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Review

Clinical and Molecular Features of Laron Syndrome, A Genetic Disorder Protecting from Cancer

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Abstract. *Laron syndrome (LS) is a rare, genetic disorder inherited in an autosomal recessive manner. The disease is caused by mutations of the growth hormone (GH) gene, leading to GH/insulin-like growth factor type 1 (IGF1) signalling pathway defect. Patients with LS have characteristic biochemical features, such as a high serum level of GH and low IGF1 concentration. Laron syndrome was first described by the Israeli physician Zvi Laron in 1966. Globally, around 350 people are affected by this syndrome and there are two large groups living in separate geographic regions: Israel (69 individuals) and Ecuador (90 individuals). They are all characterized by typical appearance such as dwarfism, facial phenotype, obesity and hypogenitalism. Additionally, they suffer from hypoglycemia, hypercholesterolemia and sleep disorders, but surprisingly have a very low cancer risk. Therefore, studies on LS offer a unique opportunity to better understand carcinogenesis and develop new strategies of cancer treatment.*

According to data published by the International Agency for Research on Cancer, in 2012, over 14 million new cases of cancer and more than 8 million deaths caused by this disease were registered worldwide (1). It is predicted that in 2030, the number of new cancer cases will increase by more than 50%, mainly due to the growth and aging of the human population, as well as the propagation of certain lifestyles related to, amongst others, tobacco and alcohol consumption, improper diet and lack of physical activity (2). However, there is a small population of people with a genetic syndrome known as Laron syndrome (LS) who have a very low probability of cancer development (3).

Laron syndrome (syndrome of hereditary determined resistance to growth hormone, Laron dwarfism) was first described by the Israeli physician Zvi Laron in 1966 in three siblings (4). It is classified into the group of diseases associated with deficiency of insulin-like growth factor type I (IGF1) (5). The characteristic biochemical features which allow LS to be distinguished from other diseases of this group are a high concentration of growth hormone (GH) and low level of IGF1 in serum (6).

Globally, an estimated 350 people are affected by LS, with two relatively large groups of affected individuals living in separate geographic regions. One is the 'Israeli cohort', currently consisting of 69 individuals living in Israel (3), and the second is the 'Ecuadorian cohort', which now has 90 individuals who inhabit the villages of the Loja province in southern Ecuador (7, 8). There are also some isolated cases in Central and North America, Europe, Asia and Mediterranean countries.

Long-term observations have shown that patients with LS are protected from cancer (3, 7-9). Therefore, knowledge of the molecular basis responsible for the development of this syndrome should lead to a better understanding of carcinogenesis and the introduction of new cancer treatment strategies.

Molecular Basis of LS

Laron syndrome is a rare, genetic disease inherited in an autosomal recessive manner and characterized by insensitivity to GH. The disorder is caused by mutations of the gene encoding the corresponding receptor (GHR), leading to defective functioning of the GH–IGF1 signalling pathway (10).

GHR is predominantly expressed in the liver and activated by GH. Under physiological conditions, GH, secreted by the pituitary gland, reaches the liver with blood (endocrine effect

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of GH) and binds to GHR (Figure 1a). This leads to receptor dimerization and synthesis of somatomedins, mainly IGF1 (11). IGF1 binds to its receptor (IGF1R) localized on the surface of many different types of cells. In consequence, adaptor proteins are recruited and phosphorylated. Next, the signal is transmitted through rat sarcoma virus homologue/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (RAS/RAF/MAPK) or phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase/mammalian target of rapamycin kinase (PI3K/AKT/mTOR) pathways. The former stimulates cell proliferation and the latter regulates cell growth, metabolism and apoptosis (through inactivation of proapoptoptic B-cell lymphoma 2-associated death protein) (12). Besides that, IGF1 acts as a negative feedback regulator of GH secretion (11).

In patients with LS (Figure 1b) GH, similarly to physiological conditions, is secreted by the pituitary gland and the hormone reaches the liver but does not activate GHR because the receptor is mutated (11, 13-19). Changes of *GHR* gene sequence lead to formation of abnormal receptor, which does not function properly, causing IGF1 deficiency in the cells and inhibiting downstream signal transduction. Under such conditions, IGF1 negative feedback is also reduced. Therefore, in patients with LS, a high serum level of GH and low IGF1 concentration are observed and recognized as the diagnostic features of LS (6).

In LS, over 70 different *GHR* mutations (deletions, splice, nonsense, missense or frameshift mutations) have been reported (11, 13-19), localized within exons and introns. Changes in the extracellular domain of the receptor are much more frequent than those in transmembrane or cytoplasmic domains. The most prevalent *GHR* defect is E180 splice mutation in exon 6, identified in the vast majority of the Ecuadorian cohort which lives in isolation (14). Exon splicing is disrupted through substitution of adenine for guanine (c.594 A>G) leading to in-frame deletion of eight amino acids (p.V199_M208 del) within the extracellular domain (19). The mutation probably originated from a single common ancestor (a founder effect) from the Sephardic Jew community from the Iberian Peninsula who later emigrated to Central America (14, 20). In contrast, in the multiethnic Israeli cohort, many different *GHR* molecular defects were registered (10).

Since IGF1 is the main transmitter of the GH signal affecting almost every type of cell, in patients with LS, the resulting changes in the GH–IGF1 signalling pathway lead to a set of characteristic clinical features.

Clinical Characteristics of Patients with LS

Phenotypic features. There are many phenotypic characteristics of LS. The main one is dwarfism, noticeable from birth. The body length of infants with LS ranges between 42 and 45 cm and their weight is usually about 2,500 g (however, sometimes it is lower than 2,100 g) (17). Generally, growth of these patients is retarded and the final height reached by women is 108-136 cm, whereas by men it is 116-142 cm (17). Laron documented that untreated patients have small hands and feet (acromicria), as well as small internal organs (organomicria), and because of their body size, their heads seem to be larger than normal (6). Additionally, underdevelopment of the facial bones is observed. This leads to formation of a protruding forehead, saddle nose and sunset look. Slowly growing sparse hair and nails, as well as crowded defective teeth are also typical. Moreover, patients with LS (especially women) have a high-pitched voice due to having a narrow oropharynx and larynx. In addition, they are obese and their obesity increases progressively with age (21). An interesting phenomenon is that both genders reach full sexual development and reproductive potential, despite their hypogenitalism, hypogonadism (mainly in boys) and delayed puberty (by 3 to 7 years compared to healthy individuals) (22).

Biochemical characteristics. Patients with LS have an elevated level of GH and undetectable, or very low IGF1 concentrations in serum (7). Therefore, these features are recognized as those allowing for diagnosis of LS. IGF1 increase is not observed, even after exogenous GH administration (23). Untreated patients also have a tendency for a higher serum level of prolactin (24). Total cholesterol and low-density lipoprotein fraction are high even in young patients, whereas the high-density lipoprotein fraction stays within the normal range (25).

Incidence of cancer and other diseases. Increased level of GH, overexpression of its receptor and a higher IGF1 level have been reported in breast and prostate cancer, and melanoma, as well as in the serum of oncological patients (26). Therefore, these features are considered as risk factors for the development of malignancies. It is hypothesized that increased cancer risk is related to the link between GH–IGF1 signalling and the main pathways (RAS/RAF/MAPK and PI3K/AKT/mTOR) involved in the regulation of cell growth, proliferation, differentiation and apoptosis (27).

Indirect evidence of the significance of these features for cancer development is also provided by long-term observations of patients with LS. In 2011, the research group under the direction of Laron presented data concerning 538 patients who were characterized by a variety of congenital diseases associated with a lack of a properly functioning GH–IGF1 signalling pathway (28). Among them, there were 230 patients with LS. Researchers have shown that none of them developed malignancy, compared to 39 cases of cancer reported among 349 of their healthy relatives (proven or

suspected as heterozygotes for LS). Similarly, morbidity and mortality data for 99 Ecuadorian individuals with LS have been collected since 1988 by a group of researchers under the direction of Jaime Guevara-Aguirre (29). They found one case (1.0%) of death from malignancy (papillary serous epithelial tumour of the ovary), whereas in about 1500 healthy relatives, mortality from cancer was at 20%.

The data concerning the incidence of diabetes in patients with LS are not so evident as for cancer. In the Ecuadorian cohort, Guevara-Aguirre *et al*. documented no cases of diabetes (despite patients' obesity) in contrast to 6% prevalence in their healthy relatives (8, 9). In this cohort, markedly enhanced insulin sensitivity was also noted, hence it was hypothesized that absence of diabetes in individuals with LS is related to increased insulin sensitivity (29). In contrast, in the Israeli cohort, hypoglycemia was found in infancy, but with progressing age, insulin resistance developed and two cases of diabetes with complications were registered (30).

Despite protection from some serious diseases, patients with LS complain of other health problems, such as sleep disorders, mainly sleep apnoea caused by narrow oropharynx and larynx (31), or knee pain resulting from obesity and reduced muscle force and endurance (17).

Cancer Protection and LS – Experimental Studies

The presented epidemiological data on the incidence of cancer in patients with LS are supported by *in vitro* and *in vivo* studies on animal models. It was shown that serum from Ecuadorian patients with LS when added to human mammary epithelial cells treated *in vitro* with hydrogen peroxide, reduced DNA breaks and increased apoptosis (29). In these cells, a decrease in expression of RAS, protein kinase A, and mTOR genes (encoding proteins functioning as second messengers in RAS/RAF/MAPK and PI3K/AKT/mTOR pathways) and overexpression of the gene encoding superoxide dismutase (an enzyme involved in defence against free radicals) were demonstrated. The described changes promote protection from mutagens and increase the lifespan of the cell. In turn, in some tumour cell lines (melanoma), nearly 5-fold higher expression of GHR, as compared to other cancer cell lines, was found (32).

In studies on animal models (mice and rats), it was demonstrated that disruption of GH signalling significantly inhibited prostate carcinogenesis, and direct GH stimulation played an important role in the progression of prostatic neoplasia to malignant and invasive prostate cancer (33). It was also found that GH-deficient rats were resistant to chemical induction of mammary carcinogenesis (34). It is worth noting that in 2015, a miniature pig model for human LS was developed, which can serve as an optimal model for disorder studies (35).

All experiments indicated that lack of proper GH–IGF1-downstream pathway signal transduction protected from cancer, as occurs in patients with LS.

Laron Syndrome and New Perspectives for Cancer Therapy

Understanding the molecular mechanisms responsible for the occurrence of LS and its association with a reduced risk of cancer may help develop new strategies for oncological treatment (36). A genome-wide association study showed that the GH–IGF1 pathway is the third most important, the functioning of which is disrupted in breast cancer (37), as well as in cancer of the lung, prostate, rectum, liver, kidney and pancreas, and in sarcomas (38). Therefore, it seems that one of the potential strategies should be to block GH action or inhibit IGF1, or both of these, as occurs in patients with LS (38). In experimental, preclinical and some clinical studies, three such strategies have been tested to date: (i) treatment with antibodies affecting IGF1, (ii) administration of monoclonal antibodies targeting IGF1R, and (iii) the use of small-molecule inhibitors blocking IGF1R kinase activity (Figure 2) (12).

The group of antibodies that selectively bind to IGF1, includes MEDI-573 antibody, which reacts with IGF1 leading to blockade of its attachment to the receptor. Based on *in vitro* and *in vivo* studies on animal models, it has been shown that the use of MEDI-573 inhibited cell proliferation, inducing slowdown of tumour growth and reduction of glucose uptake by tumour cells (39). The drug had no effect on glucose tolerance. These results led to the initiation of ongoing clinical trials that include patients with breast cancer and other advanced solid tumours (40, 41).

The GH–IGF1 pathway may be also inhibited by monoclonal antibodies to IGF1R. Among them, figitumumab (CP-751.871) and dalotuzumab (MK-0646) are the most frequently used in clinical trials (42). Figitumumab was tested in patients with soft-tissue sarcomas (43), Ewing's sarcoma (43, 44) and advanced non-small cell lung cancer (45). In these trials, the antibody was administrated in combination with chemotherapy or targeted therapy (inhibitors of mTOR). The most promising results were achieved in patients with sarcoma: In 24-71% of patients, stable disease was shown after treatment with figitumumab. The highest percentage of positive responses was obtained in patients with Ewing's sarcoma (43). In contrast, in the group of patients with non-small cell lung cancer, no influence on overall and progression-free survival was recorded (45). It should be noted that treatment with this antibody caused induction of insulin resistance and thus increased secretion of GH, hyperinsulinemia and mild reversible hyperglycemia (43-45). In clinical phase I and II studies performed on a group of patients with advanced breast cancer dalotuzumab was tested

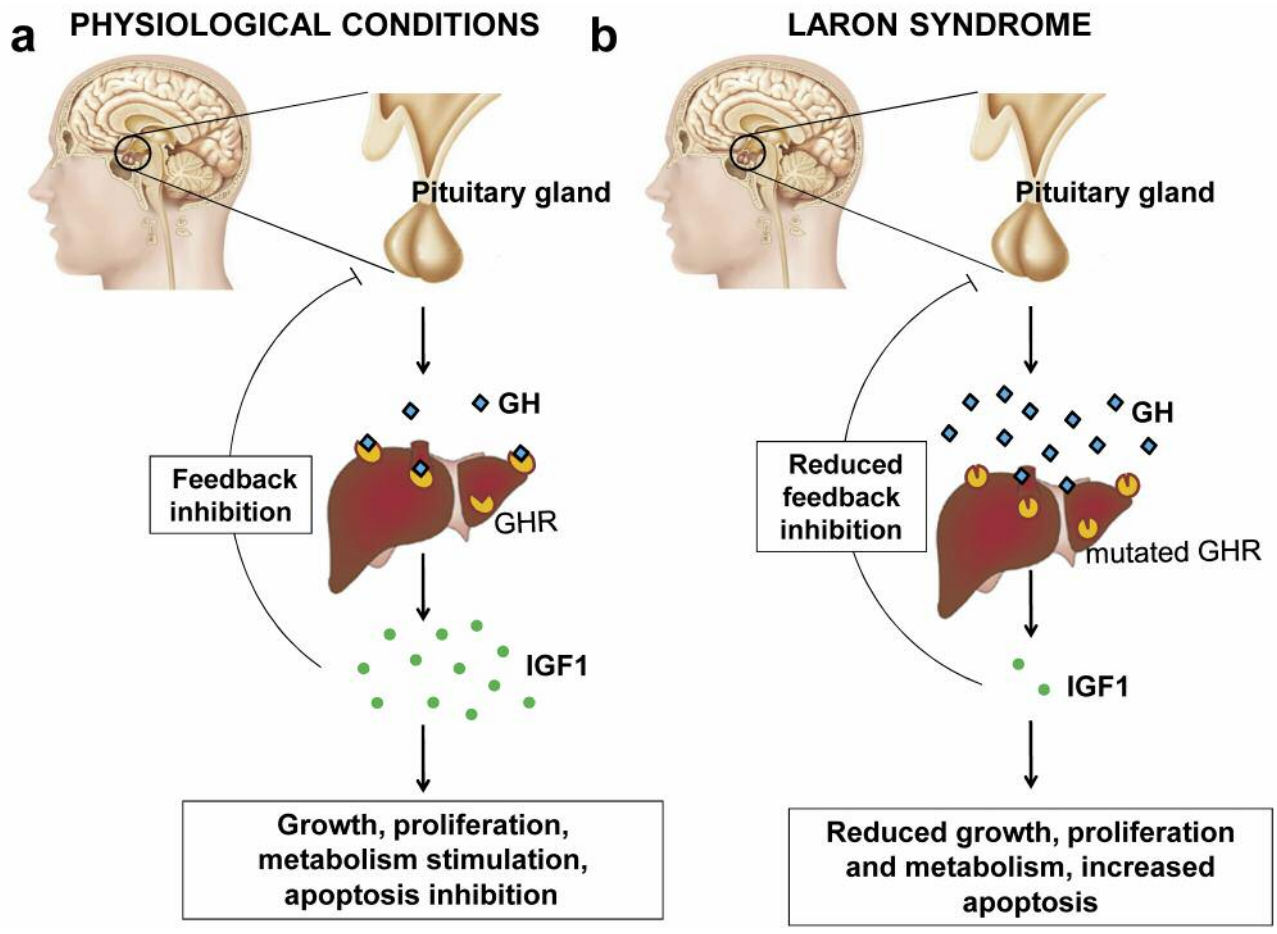

Figure 1. *Growth hormone–insulin like growth factor 1 (GH–IGF1) signal transduction in physiological conditions (a) and in patients with Laron syndrome (b). Under physiological conditions, the pituitary gland secretes GH which reaches the liver with blood and binds to membranous GH receptor (GHR). This leads to synthesis and secretion of somatomedins, mainly IGF1, acting as a negative feedback regulator of GH secretion. In patients with Laron syndrome, GH is still secreted by the pituitary gland, but cannot activate the mutated receptor, hence IGF1 synthesis is reduced. Based on modification of (11).*

in combination with temsirolimus (inhibitor of mTOR) (46), exemestane (steroidal aromatase inhibitor) (47) and fulvestran (estrogen receptor antagonist) (48). However, its administration did not significantly improve the treatment outcome in any of these studies.

Most of the currently tested small-molecule inhibitors of IGF1R kinase activity belong to the group of ATP antagonists, which compete with ATP for binding the kinase and thus block its function. This class of inhibitors includes linsitynib, for which antitumour activity was demonstrated in preclinical studies (49) and which is currently being tested in phase II clinical trials in patients with ovarian cancer (in combination with docetaxel) and non-small cell lung cancer (in combination with erlotinib) (50).

Another interesting option for cancer treatment may also be pegvisomant, a drug currently used in the treatment of acromegaly (51). Pegvisomant inhibits the binding between GH and its receptor in the liver (endocrine effect) (52) and additionally blocks direct paracrine/autocrine effect of GH in other tissues (53). This dual mechanism of action offers a unique opportunity for effective cancer therapy. In an experimental murine model, it was demonstrated that pegvisomant inhibits the growth of breast (53) and rectal tumours (54). Yin *et al*. have shown that this drug reduced the level of IGF1, but increased that of GH in serum of healthy persons (reflecting the status observed in individuals with LS) (55).

Summing up, the studies on the therapeutic potential of blocking the GH–IGF1 pathway indicate the benefits of this strategy, especially for patients with Ewing's sarcomas. The less optimistic results concerning other types of malignancies may be related not only to inefficient action of the tested

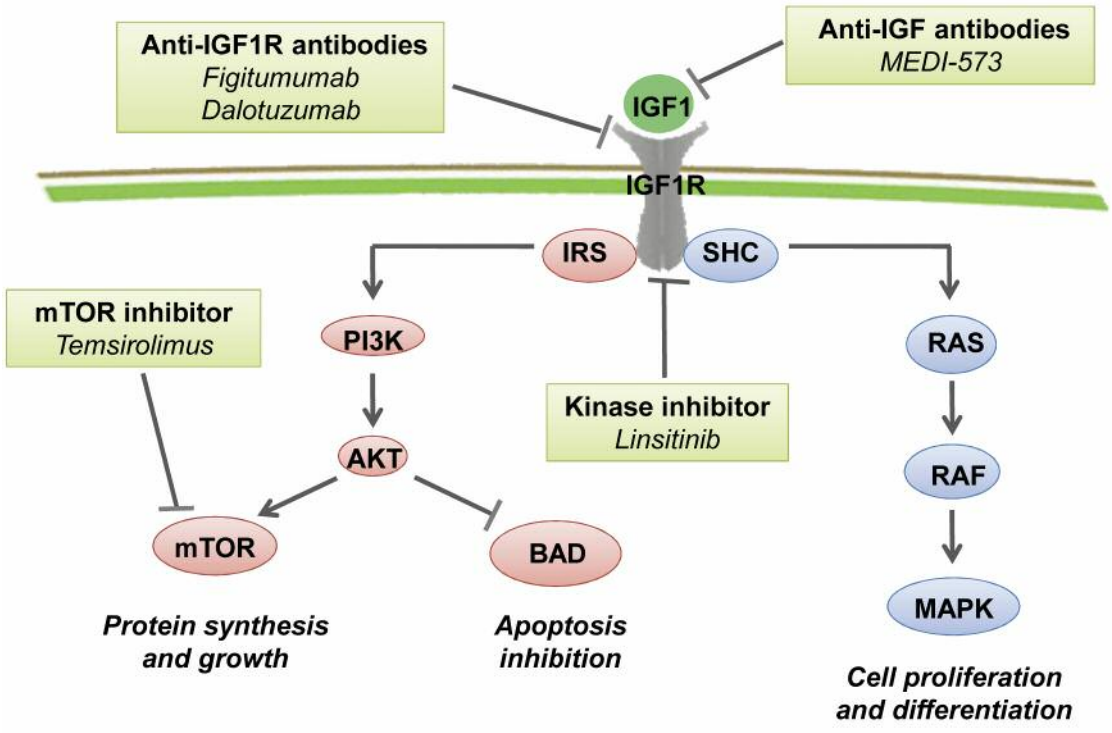

Figure 2. *Insulin-like growth factor 1 (IGF1) signalling pathway and potential agents for targeted therapy. IGF1 affects cells through binding to its receptor IGF1R. In consequence, Src homology and collagen protein (SHC) or insulin receptor substrate (IRS) (adaptor proteins) are recruited and phosphorylated, which activates rat sarcoma virus homologue/rapidly accelerated fibrosarcoma/mitogen-activated protein kinase (RAS/RAF/MAPK) and phosphatidylinositol-4,5-bisphosphate 3-kinase/protein kinase/mammalian target of rapamycin kinase (PI3K/AKT/mTOR) signalling pathways. The former determines cell proliferation and differentiation and the latter stimulates protein synthesis and blocks apoptosis (through inactivation of proapoptoptic B-cell lymphoma 2-associated death protein (BAD) protein). Potential targeted therapy agents for inhibiton of GH–IGF1 signalling pathway are shown in boxes. According to Iams and Lovly (12), own modification.*

drugs, but also to inappropriate targeting of therapy. It appears that the second of these possibilities is unlikely, keeping in mind the results of experimental studies that showed inhibition of cell proliferation and tumour growth after blocking the GH–IGF1 pathway (12, 46, 49, 51).

It should also be pointed out that there are no predictive factors for therapy inhibiting the GH–IGF1 pathway. Clinical trials carried out in patients with the same tumour types and receiving the same therapy showed that only some of them had better treatment outcomes. It seems that studies focusing on the identification of such factors should be performed at different levels of the GH–IGF1 cascade (55). This should help to increase the number of patients benefiting from the treatment.

In summary, LS is a genetically determined disease, inherited in an autosomal recessive manner. The pathogenesis of this syndrome is related to the presence of different type of mutations in the gene encoding the receptor for GH. These mutations lead to a decrease in the level of IGF1, resulting in characteristic phenotypic features such as dwarfism, abdominal obesity and characteristic facial appearance. On the other hand, individuals with LS are characterized by a low cancer risk. Therefore, the research into the molecular basis of LS may help in better understanding carcinogenesis and in the development of new oncological treatment strategies.

Conflicts of Interest

The Authors declare that they have no conflict of interest in regard to this article.

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