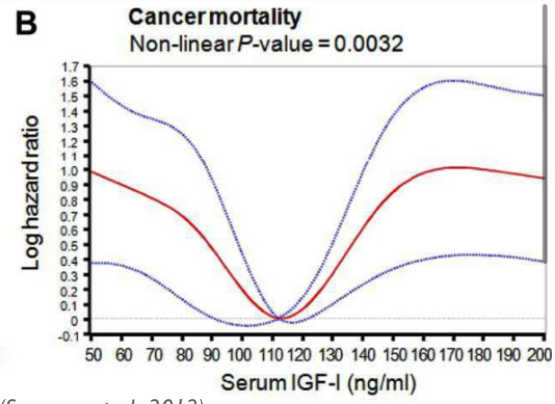
Studies on mice were done to provide evidence to this relationship. Transgenic mice with human GH and agonist for the IGF-1 receptor have increased incidence of breast tumor development. On the other hand, mice with a non-functioning GH receptor (serum GH/IGH-1 levels of ten percent the normal), showed inhibition of growth of transplanted breast cancer cells. Even the serum was less mitogenic to breast cancer cells in vitro than a control serum, this changed once IGF-1 was added to the serum. Recent studies have shown that mice transfected with growth hormone receptor antagonists have less incidences of carcinogenesis (Guevara-Aguirre et. al., 2011).

Another study done on mice was used to prove the influential effects IGF-1 exerts on the metastatic power of cancers (Guevara-Aguirre et. al., 2011). This is an extremely important aspect of cancer as the metastatic spread of cancer is usually what causes mortality. A cell from the LCC6 metastatic breast cancer cell line was transfected with a truncated IGF-1 receptor that silenced the expression of IGF-1 receptor and inhibited IGF-1 signaling. These cells were transplanted into mice and the metastatic spread was measured. Mice that were transplanted with wild type cells had multiple pulmonary metastases, but the mice transplanted with the transfected cells were completely absent of any metastases (Guevara-Aguirre et. al., 2011).

Another reason how the GH/IGF-1 axis can cause cancer is by promoting an increased DNA damage. Experiments on Saccharomyces cerevisiae yeast indicate that mammalian growth signaling pathway genes promote an increase in DNA mutations by elevating superoxide production and increasing DNA damage. This is particularly important because it hypothesizes that, in addition to the possibility that the GH/IGF-1 axis may promote cancer by preventing apoptosis of the damaged cells, it can increase DNA damage in cells that can ultimately lead to cancer. To test this hypothesis, human mammary epithelial cells (HMECs) were placed in a medium that contained 15% serum from either Laron syndrome subjects or their relatives. The cells were then treated with H2O2 followed by comet analysis to detect DNA strand breaks. The comet analysis indicated that cells incubated in serum from GHRD patients had fewer DNA breaks after treatment in comparison to cells incubated in serum from relatives. This teaches that serum from GHRD subjects can protect against oxidative DNA damage independently of cell division. It was determined that that IGF-1 signaling was responsible for the sensitization of cells to oxidative damage via analysis of DNA damage in MEF cells lacking the IGF-R or overexpressing the human IGF-1R cell (R+ cells). R+ cells had more DNA damage than did R-cells. (Guevara-Aguirre et. al., 2011).

A study done by Wang and colleagues on rats explains that down-regulation of GH signaling could block carcinogenesis in rats. Human prostate cancer cell lines express GH receptors at levels greater than normal. A rat that does not have GH because of a mutation was crossed with the Probasin/Tag rat, a rat which develops prostate carcinomas at 100% incidence rate. The rats that were homozygous for the GH deficiency had prostrate tumor incidence and tumor latency reduced relative to wild type rats. At 25 weeks of age, the rats with no GHR resulted in a 20% and 80% decrease of carcinoma in the dorsal and lateral lobes, respectively. At 52 weeks of age, invasive prostate adenocarcinomas were observed in all Probasin/ Tag rats positive for the Growth Hormone. Conversely, majority of the Tag rats with the mutation that makes them GH deficient did not develop invasive tumors (Wang et. al. 2008).

The potent antiapoptotic and mitogenic properties of IGF-1 is linked to an increased risk in developing cancer. It is documented that IGF-1 can promote carcinogenesis at the cellular



(Svensson et. al., 2012)

level, but evidence is accumulating that circulating IGF-1 can also promote carcinogenesis. For example, reduction of IGF-1 by dietary restriction slows tumor progression and increase apoptosis in tumor cells of animal models. And when these models were treated with recombinant IGF-1 the effects were reversed. Additionally, IGF-1 gene deletion in mice is linked to a 75% decrease in circulating IGF-1 levels. Tumor growth and development was much higher in the control group than transgenic mice.

Biological interactions among insulin, IGF-1 and IGFPBS

As stated above there are many clinical studies that suggest that high serum IGF-1 levels associate with increased risk of cancer. Increasing clinical evidence suggests that low IGF-1 levels are associated with cancer mortality in older men. In numerous studies, the association between circulating IGF-1 levels and cancer mortality was U-shaped with increased levels of mortality at both the low and high serum IGF-1 levels.

Serum IGF-1 was extracted from the blood of a large cohort of elderly men from Sweden. The measurements of serum IGF-1 levels were obtained. The reason for mortality was documented on the death certificate of the subjects and then used in the study. Cox proportional hazards was used to analyze the association between serum IGF-1 levels and mortality by cancer. Cox regression analysis showed that both low and high serum IGF-1 concentration was associated with increased cancer mortality. The patients with a history of cancer were excluding from the analysis (Svensson et al, 2012).

IGF-1R Inhibitors as an Anti-Cancer

Because of the role that IGF signaling plays in the promotion of cell growth and inhibition of apoptosis, IGF blocking is being developed as a therapeutic potential to protect against cancer. Currently there are many clinical studies targeting and inhibiting the IGF pathway to promote anti-tumor activities. There are three main classes of IGF/IGF-1R inhibitor antibodies being studied in clinical trials; each class inhibits IGF-1R signaling but through different mechanisms. There has been some small success in treating patients with select tumor types, but many trials have been unsuccessful. Researchers are trying to identify patient selection markers to attain future success in IGF-1R inhibitor development (Chen & Sharon, 2013).

IGF blocking is also being used to overcome chemotherapy sensitivity. Resistance to chemotherapy is common nowadays. IGF is implicated in chemotherapy resistance because it promotes proliferation and inhibits apoptosis. Researchers have tested this hypothesis and have found that IGF-1R inhibitors have caused significant tumor growth inhibition. Currently, researchers are testing the combined effect of IGF-1R inhibitors with a chemotherapeutic (Weroha & Haluska, 2008).

Conclusion

Laron Syndrome subjects participate in groundbreaking genetic studies to explore the relationship between the deficiency in the growth hormone receptor and immunity to cancer. This syndrome is providing insight to, and revolutionizing, the way cancer is treated and prevented. Because Laron Syndrome subjects have decreased levels of IGF-1 they are protected against numerous and potentially harmful effects of IGF-1 including cellular proliferation, apoptosis, angiogenesis, and metastasis. The increased proliferation and decreased apoptosis causes survival of damaged cells that then spread easily throughout the body, which could lead to the development of cancer. Because Laron Syndrome subjects have decreased levels of IGF-1 they are immune to cancer. The implications of IGF/IGF-1R in cancer development, maintenance, and progression, is what led to replicating the IGF-1 levels of LS patients to use as an anti-cancer target. IGF-1 has been successfully inhibited in animal models to prevent cancer cell growth. Now researchers are beginning to use IGF-1 reducing agents and blockers as a chemotherapeutic to prevent cancer.

Abbreviations

IGF-1	Insulin Growth Factor 1
LS	Laron Syndrome
GH	Growth Hormone
GHR	Growth Hormone Receptor
GHD	Growth Hormone Deficiency
GHRD	Growth Hormone Receptor Deficiency
CNS	Central Nervous System
rhIGF-1	Recombinant Human Insulin Growth Factor 1
IGFBP	Insulin Growth Factor Binding Proteins
HMEC	Human Mammary Epithelial Cells

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