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Laron Syndrome- A Disorder Associated with a Reduced Risk of Cancer: A Review on the Molecular Aspects

Ksheera Karumbaiah[1], Gopenath TS[2], Raghu Nataraj[1] and Kanthesh M. Basalingappa[1*]

[*1]Division of Molecular Biology, Faculty of Life Sciences, JSS Academy of Higher Education and Research, SS Nagara, Mysuru, Karnataka, Pin code: 570015, India
[2]Division of Biotechnology, Faculty of Life Sciences, JSS Academy of Higher Education and Research, SS Nagara, Mysuru, Karnataka, Pin code: 570015, India

ABSTRACT
Laron syndrome (LS) or primary growth hormone insensitivity is a genetic disorder known for a type of dwarfism characterized by short stature, facial phenotype, obesity and unexpected high serum GH levels. The disorder is caused due to the mutation of Growth Hormone receptor (GHR) gene whose inability to synthesize IGF-I and other related molecules leads to insulin-like growth factor-1 (IGF-1) deficiency and was first described by Zvi Laron *et al.*, in 1966 as a new type of dwarfism and has garnered interest among genetics and medical fraternities where the LS patients are known to have a lower cancer risk. The review presents the baseline clinical and genetic aspects of the condition along with a broader overview of hypothesized disease presentations of possible protective mechanisms against cancer induction.

Keywords: Laron syndrome**,** Growth hormone receptor**,** Insulin-like growth factor-1**,** Dwarfism**,** Cancer protection

Introduction

Laron syndrome (LS) or Primary Growth Hormone Insensitivity is a form of genetic syndrome caused by the mutation of Growth Hormone receptor (GHR) gene leading to insulin-like growth factor-1 (IGF-1) deficiency [2]. It is also known as congenital GH insensitivity or resistance and is an autosomal recessive disease leading to defects in the post receptor pathways. Individuals with LS are unable to generate IGF-1 and the anabolic effector hormone of pituitary GH due to the defects in GH signal- intensity transmission. They also consequently fail to respond to GH of either endogenous or exogenous origin [1,3,5]. The condition characterized by Hypoglycemia, hypercholesterolemia and sleep disorders was first described by Zvi Laron*et al*., in 1966, as a new type of dwarfism with unexpected high serum GH levels and inability to synthesize IGF-I and other related molecules such as IGFBP-3. This heterogeneous condition also exhibits GH receptor deficiency, IGF-I synthetic defect, GH-GH receptor signal transduction defect, IGF-I/IGF-I receptor signal transduction defects and IGF-I receptor deficiency [4,5].

Laron syndrome has a prevalence rate of 1 in 1,000,000,and it is characterized by short stature, low GH binding protein levels, decreased IGF-1 production, normal or increased serum GH level and low IGF- 1 levels [8]. Various studies about increased GH, IGF-I secretion and cancer have found that homozygous patients with Laron syndrome and low serum IGF-I are protected from developing cancer [14]. These findings are of major scientific and clinicalrelevance.

***Corresponding Author**
kantheshmb[at]jssuni.edu.in

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Clinical Characteristics of Laron Syndrome

1. Characteristics seen during pregnancy anddelivery

A weaker movement of the fetus affected with LS is observed when compared with the normal siblings. New borns have a length of 42–46 cm which can be correlated to either hGH gene deletion or a defect in IGF-I gene [5], [19]. Birth weight is about 2500g but some new borns are weighed less than 2100g [5]. Retardation in growth is observed which might be due to due to a lower GH impact on gestational growth. Skeletal maturation and growth of organs are also compromised [4]. A study on two LS infants showed congenital dislocation of one hip joint in one of the male and mild aortic stenosis in the other. Congenital cataracts or convergent strabismus was observed in two female patients [5].

2. Phenotypic and biochemical characteristics

Among several phenotypic characteristics associated with Larson Syndrome, one of the main is dwarfism, which can be noticed from birth. Infants affected with LS will have body weight of usually about 2,500 g and a length of about 42 to 45 cm. Among adults, women reach a final height of 108-136 cm whereas men reach 116-142 cm [5]. LS is found to be more prominent in the Ecuadorian cohort, where females reach a height of 95–124 cm males reach a height between 106–141 cm [21,22]. A prominent protruding forehead with a small brain, reduction in the vertical dimension of the face, hypoplasia of mid face (figure-1) and the nasal bridge are common in affected people [4]. The head circumference is below normal which seems quite large compared to the body size and along with these features, sunset look, under development of the facial bones and saddle nose and are also found in the patients [5,20,21]. Hair is thin and silky; growth of hair and nails is slower compared to that of healthy individuals. The eyes of the patients have blue sclera which is due to the decreased thickness of connective tissue [4,5].

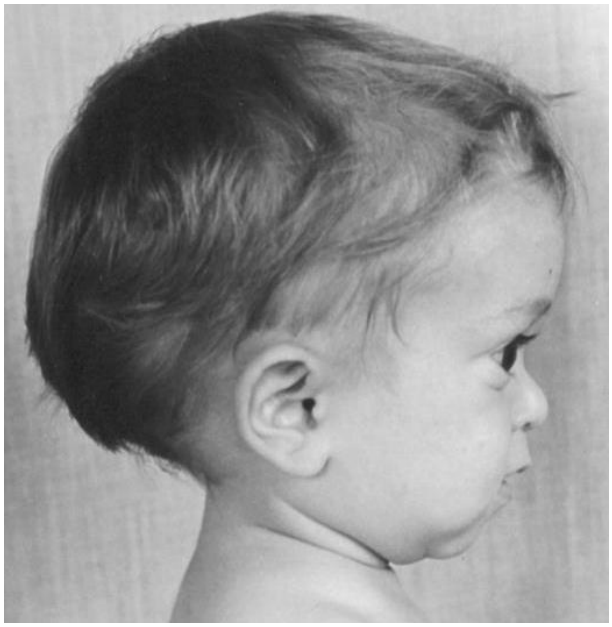

Figure 1: Typical facial appearance of a 5-yr-old boy with LS. The picture depicts a thin and silky hair, protruding forehead and saddle nose. Picture courtesy: Laron Z., 1999 [6].

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Obesity is common among young children though they eat very little and the condition becomes progressive throughout childhood and becomes excessive duringadulthood. Boys show hypogenitalism and hypogonadism [5]. Onset of teething is delayed. A very high-pitched voice is seen in childrenand even in some adult females due to a narrow oropharynx [5,20]. The axial lengths of the eye and the anterior chamber are smaller. The axial length of the globe is shorter than normal [1]. Though some of the LS patients have a long life, generally over 70, they can be noticed to have early aging signs such as thinning and wrinkling of skin [5]. Additional problems like weakness, osteoporosis, higher cholesterol and insulin levels in blood (glucose intolerance) are also seen in LS patients [23], [24]. Serum of LS patients is found to have low IGF1 and high GH levels. Even after administration of exogenous GH, increase in IGF1 is not observed. High-density lipoprotein fractions are within the normal range but low-density lipoprotein fractions and total cholesterol levels are high even in young patients. Higher serum level of prolactin can be observed in untreated patients [9].

3. Body proportions and growth

Special growth charts are used to understand the growth of the patients, and these charts are derived by comparing the length parameters of untreated patients [2]. The velocity of growth is slow. The upper and lower segment of the body is above norm for sex and age, which denotes that the limb size is relatively shorter for the size of the trunk. The patients fingers in hands and toes of feet are small, a condition called acromicria. Walking is delayed among the children due to underdevelopment of the muscular system [4], [5].

4. Sleeping disorders

Sleep disorders are common in adult patients. The upper airways are constricted due the narrow oropharynx and the patients are prone to sleep apnea due to marked obesity. Obstructive sleep apnea syndrome causes severe breathing difficulties; these patients require the use of continuous positive airway pressure to control the breathing problem [5], [20].

IGF-1 in LS

LS are an autosomal recessive rare genetic disorder which is inherited and is characterized by insensitivity to growth hormone (GH). As discussed above, this disorder is caused by defective functioning of the GH–IGF1 signaling pathway achieved by mutations of the gene encoding the growth hormone receptor (GHR) [9]. GHR is activated by GH but, is predominantly expressed in the liver. Binding of GH to GHR results in dimerization of the receptor which leads to the synthesis of somatomedin, mainly IGF1 [10]. The insulin-like growth factor 1 (IGF-1) is a polypeptide hormone with 70 amino acids (figure-2) which is involved in paracrine, endocrine, and autocrine functions. It is similar to pro insulin and also mimics the activity of insulin which stimulates uptake of glucose in the cells. Studies have shown that IGF-1 has mitogenic capabilities [4].

Normally IGF1 binds to its receptor (IGF1R) expressed on the surface of different types of cells. The mechanism involves phosphorylation of the adaptor proteins followed by the signal transmission either through RAS/RAF/MAPK or PI3K/AKT/mTOR pathways. Through these pathways cell proliferation, regulation of cell growth, metabolism and apoptosis occurs (figure-3) [11]. Apart from the above functions, IGF1 also regulates the secretion of GH through a negative feedback loop [10].

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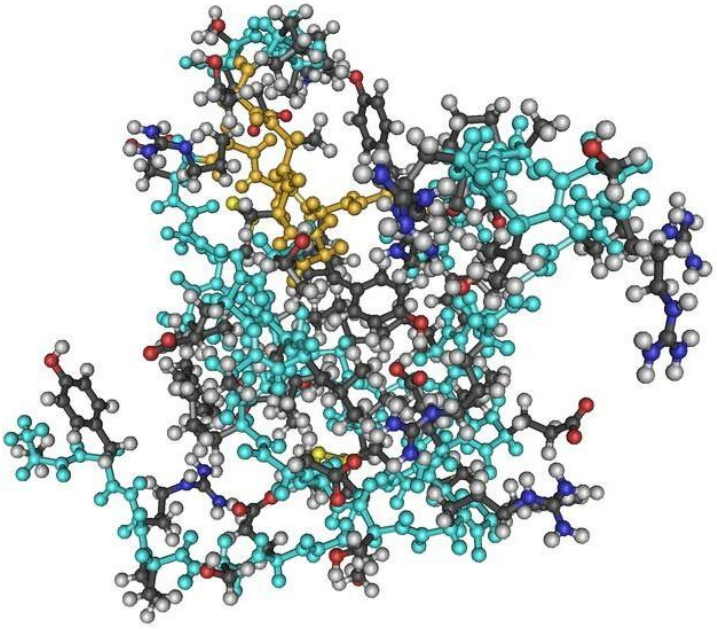

Figure 2: Insulin-like growth factor-1; Picture courtesy:https://www.ncbi.nlm.nih.gov/Structure/

But in case of LS patients, though GH is secreted by the pituitary gland and reaches the liver, it does not activate its receptor (GHR) as it is mutated [9,10,12]. LS patients are characterized by an extreme low level of insulin-like growth factors which is almost below the 0.1 percentile. Also, the patients exhibit very low levels of insulin- like growth factor binding proteins (IGFBPs), specifically that of IGFBP-3 [15]. A single gene located on the short arm of chromosome 5 (5p13-p12) encodes the growth hormone receptor. The growth hormone receptor gene undergoes a variety of homozygous point mutations which causes mutations in the extracellular domain interfering with binding of growth hormone, thereby resulting in Laron syndrome [25]. The formation of an abnormal receptor due to the mutation of GHR gene sequence leads to interruption of the JAK-STAT signaling pathway which, under normal conditions, stimulates the production of IGF-1. The deficiency of IGF1 in the cells further leads to inhibition of downstream signal transduction. Therefore IGF1 negative feedback is compromised leading to a high level of GH and low IGF1 concentration in serum are observed and these serve as diagnostic features of LS [9,15]. Among more than 70 different GHR mutations which include deletions, splice, missense, nonsense or frame shift mutations reported in LS [9,10,12]. E180 splice mutation observed in exon 6 is the most prevalent type of GHR defect [7]. In-frame deletion of eight amino acids within the extracellular domain occurs through substitution of adenine for guanine which disrupts the exon splicing [13].

Sometimes GH concentration is found to be below normal to elevated in spite of low levels of serum IGF1, which might be due to the following conditions such as: (a) Gene defects in GH receptor (GH-R), (b) Deletion of IGF1 gene, (c) Defects in GH-releasing hormone-receptor (GHRH-R) gene, (d) Post-GH-R signaling defects (e.g. STAT5 defects) and (e) Deletion of GH gene [16,17,18,19].

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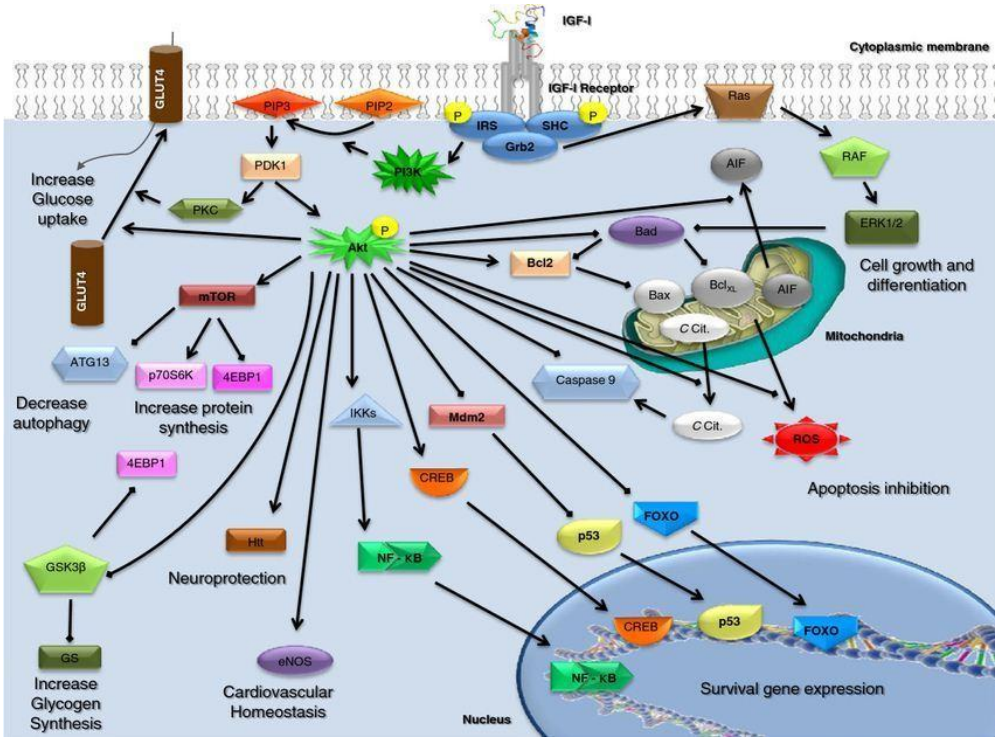

Figure 3: IGF-I receptor pathway; Picture courtesy: J.E. Puche*et al*., 2012 [4]

LS Response to Cancer

Cancer cells have the ability of self proliferate, insensitiveness to growth inhibitory signals, escape apoptosis and angiogenesis capacity, which distinguish them from normal cells [32]. Many causes of cancer are known but the most common causes include genetic predisposition, infections agents and gene-environment interactions. The GH and IGF-I are among the risk factors. Interestingly, it is found that homozygous patients with Laron syndrome who have low to undetectable serum IGF-I levels are protected from developing cancer. Such patients who were treated with IGF-I to enhance their linear growth were also found to be immune to cancer [14]. It is worthwhile to mention that patients with breast cancer, prostate cancer, and other oncological history are found to have increased level of GH, IGF1 and overexpression of its receptor reported in earlier studies [9], [33]. GH–IGF1 signalling and the main pathways involved in the regulation of cell growth, differentiation, proliferation and apoptosis (RAS/RAF/MAPK and PI3K/AKT/mTOR) are said to increase the cancer risk [33]. Growth factors can help in increasing the risk of mutation but do not directly lead to malignant transformation; here time for DNA repair is reduced during rapid progression of the cell cycle which might result in cancer [35]. Possible signaling pathways and mechanisms found in LS patients related to these growth hormones and protection from cancer development are discussed below.

1. Congenital IGF1 Deficiency

Many epidemiological studies have proved that high circulating IGF1 dosages are linked to cancer risk. As discussed earlier, IGF1R is overexpressed in malignantly transformed cells and it shows strong proliferative and anti-apoptotic activity. An increase in IGF1R concentrations in cancer cells help them to rapidly proliferate and progress through the cell cycle [26], [27]. But, in LS cells, total and phosphorylated levels of IGF1R have been found to be decreased drastically [42]. In an

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epidemiological study involving 538 congenital IGF1 deficient patients, none of the patients with LS were found to have cancer of any type except one. Close family members of LS patients reported eighteen cases of cancer, while another twenty five members among further relatives were reported for tumors [27].

In another study conducted in Ecuador, LS patients were investigated for more than thirty years and most of the deaths were not related to cancer [28]. These reports on cancer protection were further corroborated using GH-R/GH-binding protein knock-out mouse models [29,30]. Cancer-protecting pathways, including apoptosis and autophagy are activated in LS due to lack of exposure to IGF1 and the fact that immune deficiency is associated with congenital IGF1 deficiency proves that cancer protection in LS is mainly due to a reduction in events that leads to initiation of tumor and is not related to improved immune surveillance [31]. *In vitro* studies showed that when serum from LS patients is added to hydrogen peroxide treated human mammary epithelial cells, reduced DNA breaks and increased apoptosis is observed [28]. Further analysis confirmed an up regulation of superoxide dismutase gene and a decrease in expression of RAS, protein kinase A, and mTOR genes. These changes help in protecting the cells from mutagens. All these experiments show that defects in downstream signaling cascades of GH–IGF1 pathway provide protection from cancer in cells in vitro [34].

2. Differential expression of genes and signaling pathways

Epstein-Bar virus (EBV) immortalized lymphoblastoid subjected to genome-wide profiling analyses was conducted in one of the studies by Werner H *et al*., where they discovered that genes are expressed differentially in LS individuals when compared to controls (Table-1) and, they identified signaling pathways that are linked to cancer protection [26]. Some experiments using One-way ANOVA and Principal component analysis (PCA) revealed a list of differentially expressed genes and signaling pathways. Some of these signaling pathways include G-protein signaling cascade, metabolic pathways, cell adhesion, cell motility and migration, Jak-STAT signaling and apoptosis. LS and healthy cells exhibiteddifferences in their proliferative capacities, cell cycle and autophagy [26].

While one of the important functions of autophagy is maintaining homeostasis [37], [38], it also plays a major role in oxidative stress and tumor genesis. Autophagic markers like LC3 and p62 are differentially expressed in LS cells suggesting that this feature might provide protection against cancer [36].

OR5H1	VCAN	ASB2	ZYG11A
GPC5	SELL	GTSF1	CDYL2
OR5H7P	F13A1	IGJ	TTC39C
OR5H6	RGNEF	INPP5F	TRERF1
OR5K3	TANC1	ADTRP	GPR160
OR5H2	CD244	CAPN2	FAMI29C
OR5K4	CCNA1	DNAJC12	CDKL5
OR5H14	SERPINB2	TXNIP	ARHGAP44
ITGA5	NPNT	UGT2B15	UGT2B17

Table 1: Genes differentially expressed in LS individualsCourtesy: Werner H *et al*., 2019 [26].

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3. Expression of IGBPs (IGF bindingproteins)

Lymphoblastoid derived from LS patients show differential expression of IGFBPs. While there was no difference in IGFBP-4 mRNA levels in LS lymphoblastoid and healthy cells, IGFBP-3 mRNA levels were found to be increased in LS cells. However, mRNA levels of IGFBP-2, IGFBP-5, and IGFBP-6 were found decreased in LS compared to healthy control cells. The protein levels also correlated to these differences in mRNA levels [2]. IGFBP-2 and IGFBP-3 are found to have opposite functions, where the former is pro-tumorigenic, leading to an increase in T-cell proliferation, while the latter is an anti-oncogene reported in a number of tumors [26,39]. Likewise, IGFBP-5 is found to promote T-cell migration while IGFBP-6 acts as a chemotactic agent for T-cells. Therefore, protective activity against cancer is directly correlated to the differential expressions of these IGFBPs [26].

4. Thioredoxin-Interacting Protein (TXNIP)

The gene encoding thioredoxin-interacting protein (TXNIP) is found to be stimulated by vitamin D3 in leukemia. TXNIP acts as a tumor suppressor but in cancer cells they are frequently silenced by genetic or epigenetic mechanisms. The levels of TXNIP mRNA have been reported to be more than 2-fold higher in cells of LS patients compared to healthy cells [26]. At the transcriptional level,TXNIP gene expression is mediated by the effect of IGF1. TXNIP expression is increased under oxidative and glucose stress but attenuated when supplemented with IGF1. Thus enhanced TXNIP expression in LS might be responsible for tumor protection [26,40].

5. Expression of Oncogenes and Anti-Oncogenes

In LS patients gene transcripts like cyclin A1, cyclin D1, serpin B2, versican, and zinc-finger are found to be in low levels and are found to be linked to progression of cell cycle and oncogenic transformations. On the other hand, tumor suppressors, or anti-oncogenes are expressed in higher levels, and they are associated with activation of cell protection mechanisms. Low endocrine levels of IGF1 in LS patient's up regulate genes that provide protection from malignant transformation and at the same time down regulate genes that are related to cell proliferation and mitogenesisin order to control initiation of tumor [26]. On another note, when we look at regulation of IGF1R gene, LS cells showed a marked reduction of genes that are associated with transcriptional activation (i.e. transcription factor SP1) [43]. Studies on most types of cancers reported an over expression of the IGF1R gene [41] but Zinc finger protein SP1, along with its role in IGF1R gene activation, plays a major role in oncogenesis and cellular transformation. Reduced levels of SP1 in LS patients suppress the activity of IGF1R sand provide protection from cancer development [36].

CONCLUSION

Laron Syndrome is an inherited, autosomal recessive and genetically determined disorder. The syndrome is characterized by the presence of different type of mutations in the gene encoding the receptor for GH. These mutations further leads to a decrease in the level of IGF1 resulting in some of the phenotypic and biochemical characteristic such as dwarfism, abdominal obesity, high levels of serum GH, inefficiency to produce IGF-I and characteristic facial appearance. Though LS is characterized by the above mentioned defects, an interesting fact is that individuals with LS have a low risk of cancer. Many genes and signaling pathways function differently in LS which have been studied and reviewed to be the reason for their low cancer risk. Further understanding of the molecular signaling pathways of LS, particularly in relation to cancer inhibition studies are inevitable which might lead to development of new treatment strategies for cancer.

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