THEMATIC REVIEW

Congenital IGF-1 deficiency protects from cancer: lessons from Laron syndrome

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This paper is part of a themed collection on the role of Growth Hormone in Endocrine Cancers. The Guest Editor for this collection was John Kopchick, Ohio University, USA.

Abstract

Many clinical and experimental studies have implicated the growth hormone (GH)–insulin-like growth factor (IGF-1) axis with the progression of cancer. The epidemiological finding that patients with Laron syndrome (LS), the best-characterized disease under the spectrum of congenital IGF-1 deficiencies, do not develop cancer is of major scientific and translational relevance. The evasion of LS patients from cancer emphasizes the central role of the GH–IGF-1 system in cancer biology. To identify genes that are differentially expressed in LS and that might provide a biological foundation for cancer protection, we have recently conducted genome-wide profiling of LS patients and normal controls. Analyses were performed on immortalized lymphoblastoid cell lines derived from individual patients. Bioinformatic analyses identified a series of genes that are either over- or under-represented in LS. Differential expression was demonstrated in a number of gene families, including cell cycle, metabolic control, cytokine–cytokine receptor interaction, Jak-STAT and PI3K-AKT signaling, etc. Major differences between LS and controls were also noticed in pathways associated with cell cycle distribution, apoptosis, and autophagy. The identification of novel downstream targets of the GH–IGF-1 network highlights the biological complexity of this hormonal system and sheds light on previously unrecognized mechanistic aspects associated with GH–IGF-1 action in the cancer cell.

Key Words

- Laron syndrome
- insulin-like growth factor-1 (IGF-1)
- IGF-1 deficiency
- growth hormone (GH)
- GH receptor (GHR)
- growth hormone insensitivity
- cancer protection

Endocrine-Related Cancer (2023) **30**, **e220394**

The growth hormone–insulin-like growth factor endocrine system

The growth hormone (GH)–insulin-like growth factor-1 (IGF-1) endocrine system plays an essential role in the regulation of multiple metabolic and growth processes throughout life (LeRoith *et al.* 2001, Yakar & Adamo 2012). While the role of GH in physiological growth, particularly during puberty, has been recognized early on following the discovery and initial characterization of the hormone, the involvement of the GH axis in malignant growth became evident only later (Holly *et al.* 1999, Chhabra *et al.* 2011, Boguszewski & Boguszewski 2019). The controversial question whether GH acts in a direct fashion or, alternatively, that all (or most) of its growth-promoting actions are mediated via IGF-1 has not yet been resolved. Technological developments over the past two decades are having a major impact on our understanding of fundamental aspects of the biology of the GH–IGF-1 system. These advances include the use of modern high-throughput platforms, mainly

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genomic and proteomic approaches, as well as robust bioinformatic capabilities (Domené *et al*. 2021). Given that the GH–IGF-1 system, as described below, emerged as a promising therapeutic target in oncology, the identification of biological networks linked to GH–IGF-1 action (*GH–IGF-1 signatures*) is of high translational relevance (Werner & Bruchim 2010, Sarfstein *et al*. 2020*b*). The present review highlights new paradigms that stem from analyses of Laron syndrome (LS) patients, a prototypical case of congenital IGF-1 deficiency. The identification of novel GH–IGF-1 downstream targets reflects the key role of this axis in cancer as well as the complexity of the mechanisms responsible for cancer protection.

Classification of congenital IGF-1 deficiencies

Prenatal IGF-1 expression is GH-independent though it becomes dependent on GH secretion shortly before birth (Klammt *et al*. 2008). Hepatic IGF-1 biosynthesis remains dependent on hypophysial GH output throughout postnatal life. Congenital IGF-1 deficiencies are classically defined by low circulating IGF-1 concentrations but normal to elevated GH values (Rosenfeld 2003, 2006, Domené & Domené 2018). This cluster of diseases results from a number of molecular defects mostly localized within the hypothalamic-pituitary axis. These conditions include the following:

1. GH-releasing hormone-receptor (*GHRH-R*) defect (Wajnrajch *et al*. 1996);
2. *GH* gene deletion (isolated GH deficiency, IGHD) (Phillips *et al*. 1981, Rosenfeld 2005);
3. GH receptor (*GHR*) gene deletion or mutation (Laron syndrome, LS) (Amselem *et al*. 1989, Godowski *et al*. 1989);
4. *IGF-1* gene deletion (Woods *et al*. 1996);
5. IGF-1 receptor gene mutation (Abuzzahab *et al*. 2003, Solomon-Zemler *et al*. 2017, Walenkamp *et al*. 2019);
6. Defects of post-GHR signaling (e.g. *STAT5* mutation) (Kofoed *et al*. 2003);
7. Disorders associated with reduced IGF-1 stability (e.g. acid-labile subunit, ALS, mutation (Domené *et al*. 2004); and metalloproteinase pregnancy associated plasma protein A2, PAPP-A2, defect (Dauber *et al*. 2016, Argente *et al*. 2017)).

All of the above conditions are regarded as very rare genetic disorders. The best characterized entity under the spectrum of the congenital IGF-1 deficiencies is Laron syndrome.

Laron syndrome (OMIM#262500): historical aspects

The report of a so far unknown recessively inherited endocrinopathy, described by Laron *et al.* in 1966, paved the way for extensive genetic, clinical and experimental analyses over more than 55 years (Laron *et al*. 1966). In an era in which receptors were yet to be discovered and somatomedin was developing its biochemical and physiological identity, the identification of this new clinical entity had a major impact on the early drawing of endocrine blueprints and, moreover, on our understanding of the clinical implications of pathological disruption of the GH–IGF-1 network. The first patients were observed in 1958 in children from newly immigrant consanguineous Jewish families from Yemen (Laron *et al*. 1966, 1968). These patients had distinct clinical features such as dwarfism, acromicria (small extremities), small facies resulting in frontal basing, saddle nose, retarded sexual development and obesity (Fig. 1). While, in general, these patients resembled children with GH deficiency, the development of a radioimmunoassay for GH in the 1960s revealed very high levels of the hormone in the patient's blood (Glick *et al*. 1963). To assess whether the disease was associated with a biologically inactive or modified GH species, immunological analyses were

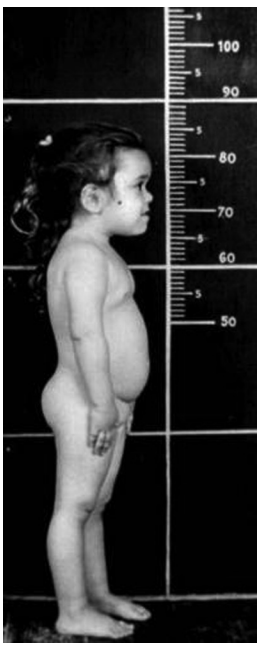

Figure 1
Typical appearance of a 7-year-old girl with Laron syndrome. Note protruding forehead, dwarfism and obesity.

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conducted. These studies proved that the structure of the circulating GH molecule was normal (Eshet *et al.* 1973, Eshet *et al.* 1985).

Administration of exogenous GH to patients caused no metabolic effects, suggesting resistance to the hormone (Laron *et al.* 1971). The conclusive proof of GH insensitivity was provided by binding assays performed on liver biopsies derived from two patients. These studies, using iodinated GH, showed that, *in vitro*, GH did not bind to liver membranes (Eshet *et al.* 1984). The hypothesis that a structural defect in the GHR molecule was linked to the etiology of the disease was confirmed 20 years later with the cloning of the *GHR* gene (Leung *et al.* 1987). Genetic analyses of LS subjects identified various exon deletions and mutations in this gene (Amselem *et al.* 1989, Godowski *et al.* 1989).

After our original publications, LS patients were reported in different parts of the world, all of them belonging to consanguineous families (Rosenfeld *et al.* 1994, Iida *et al.* 1998). The vast majority of the patients were from the Mediterranean and South Asian areas (Laron 2004). In addition, a large number of patients were diagnosed in South and Central America (Rosenbloom *et al.* 1998, Jorge *et al.* 2005, Rosenbloom & Guevara-Aguirre 2008). Of historical interest, this last group of patients is believed to originate from Jews fleeing the Spanish Inquisition in the 15th century (Rosenbloom & Guevara-Aguirre 2008, Gonçalves *et al.* 2014). This cohort is described by Guevara-Aguirre and colleagues in another article of this Themed Collection (Guevara-Aguirre *et al.* 2023). Genetic analyses of patients with LS identified over 70 types of mutation in the *GHR* gene (Shevah & Laron 2006, 2011). Despite the variability in these molecular events, the phenotypes observed were essentially identical or very similar. Finally, extended follow-up of a large cohort of IGF-1-treated and non-treated patients enabled us to study the clinical and laboratory changes induced by the long-standing IGF-1 deficiency (Laron *et al* 2017). The linkage between diminished IGF-1 concentrations and protection from cancer is described in the next section.

Link between congenital IGF-1-deficient patients and cancer protection

Epidemiological studies conducted over the past 30 years have established a linkage between high IGF-1 concentrations and cancer risk (Hankinson *et al.* 1998, Giovannucci *et al.* 2000, Pollak *et al.* 2004, Renehan *et al.* 2004, Clayton *et al.* 2011). Specifically, studies have demonstrated that elevated endocrine IGF-1 levels confer an augmented risk for breast, prostate, lung, sarcoma and colorectal cancer. These reports highlighted the cardinal role of the GH–IGF-1 axis in cancer etiology. Therefore, it was of basic and clinical interest to investigate the impact of lifelong IGF-1 deficiency on cancer incidence. Our initial (and surprising) observations were that adult LS patients did not have any malignancy (up to the age of 85) (Shevah & Laron 2007), even when treated for several years with IGF-1 in their childhood. These observations were extended to a larger group of patients (Steuerman *et al.* 2011).

The cohort examined included 538 patients, divided into the following categories: (1) LS (n = 230 patients); (2) congenital IGHD (n = 116 patients); (3) *GHRH-R* mutations (n = 79 patients); and (4) congenital multiple pituitary hormone deficiency (cMPHD) (n = 113 patients). The analyses revealed that none of the 230 LS patients had a history of cancer, despite the fact that 66 of them had been treated with IGF-1 and 2 had received hGH as well. Eighteen (8.3%) instances of malignancy were reported among 218 first-degree relatives, 25 (22.1%) cases were reported in 113 further relatives, and 5 (5.8%) tumors were reported in 86 siblings of LS patients (Table 1). Despite the relatively small size of our cohort, differences between patients and controls were regarded as statistically significant. Studies were conducted by replying to a questionnaire that was filled in by the primary care physician.

Reduced cancer incidences were also observed in the other conditions. Thus, out of the 116 patients with cIGHD, only one boy who suffered from xeroderma pigmentosum had a basal cell carcinoma

Table 1 Epidemiological analysis of cancer incidence in patients with Laron syndrome.

	Total number (n)	**Malignancies** (events)	**Prevalence of malignancy** (%)	***P*-value** (vsLS)
Laron syndrome	230	0	0	–
First-degree relatives	218	18	8.3	<0.001
Further relatives	113	25	22.1	<0.001
Siblings only	86	5	5.8	0.005

Cancer incidence in LS patients and relatives was assessed by replying to a questionnaire that was filled in by the primary care physician. Modified from Steuerman *et al.* 2011.

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(Steuerman *et al.* 2011). Out of the 79 patients with GHRH-R mutations 3 had cancer and so had 3 out of 113 patients with cMPHD. On the other hand, out of 752 first-degree relatives, 30 instances of cancer were reported in 26 individuals. Out of 131 further relatives, 30 reported 31 instances of cancer. The majority of tumors were in lung, breast and prostate, followed by colon and gastric cancer. Even secretion of very small amounts of GH, observed in several patients with multiple pituitary hormone deficiencies, did not offer protection from cancer in patients with incomplete GHRH deficiency (Marinho *et al.* 2018). Given that congenital IGF-1 deficiencies are very rare conditions, the number of patients included in these epidemiological analyses represents a major portion of the entire worldwide population of the diseases.

Reports of protection from cancer were also reported by Guevara-Aguirre and colleagues in the Ecuadorian cohort of LS patients (Guevara-Aguirre *et al.* 2011). The discovery that LS patients are protected from cancer is of major translational relevance (Laron *et al.* 2017). The interpretation of data validates the concept that the GH–IGF-1 axis has a key role in predisposing progenitor and somatic cells to transformation. Conversely, IGF-1 deficiency might confer protection against the future development of a tumor.

Genomic analyses of Laron syndrome patients

To facilitate the study of the molecular genetic mechanisms of cancer protection, we established a bank of immortalized lymphoblastoid cells from our LS patients and relatives. Lymphocytes were immortalized by infection with the Epstein-Barr virus and are maintained at the National Laboratory for the Genetics of Israeli Populations (Tel Aviv University, Israel).

To identify differentially expressed genes in LS patients in comparison to healthy controls, a genome-wide profiling analysis was conducted. For this purpose, RNA obtained from lymphoblastoids derived from four female LS patients and four controls of the same age range (LS, 44.25 ± 6.08 years; controls, 51.75 ± 11.3 years; mean ± S.D.; *P*-value = 0.29) and ethnic origin (Iraq, Iran, Yemen) was used. A list of differentially expressed genes was created by means of one-way ANOVA using Partek Genomics Suite. Thirty-nine annotated genes that were differentially expressed in LS patients were identified (with a *P*-value of <0.05 and fold-change difference cutoff >|2|) (Lapkina-Gendler *et al.* 2016, Werner *et al.* 2017, 2019). A partial list of genes that were either over- or underrepresented in LS and that may explain cancer evasion is presented in Table 2.

Functional analyses were conducted to find co-expressed genes sharing the same pathways. Analyses provide evidence of a number of shared pathways, including cell adhesion, G-proteins, cell migration and motility, immune response, Jak-STAT signaling, apoptosis and metabolic pathways (Table 3). For the most part, genes involved in the control of cell cycle, motility, growth and differentiation were downregulated in LS-derived cell lines compared to controls. These genes include, among others, *cyclin A1*, *cyclin D1*, *serpin B2*, *versican* and *transcription factor Sp1*. The implication of reduced expression of this group of genes on the proliferative properties of LS cells is described below. On the other hand, profiling identified high expression of a number of metabolic genes, including genes involved in mitochondrial redox regulation and genes responsible for protection from toxic xenobiotic metabolites.

LS cells display enhanced protection from oxidative and genotoxic insults

Genomic and bioinformatic analyses identified the uridine 5′-diphosphate-glucuronosyltransferase (UGT) gene family as the top upregulated genes in LS cells. Specifically, the levels of UGT2B15 and UGT2B17 mRNAs

Table 2 Selected differentially regulated genes in LS.

Genes upregulated in LS	Biological role
UDP glucuronosyltransferase 2 family	Elimination of xenobiotic metabolites
G-protein-coupled receptor	Cell signaling
Thioredoxin-interacting protein	Mitochondrial control of redox reactions
ZYG11A	Cell cycle regulation
CAPN2	Extracellular matrix disassembly
Genes downregulated in LS	**Biological role**
Cyclin A1	Cell cycle regulation
AKT3	Apoptosis
Transcription factor Sp1	Gene regulation
Olfactory receptor	Detection of odor molecules
Nephronectin	Cell adhesion
Serpin B2	Apoptosis and proliferation
Vesican	Extracellular matrix proteoglycan

Genomic and bioinformatic analyses identified families of genes that are differentially expressed in LS compared to controls. A significant portion of these genes were not previously linked to the IGF1 signaling pathway.

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Table 3 Functional analysis of differentially represented signaling pathways in LS.

Functional categories	Percentage of genes (%)
G-protein-coupled receptor signaling pathways	17
Metabolic pathways	15
Cell adhesion	13
Immune response	12
Cell migration and motility	9
Pathways in cancer	7
Regulation of cytokine production	6
Efg-like domain genes	6
Toll-like receptor signaling pathway	5
Jak-STAT signaling pathways	4
Apoptosis	3
Metabolism of xenobiotics by cytochrome P450	3

Functional categories of differentially expressed genes were identified using the *David* and *WebGestalt* platforms.

were ~7- and 11-fold higher in LS patients than in healthy controls, respectively (Lapkina-Gendler *et al*. 2016). UGT constitutes a superfamily of enzymes involved in drug detoxification in the mammalian liver (Grant *et al*. 2017). The UGT enzymes are of high importance in the conjugation and subsequent elimination of potentially toxic xenobiotic compounds (Bélanger *et al*. 2003, Chouinard *et al*. 2007). These enzymes display activity toward several classes of xenobiotic substrates, including phenolic compounds, flavonoids, antraquinones and a number of drugs and their hydroxylated metabolites (Fujiwara *et al*. 2016). The UGT enzymes inactivate substrates by addition of the hydrophilic glucuronyl moiety to acceptor molecules (Rowland *et al*. 2013). As a result, the polar metabolites can no longer interact with their receptors, leading to metabolite excretion. This elimination is facilitated by an increase in water solubility. The UGT2B15 and UGT2B17 enzymes display substrate specificity for a group of androgens, including testosterone, dihydrotestosterone (DHT) and DHT metabolites (Turgeon *et al*. 2000, 2001).

Consistent with its high level of expression in LS, *UGT2B15* gene expression was negatively regulated by IGF-1 and insulin in endometrial and breast cancer cells containing a wild-type p53 gene. The fact that *UGT2B15* gene expression was markedly reduced in uterine and breast cancer cell lines expressing a mutant p53 indicates that the expression and, probably, the action of *UGT2B15* require a functional p53 pathway. Given the fact that the *UGT2B15* and *UGT2B17* genes encode for enzymes responsible for the conversion of endobiotic and xenobiotic substances into excretable metabolites, our results imply that increased UGT2B15/17 levels in LS might confer upon cells a protective effect against oxidative and, potentially, genotoxic damage (Sarfstein *et al*. 2022). This protective role of the UGT enzymes is expected to translate into a broad 'shield' against malignant transformation.

TXNIP, a mitochondrial redox regulatory protein, is highly expressed in LS

Thioredoxin-interacting protein (TXNIP), also known as vitamin D3-upregulated protein-1 (Chen & DeLuca 1994) or thioredoxin-binding protein-2 (Nishiyama *et al*. 1999), plays a central role in a number of cellular processes, including metabolism, growth, pyroptosis and apoptosis (Takeuchi *et al*. 2000, Goldberg *et al*. 2003, Aitken *et al*. 2004, Patwari *et al*. 2006). TXNIP binds to the catalytic active center of reduced thioredoxin (TRX) and inhibits its expression and activity (Junn *et al*. 2000, Shah *et al*. 2013). TXNIP has a critical role in redox regulation and, in addition, regulates cell metabolism by inhibiting glucose uptake (Chutkow *et al*. 2008, Zhang *et al*. 2019). Genomic analyses identified *TXNIP* as one of the top upregulated genes in LS (Lapkina-Gendler *et al*. 2016, Nagaraj *et al*. 2018).

Consistent with its elevated expression in LS, IGF-1 and insulin inhibited TXNIP mRNA and protein levels in a number of cultured cell lines. Animal studies using GHRKO (*Laron*) mouse corroborated the *in vitro* data (Yakar *et al*. 2005). Transfection assays indicate that the negative effect of IGF-1 on *TXNIP* gene expression was mediated at the transcription level. In addition, TXNIP was able to act on its own promoter, leading to *TXNIP* autoregulation. Given the interplay between TRX and TXNIP in regulation of adipogenesis, it is plausible that this autoregulatory loop may be of importance in adipocyte control.

TXNIP has been shown to function as a tumor suppressor that is often silenced in cancer cells

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(Han *et al*. 2003, Minn *et al*. 2005). Given the fact that patients with LS are subject to lifelong low IGF-1, it is conceivable that elevated TXNIP levels in LS result from the relaxation of inhibitory control by insufficient IGF-1. Studies reported that TXNIP provides an integration point for both short- and long-term metabolic and signaling information, permitting the appropriate types and levels of cellular response to glucose availability and demand (Waldhart *et al*. 2017). Of interest, LS cells display protection from oxidative stress (Lapkina-Gendler *et al*. 2016). Hence, it is reasonable to assume that enhanced TXNIP levels in LS might be responsible for protection from oxidative stress and, in turn, may account for cancer protection in this pathology.

Identification of olfactory receptor genes as targets for IGF-1 action

Comprehensive profiling of LS patients revealed that ~17% of the genes shown to be differentially represented in LS were members of the G-protein-coupled receptor (GPCR) superfamily. A particular member of this family, the olfactory receptor 5 subfamily H member 2 (*OR5H2*), was the top downregulated gene in LS, its expression level being 5.8-fold lower than in controls ($P=0.0018$) (Lapkina-Gendler *et al*. 2016, Shibel *et al*. 2021).

Olfactory receptors (ORs) are a large family of GPCRs, including ~380 functional genes (Antunes & Simoes de Souza 2016). ORs are predominantly located in the olfactory epithelium; however, a large number of ORs are ectopically expressed in multiple tissues and organs, including the testes, lung, intestine, skin, heart and blood (Massberg & Hatt 2018). Ectopic ORs participate in multiple physiological processes such as regulation of blood pressure, glucose homeostasis, etc. (Chen *et al*. 2018). In addition, ORs play important roles in certain pathologies, including cancer, and have been validated as biomarkers in prostate tumors (Weng *et al*. 2006, Xu *et al*. 2006, Cui *et al*. 2013, Giandomenico *et al*. 2013, Morita *et al*. 2016). Furthermore, specific ORs were correlated with a series of breast cancer features (Masjedi *et al*. 2019).

Based on our genomic findings, we postulated that *OR5H2* expression is under positive IGF-1 regulation. This hypothesis was confirmed by *in vitro* experiments showing that IGF-1 stimulated *OR5H2* mRNA levels by 4.2–7.3-fold in two endometrial cancer cell lines. Enhanced mRNA values were associated with corresponding changes in *OR5H2* protein levels. Further corroboration of a role of *OR5H2* as a target for positive regulation by IGF-1 was provided by animal studies showing that olfr196 (the mouse ortholog of OR5H2) mRNA levels were markedly reduced in kidney and ovaries of *Laron* mice. In summary, our data identified a previously unrecognized link between the IGF-1 axis and a family of olfactory receptors. *OR5H2* emerged as a new target for positive regulation by IGF-1, with potential relevance in cancer biology.

LS cells express reduced levels of nephronectin, a cancer-related matrix protein

Nephronectin (NPNT) is an intracellular and secreted extracellular matrix protein with important roles in kidney development (Brandenberger *et al*. 2001, Linton *et al*. 2007). The NPNT protein contains several common structural determinants, including a secretory signal peptide, EGF-like domains, compositional bias domains and an RGD motif (Sun *et al*. 2017). NPNT is also involved in osteoblast differentiation and mineralization as well as osteogenic angiogenesis. NPNT promotes phosphorylation of p38 MAPK with ensuing increase in cell viability (Toraskar *et al*. 2018). Little information is available on the mechanisms of action of NPNT as well as on its molecular interactors. However, NPNT has been shown to interact with α8β1 integrin through the central linker segment. DNA microarray analyses revealed that NPNT levels were reduced by ~3-fold in LS-derived cells compared to controls (Lapkina-Gendler *et al*. 2016). Consistent with this finding, we demonstrated that IGF-1 stimulates NPNT expression in LS cells and various cancer cell lines. In addition, we provided evidence that NPNT silencing results in diminished activation of the AKT and ERK1/2 pathways, with ensuing decreases in cellular proliferation (Sarfstein *et al*. 2020*a*).

The role of NPNT in human cancer has been the focus of increasing interest in recent years (Sun *et al*. 2017). NPNT expression correlated with poor prognosis in breast cancer and was shown to promote metastasis via its integrin-binding motif (Steigedal *et al*. 2018). Genomic analysis of cell lines derived from a mouse model of breast cancer showed that high levels of NPNT are associated with metastatic tumors (Eckhardt *et al*. 2005). On the other hand, a decrease in NPNT expression by RNA interference inhibited spontaneous metastasis. Furthermore, NPNT expression was reduced or lost in a number of melanoma cell lines (Kuphal *et al*. 2008). Given the role of NPNT in cancer development, we postulated

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that suppression of NPNT expression in LS might be linked to the lifelong protection from tumors in this condition. The identification of NPNT as a new downstream target for IGF-1 action sheds light on potentially novel mechanistic aspects associated with the IGF-1 signaling pathway.

The LS phenotype is associated with reduced proliferation and altered cell cycle dynamics

The impact of differential gene expression in LS on biological parameters was examined using a variety of methods including proliferation, cell cycle, apoptosis and autophagy measurements. In particular, it was of importance to assess the following questions: (1) Is the proliferative potential of LS cells affected? (2) Are the different phases of the cell cycle affected in LS? (3) To what extent are the apoptotic and autophagic processes altered in LS? (Werner *et al.* 2020).

Proliferation assays showed that the propagation rate of lymphoblastoid cells derived from patients was decreased by 50% (Fig. 2) (Lapkina-Gendler *et al.* 2016). These results are in agreement with genomic analyses showing that expression of a number of genes involved in cell cycle progression (i.e., *cyclin A1*, *Sp1*, *AKT3,* etc.) (Table 2) was markedly downregulated in LS cells. Likewise, the proportion of LS cells in S phase was reduced in comparison to healthy cells. On the other hand, flow cytometry analysis of LS cells demonstrated that the proportion of apoptotic cells under basal conditions was augmented by ~40%. Finally, we investigated whether cancer protection in LS might be associated with enhanced resistance to oxidative damage. To this end, lymphoblastoid cells were exposed to *paraquat*, an oxidation agent, after which cell survival was measured. Results indicate that LS cells exhibit enhanced survivability over a broad range of the oxidative agent (Fig. 2). Taken together, biological assays along with bioinformatics data indicate that LS cells exhibit diminished mitogenic capabilities. These features might constitute the biological foundation upon which the capability of LS individuals to oppose cancer is based.

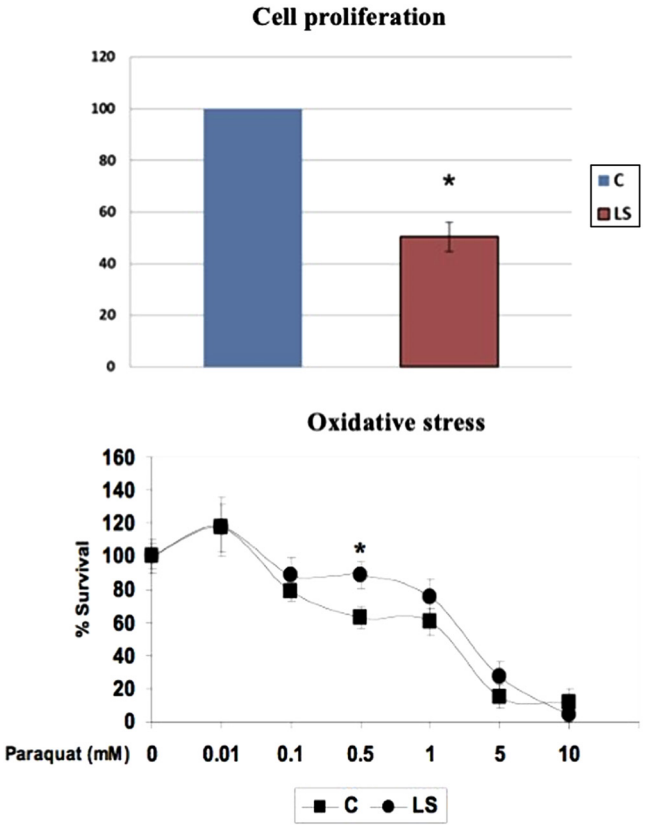

Figure 2
Effect of congenital IGF-1 deficiency on cell proliferation and response to oxidative stress. (Upper panel) LS- (red bars) and control (blue bars) lymphoblastoid cells were maintained in serum- and IGF-1-free medium for 3 days, after which proliferation was assessed using an XTT colorimetric assay. The statistical significance of differences between groups was assessed by Student's *t*-test. *significantly different vs control ($P < 0.05$). (Lower panel) Lymphobastoids were treated with increasing doses of paraquat dichloride. Paraquat generates superoxide anion, which leads to the formation of toxic reactive oxygen species and the oxidation of cellular NADPH. Proliferation in response to oxidative stress was measured using an XTT assay. The graph depicts a pair of LS (black circles) and control (black squares) cells, normalized for age and ethnic origin. A value of 100% was given to the cell number at time zero. Data from Lapkina-Gendler *et al.* (2016).

Mechanistic aspects and data integration

The finding that LS patients do not develop cancer is of an exceptional clinical and scientific value. The interpretation of epidemiological data is consistent with the notion that homozygous congenital IGF-1 deficiency confers protection against future development of cancer, whereas heterozygosity does not. This *experiment of nature* emphasizes the central role of IGF-1 in cancer. The studies described in this review article shed light on novel genetic and epigenetic mechanisms associated with evasion of congenital IGF-1-deficient patients from malignant transformation.

Our main *take-home messages* can be summarized as follows:

- Reduced circulating (and, probably, locally-produced) IGF-1 in LS is associated with multiple metabolic, enzymatic and growth-related adaptations at the organismal level.

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- Cancer protection in LS is attained despite very high concentrations of GH (Fig. 3) and pronounced obesity, in itself a risk factor for malignancy. Hence, it is reasonable to suggest that the cardinal factor that confers upon LS patients the biochemical machinery needed to evade cancer is a very low to undetectable level of IGF-1. Diminished dosages of IGF-1, in the presence of even minute doses of GH, are unable to set in motion the cellular processes associated with the acquisition of a malignant phenotype.
- LS cells express reduced levels of transcripts and proteins associated with proliferation, cell cycle progression and motility. These genes, including *cyclin A1, cyclin D1, serpin B2, AKT3, versican,* etc., were shown to constitute downstream targets for positive regulation by IGF-1. In a low IGF-1 *milieu*, such as that typical of LS, these (and other) genes are downregulated, with subsequent reductions in mitosis and other proliferation markers.
- The expression of metabolic genes associated with protection from oxidative and genotoxic insults is markedly enhanced in LS cells. For example, augmented UGT2B15 (an enzyme responsible for conjugation and elimination of potentially toxic xenobiotic substances) levels in LS might confer upon cells a shielding effect against oxidative and, potentially, genotoxic damage.
- Elevated levels of the mitochondrial redox r egulatory protein TXNIP in LS might translate into a preferential activation of specific tumor suppressor pathways. The *TXNIP* gene was identified as a target for negative regulation by IGF-1. The mechanism of action of IGF-1 involves transcriptional suppression of the *TXNIP* gene promoter. As a corollary, diminished IGF-1 levels in LS lead to upregulation of TXNIP with ensuing adoption of alternative, pro-apoptotic pathways.
- Our comprehensive genomic analyses led to the identification of previously unrecognized target genes for IGF-1. For example, our data identified the NPNT and *OR5H2* genes as new targets for stimulatory regulation by IGF-1. Consistent with this notion, the expression of both genes was largely reduced in LS. NPNT and *OR5H2* are involved in different aspects of cancer biology.

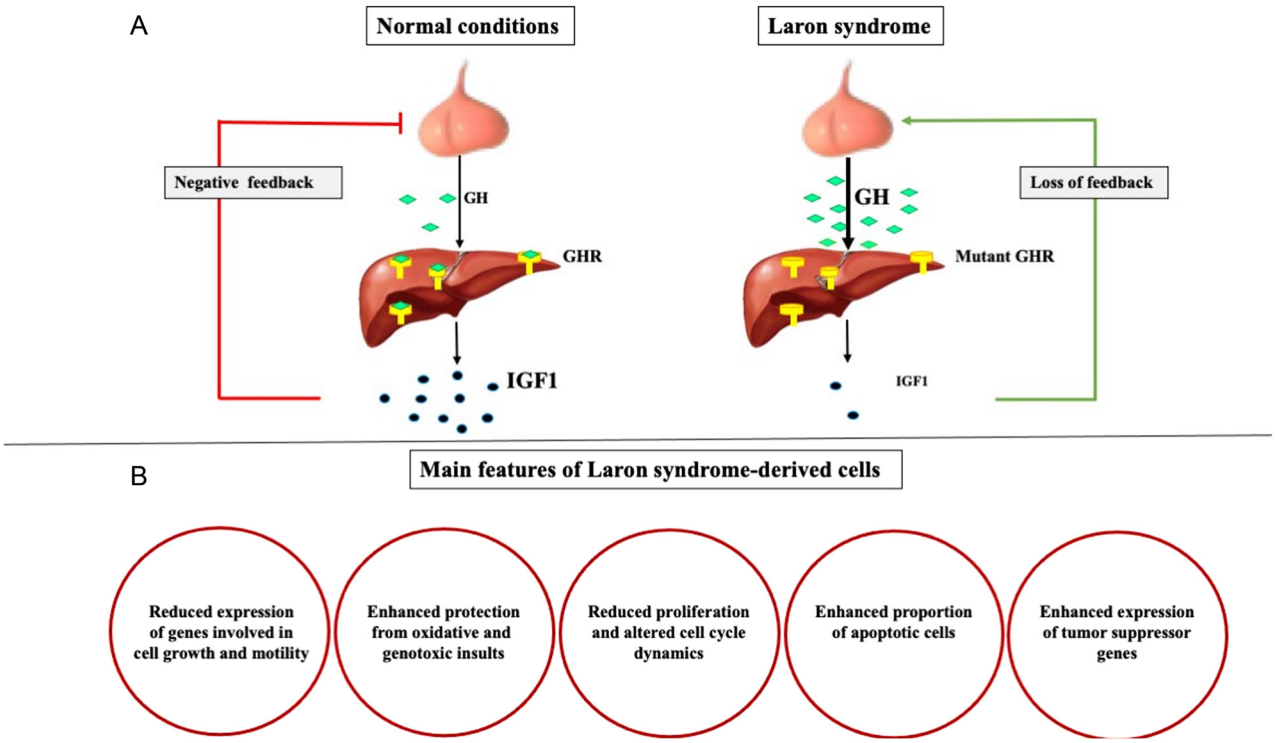

Figure 3
Schematic representation of the GH–IGF-1 axis in LS patients. (A) Pituitary-produced GH leads to IGF-1 secretion from the liver, with ensuing bone elongation and longitudinal growth. As a result of a *GH-R* mutation in LS patients, the liver (and, most probably, also other extrahepatic tissues) is no longer able to produce IGF-1 at physiological levels. Abrogation of IGF-1 production leads to impaired growth and inadequate negative feedback at the pituitary gland, leading to high circulating GH levels. (B) Selected biological features of LS-derived cells.

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- Differential gene expression in LS-derived cells, as described above, leads to major phenotypic distinctions in comparison to ethnicity-, age- and gender-matched control cells. Thus, LS cells display a markedly reduced proliferative potential, altered cell cycle dynamics and an enhanced apoptotic index.

Conclusions and future directions

In summary, by mining genomic data from LS patients, a rare condition associated with cancer protection, we were able to generate clinically relevant information. Specifically, our studies have identified new downstream targets for IGF-1 action (Werner *et al*. 2000). These previously unrecognized targets might help delineate a molecular signature associated with cancer protection. We believe that future studies will succeed in translating this information into new prophylactic and anticancer tools in oncology.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

Work in the laboratory of H Werner is supported by grants from the Israel Science Foundation, US–Israel Binational Science Foundation and the Israel Cancer Association.

Author contribution statement

Z Laron and H Werner conceived this review article, drafted the work and revised it critically for intellectual content. Both authors contributed to the article and approved the submitted version.

Acknowledgements

The authorse thank the members of our laboratory for their support and contribution to the present study.

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Received 15 December 2022
Accepted 20 June 2023
Available online 21 June 2023
Version of Record published 28 July 2023