Fifty Years on: New Lessons from the Laron Syndrome

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The report of a mysterious and profoundly atypical endocrinopathy in the *Israel Journal of Medical Sciences* in 1966 paved the way for extensive genetic, clinical and experimental analyses that were conducted by Professor Zvi Laron and collaborators over more than 50 years [1]. The patients, three siblings of Yemenite origin aged 3.5 and 1.5 years and a newborn baby, were referred in 1958 to the recently established Pediatric Endocrine Clinic at Beilinson Hospital because of marked short stature. While the patients resembled children with typical growth hormone (GH) deficiency (i.e., dwarfism, obesity, hypoglycemia), a newly developed radioimmunoassay for human GH revealed that, in fact, they had extremely high GH levels, in the acromegalic range. This new inborn error of metabolism, portrayed at the time as pituitary dwarfism with high serum concentrations of GH, was later termed Laron-type dwarfism and, more recently, Laron syndrome (LS) [2].

In an era in which receptors were yet to be discovered, and somatomedin (known today as insulin-like growth factor-1, IGF1) was developing its biochemical and physiological identity, the identification of this new genetic entity had a huge impact on the early drawing of endocrine networks and blueprints and, moreover, on the clinical implications of pathological disruption of the GH-IGF1 circuit [3]. Cloning of the GH receptor (*GH-R*) gene in the late 1980s provided evidence that the genetic event underlying LS etiology was an autosomally transmitted mutated *GH-R* gene [4]. These molecular analyses confirmed results of binding assays conducted several years earlier showing defective GH binding to liver membranes obtained from biopsies of LS patients [5]. The paradigm that emerged was consistent with the concept that *GH-R* gene disruption, including nonsense, frameshift and missense mutations as well as exon deletions, leads to defective GH-R biosynthesis. The net consequence of impaired GH-R signaling is a striking reduction in liver IGF1 production, with ensuing growth and developmental deficits [Figure 1]. Abrogation of IGF1-mediated negative feedback at the pituitary gland leads, in response, to markedly elevated serum GH values, a typical trait of LS.

IGF1 constitutes a progression factor required by the cell to advance through the various phases of the cell cycle. In addition to its normal physiological role, IGF1 has been identified as a key player in the chain of biochemical and cellular events leading to malignant transformation [6]. In agreement with this pathological function, broad epidemiological studies have demonstrated that circulating IGF1 values are positively associated with cancer risk in multiple types of cancer [7]. It is, therefore, pertinent to ask whether very low IGF1 concentrations, such as those typically associated with LS and other congenital IGF1 deficiencies, might be linked to reduced cancer incidence. A recent study based on 538 patients, including 230 patients with LS and 308 patients with congenital isolated GH deficiency, GH-releasing hormone receptor (*GHRH-R)* defects and congenital multiple pituitary hormone deficiency, revealed that none of

Figure 1. Schematic representation of the GH-IGF1 axis in health and in LS patients. Pituitary-produced GH leads to IGF1 secretion from the liver, with ensuing bone elongation and longitudinal growth (left panel). 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 IGF1 at physiological levels (right panel). Abrogation of IGF1 production leads to impaired growth and inadequate negative feedback at the pituitary gland, leading to high circulating GH levels

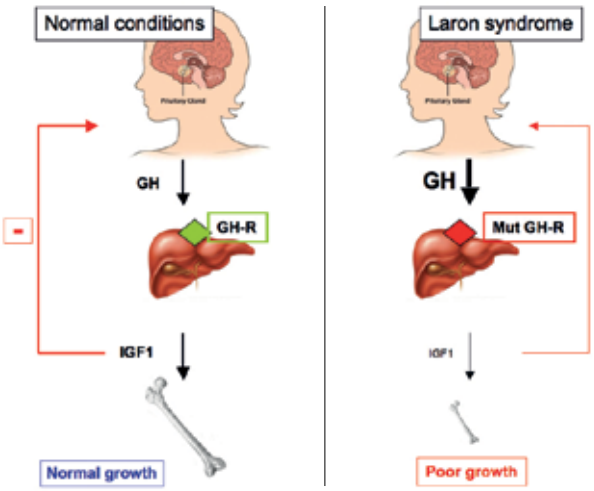

Table 1. Selected differentially regulated genes in LS patients

Genes downregulated in LS	Biological role
Cyclin A1	Cell cycle
AKT3	Apoptosis
Versican	Extracellular matrix proteoglycan
Olfactory receptor	Detection of odor molecules.
Nephronectin	Cell adhesion
Serpin B2	Apoptosis and proliferation

Genes upregulated in LS	Biological role
UDP glucuronosyltransferase 2 family	Elimination of xenobiotic substances
G-protein coupled receptor	Signaling
Thioredoxin interacting protein	Metabolic regulation
ZYG11A	Cell cycle regulator
CAPN2	Extracellular matrix disassembly

the 230 homozygous LS patients, including patients who were treated with IGF1 or GH, had a history of cancer up to the age of 85. On the other hand, 30 patients with cancer were reported among 752 first-degree heterozygote family members (4%), and 31 malignancies (mainly lung, prostate, breast and colon tumors) were reported among 131 further relatives (23.7%) [8,9]. Despite the small size of this cohort, differences in cancer incidence between LS patients and relatives were regarded as statistically significant. These epidemiological findings support the hypothesis that homozygous congenital IGF1 deficiency may confer protection against future development of a tumor.

To identify the entire collection of genes and signaling pathways associated with cancer evasion in LS, genomic analyses were recently conducted using LS-derived lymphoblastoid cells available at the National Laboratory for the Genetics of Israel Populations, Tel Aviv University [10]. Analyses identified series of genes that are either over- or under-represented in LS patients [Table 1]. Gene differential expression was noticed in a number of gene families, including cell cycle, metabolic control, cytokine-cytokine receptor interaction, Jak-STAT signaling, PI3K-AKT signaling, etc. Major differences between LS and healthy controls were also noticed in pathways associated with cell cycle distribution, apoptosis and autophagy. The identification of novel downstream targets of the GH-IGF1 endocrine network by genome-wide analyses highlights the key role of the GH-IGF1 axis in the initiation and progression of cancer. Future studies will address the transcriptional and epigenetic mechanisms responsible for IGF1 regulation of new metabolic and oncogenic genes.

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References

1. Laron Z, Pertzelan A, Mannheimer S. Genetic pituitary dwarfism with high serum concentration of growth hormone-a new inborn error of metabolism? *Isr J Med Sci* 1966; 2: 152-5.
2. Laron Z. Extensive personal experience. Laron syndrome (primary growth hormone resistance or insensitivity): the personal experience 1958-2003. *J Clin Endocrinol Metab* 2004; 89: 1031-44.
3. Laron Z, Kopchik JJ. Laron Syndrome – From Man to Mouse. Heidelberg-New York: Springer-Verlag, 2011.
4. Godowski PJ, Leung DW, Meacham LR, et al. Characterization of the human growth hormone receptor gene and demonstration of a partial gene deletion in two patients with Laron-type dwarfism. *Proc Natl Acad Sci USA* 1989; 86: 8083-7.
5. Eshet R, Laron Z, Pertzelan A, Arnon R, Dintzman M. Defects of human growth hormone receptors in the liver of two patients with Laron-type dwarfism. *Isr J Med Sci* 1984; 20: 8-11.
6. Werner H. The pathophysiological significance of IGF-I receptor overexpression: new insights. *Ped Endocrinol Rev* 2009; 7: 2-5.
7. Renehan AG, Zwahlen M, Minder C, O'Dwyer ST, Shalet SM, Egger M. Insulin-like growth factor-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* 2004; 363: 1346-53.
8. Shevah O, Laron Z. Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. *Growth Hormone IGF Res* 2007; 17: 54-7.
9. Steuerman R, Shevah O, Laron Z. Congenital IGF1 deficiency tends to confer protection against post-natal development of malignancies. *Eur J Endocrinol* 2011; 164: 485-9.
10. Lapkina-Gendler L, Rotem I, Pasmanik-Chor M, et al. Identification of signaling pathways associated with cancer protection in Laron syndrome. *Endocrine Relat Cancer* 2016; 23: 399-410.