Endocrinologia, longevità e invecchiamento
I G F 1

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ITALIAN CHAPTER

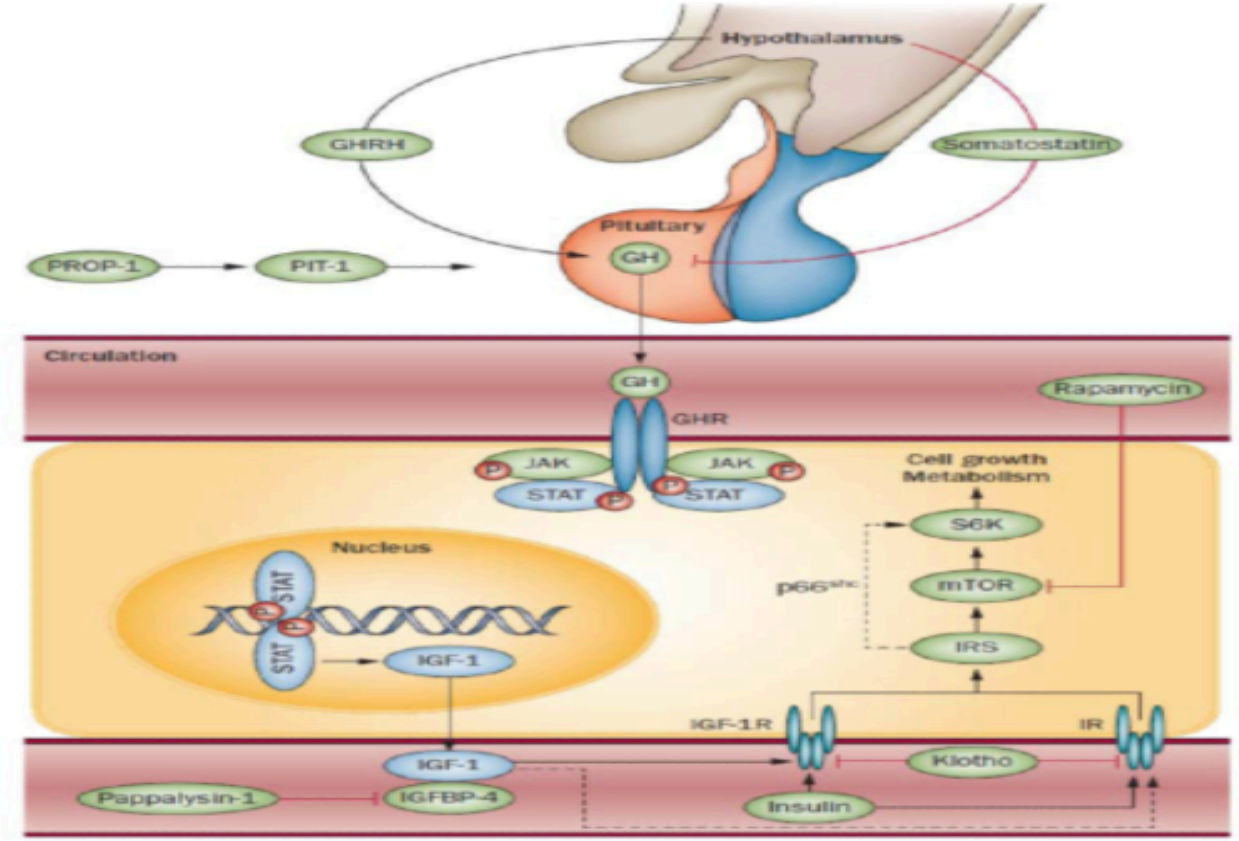
16° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

9-12 novembre 2017
Roma

IGF 1 e longevità



The embryonically expressed genes PROP1 (which encodes PROP-1) and POU1F1 (which encodes PIT-1) are involved in pituitary development, including differentiation of pituitary somatotrophic cells.

GH binds to GH receptors, which activates the JAK–STAT pathway and induces the production of IGF-1, predominantly in the liver.

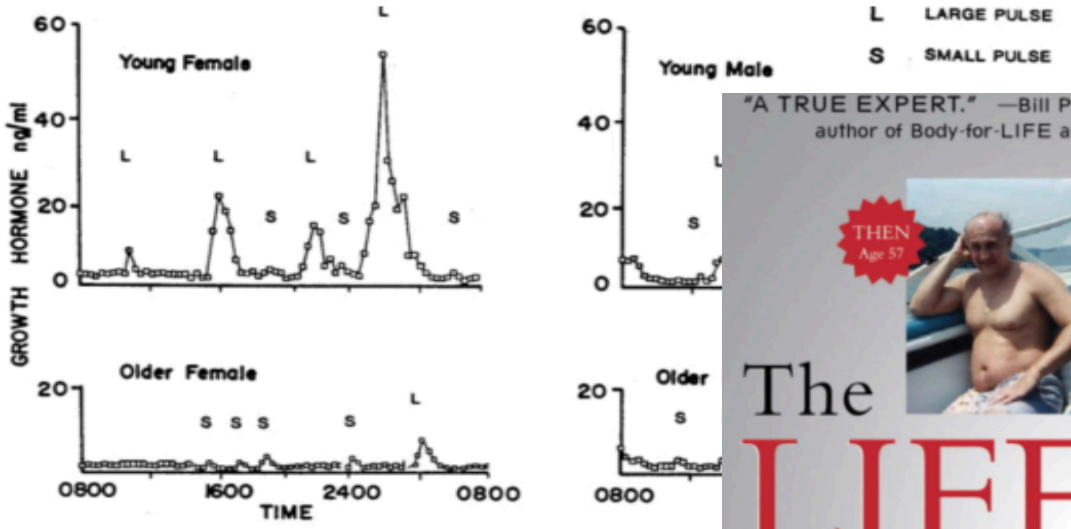
In the circulation, much of IGF-1 is bound by IGFBPs, which act as carrier proteins and regulators of IGF-1 bioavailability. Pappalysin-1 is an IGFBP-4 protease that increases IGF-1 bioavailability.

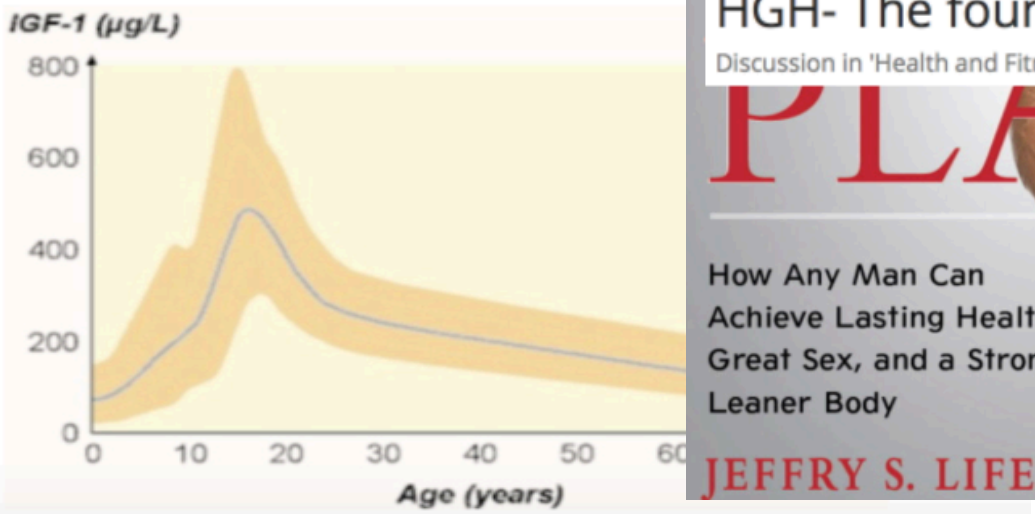
IGF-1 mediates its effects by binding to IGF-1R and, with less affinity, to IRs in many tissues. The protein klotho suppresses insulin and IGF-1 action, whereas IRS-1 and IRS-2 transduce signals from the IGF-1R and the IR, resulting in the activation of several pathways, including one that acts via S6K, a downstream effector of mTOR that is linked to IRS-1 via p66shc.

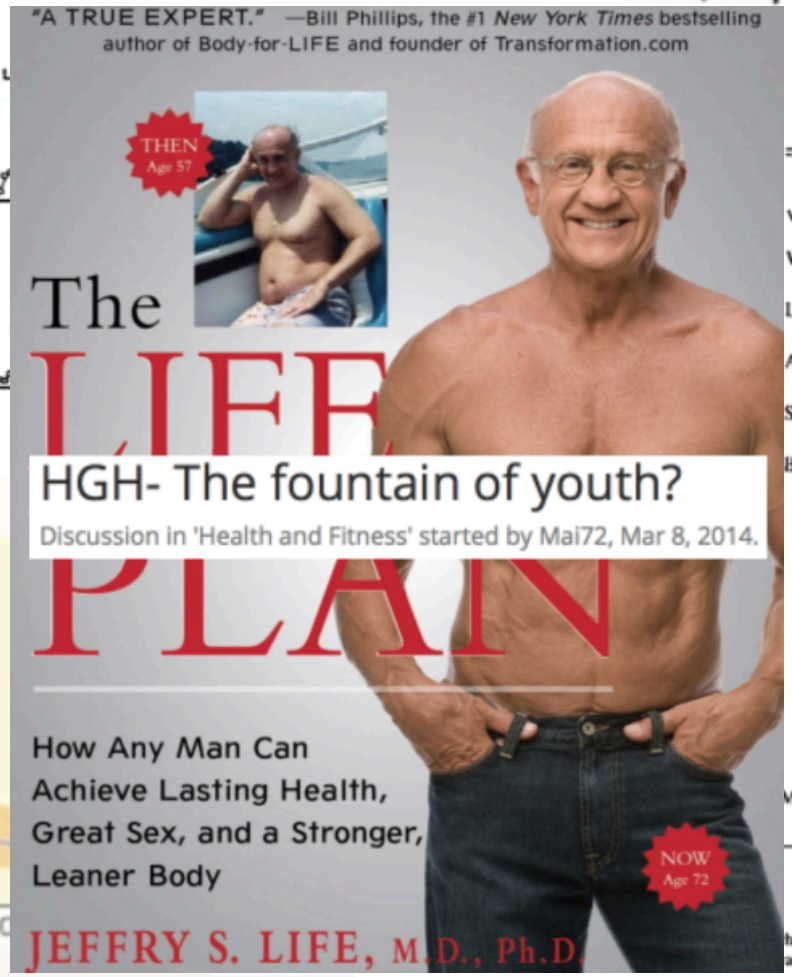
IGF 1 e longevità

Growth Hormone in Aging

LS Chertman - 2015







HGH- The fountain of youth?

Discussion in 'Health and Fitness' started by Mai72, Mar 8, 2014.

EFFECTS OF HUMAN GROWTH HORMONE IN MEN OVER 60 YEARS OLD

N Engl J Med 1990; 323:1-6

Effect of the Administration of Human Growth Hormone on Weight, Lean Body Mass, Adipose-Tissue Mass, Skin Thickness, and Bone Density in Healthy Older Men

Variable	Group	End of Base-Line Period	End of Treatment Period	P Value†	Difference in Changes‡	
Weight (kg)	1	77.2±11.4	78.2±12.1	0.26	+1.0	(−1.4 to +3.4)
	2	83.3±11.1	83.3±9.7	0.97		
Lean body mass (kg)	1	53.0±7.4	57.7±9.1	0.0005	+3.7	(+0.7 to +6.6)
	2	54.2±7.1	55.2±7.3	0.17		
Adipose-tissue mass (kg)	1	24.1±5.0	20.6±5.6	0.05	−2.4	(−5.7 to +0.8)
	2	29.0±6.4	28.0±4.0	0.43		
Sum of skin thickness at four sites (mm)	1	9.9±1.2	10.6±1.5	0.07	+0.8	(−0.1 to +1.7)
	2	9.3±0.9	9.23±0.80	0.69		
Bone density (g/cm²)						
Mid-shaft radius	1	0.74±0.10	0.74±0.12	0.85	+0.04	(−0.02 to +0.10)
	2	0.76±0.10	0.71±0.07	0.09		
Distal radius	1	0.37±0.07	0.36±0.08	0.12	−0.004	(−0.03 to +0.02)
	2	0.34±0.04	0.33±0.05	0.26		
Average, lumbar vertebrae 1–4	1	1.23±0.12	1.25±0.13	0.04	+0.006	(−0.04 to +0.05)
	2	1.29±0.25	1.29±0.26	0.64		
Ward's triangle	1	0.70±0.14	0.69±0.13	0.15	−0.018	(−0.08 to +0.05)
	2	0.70±0.17	0.70±0.17	0.69		
Greater trochanter	1	0.85±0.13	0.85±0.13	0.72	+0.007	(−0.05 to +0.03)
	2	0.81±0.15	0.81±0.13	0.55		
Femoral neck	1	0.92±0.15	0.91±0.14	0.53	−0.029	(−0.08 to +0.03)
	2	0.89±0.14	0.85±0.14	0.14		
Mandibular-height ratio	1	0.45±0.15	0.46±0.11	0.87	−0.003	(−0.07 to +0.06)
	2	0.47±0.12	0.47±0.12	0.98		

*Plus–minus values are means ±SD.

†P values are for the change from base line, by matched-pair t-test.

‡The difference in changes (12-month value minus 6-month value) is the average change in group 1 minus the average change in group 2. Values in parentheses are 95 percent confidence intervals, calculated by independent-sample, unequal-variance t-tests.

IGF 1 e longevità

Ann Intern Med. 2007 Jan 16;146(2):104-15.

Systematic review: the safety and efficacy of growth hormone in the healthy elderly.

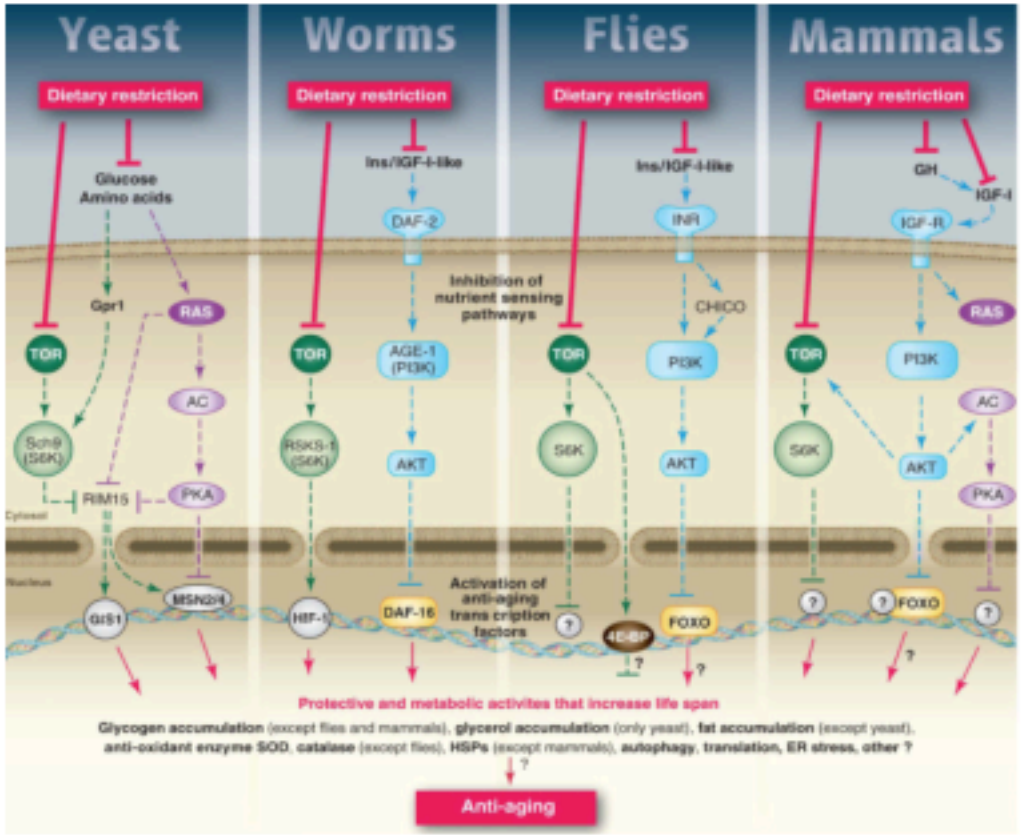
BACKGROUND:
Human growth hormone (GH) is widely used as an antiaging therapy, although its use for this purpose has not been approved by the U.S. Food and Drug Administration and its distribution as an antiaging agent is illegal in the United States.
PURPOSE:
To evaluate the safety and efficacy of GH therapy in the healthy elderly.
DATA SOURCES:
The authors searched MEDLINE and EMBASE databases for English-language studies published through 21 November 2005 by using such terms as growth hormone and aging.
STUDY SELECTION:
The authors included randomized, controlled trials that compared GH therapy with no GH therapy or GH and lifestyle interventions (exercise with or without diet) with lifestyle interventions alone. Included trials provided GH for 2 weeks or more to community-dwelling participants with a mean age of 50 years or more and a body mass index of 35 kg/m2 or less. The authors excluded studies that evaluated GH as treatment for a specific illness.
DATA EXTRACTION:
Two authors independently reviewed articles and abstracted data.
DATA SYNTHESIS:
31 articles describing 18 unique study populations met the inclusion criteria. A total of 220 participants who received GH (107 person-years) completed their respective studies. Study participants were elderly (mean age, 69 years [SD, 6]) and overweight (mean body mass index, 28 kg/m2 [SD, 2]). Initial daily GH dose (mean, 14 microg per kg of body weight [SD, 7]) and treatment duration (mean, 27 weeks [SD, 16]) varied. In participants treated with GH compared with those not treated with GH, **overall fat mass decreased (change in fat mass, -2.1 kg [95% CI, -2.8 to -1.35] and overall lean body mass increased (change in lean body mass, 2.1 kg [CI, 1.3 to 2.9]) (P < 0.001)**, and their weight did not change significantly (change in weight, 0.1 kg [CI, -0.7 to 0.8]; P = 0.87). **Total cholesterol levels decreased (change in cholesterol, -0.29 mmol/L [-11.21 mg/dL]; P = 0.006), although not significantly after adjustment for body composition changes. Other outcomes, including bone density and other serum lipid levels, did not change.**
Persons treated with GH were significantly more likely to experience **soft tissue edema, arthralgias, carpal tunnel syndrome, and gynecomastia and were somewhat more likely to experience the onset of diabetes mellitus and impaired fasting glucose.**
LIMITATIONS:
Some important outcomes were infrequently or heterogeneously measured and could not be synthesized. Most included studies had small sample sizes.
CONCLUSIONS:
The literature published on randomized, controlled trials evaluating GH therapy in the healthy elderly is limited but suggests that it is associated with small changes in body composition and increased rates of adverse events. **On the basis of this evidence, GH cannot be recommended as an antiaging therapy.**

IGF 1 e longevità

Dietary Restriction, Growth Factors and Aging: from yeast to humans

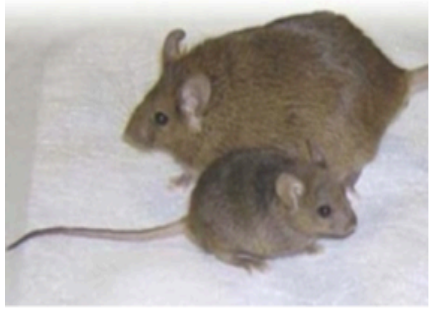
Science. 2010 April 16; 328(5976): 321–326

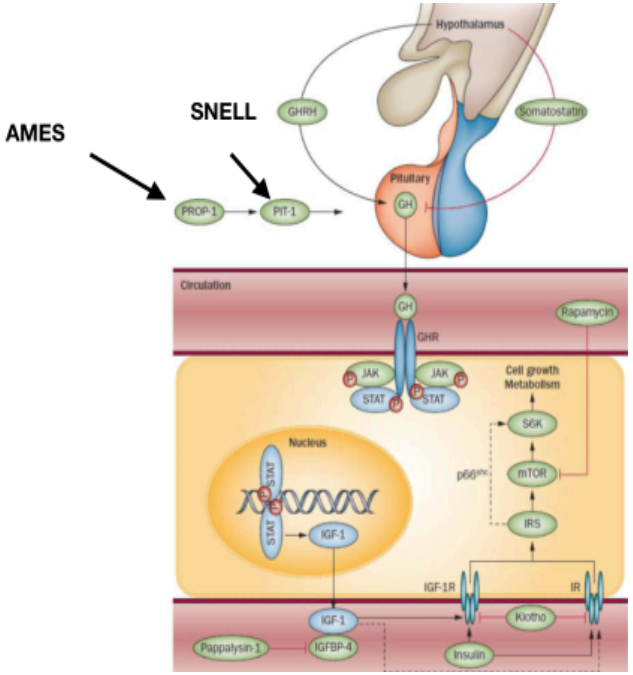
	Lifespan increase		Beneficial health effects	
	Dietary restriction	Mutations/ drugs	Dietary restriction	Mutations/ drugs
Yeast	3 fold	10 fold	Extended reproductive period	Extended reproductive period, decreased DNA damage/mutations
Worms	2-3 fold	10 fold	Resistance to misexpressed toxic proteins	Extended motility Resistance to mis-expressed toxic proteins and germ-line cancer
Flies	2 fold	60-70%	None reported	Resistance to bacterial infection, extended ability to fly
Mice	30-50%	30-50% (~100% in combination with DR)	Protection against cancer, diabetes, atherosclerosis,cardio-myopathy, autoimmune, kidney and respiratory diseases, reduced neurogeneration	Reduced tumor incidence, protection against age-dependent cognitive decline, cardio-myopathy, fatty liver and renal lesions. Extended insulin sensitivity
Monkeys	Trend noted	Not tested	Prevention of obesity, protection against diabetes, cancer and cardiovascular disease	Not tested
Humans	Not determined	Not determined (GHR deficient subjects reach old age)	Prevention of obesity, diabetes, hypertension Reduced risk factors for cancer and cardiovascular disease	Possible reduction in cancer and diabetes



IGF 1 e longevità

Deficit ipofisario multiplo: animali





Dimensioni ridotte e pubertà ritardata

Curr. Top. Dev. Biol. 2004; 63:189

Durata di vita 40 − 70% più del wild type

J. Gerontol. A Biol. Sci. Med. Sci. 2004; 59: 1244

Meno frequenti le patologie età correlate

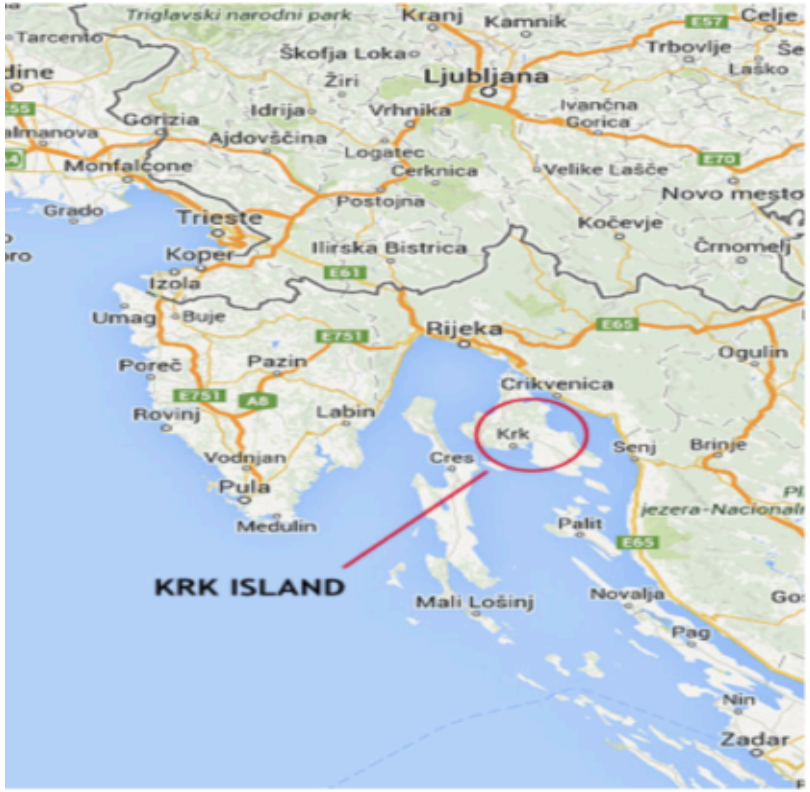
J. Gerontol. A Biol. Sci. Med. Sci. 2003; 58: 291

Somministrazione di GH nei topi Ames per sei settimane riduce significativamente la sopravvivenza

FASEB J. 2010; 24:5073

IGF 1 e longevità

Deficit ipofisario multiplo: uomo



The Journal of Endocrine Genetics, 1, 9-19 (1999)

The "Little People" of the Island of Krk - Revisited. Etiology of Hypopituitarism Revealed

Ciril Krzisnik[1], Zdravka Kolacio[2], Tadej Battelino[1], Milton Brown[3], John S. Parks[3] and Zvi Laron[4]

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ABSTRACT

Hereditary dwarfism was first recognized in inhabitants of the island of Krk in the Adriatic in 1864. Since then 24 related dwarfs have been recorded. Their pedigrees and heights are presented. Ten of these patients live in the villages Baščanska Draga and Jurandvor. Six have been studied by the authors. Clinical examination revealed dwarfism, obesity, dry wrinkled skin, and lack of sexual development. Hormonal investigations showed the absence of growth hormone (GH) unresponsive to growth hormone releasing hormone (GHRH), absence of luteinizing hormone (LH) and follicle stimulating hormone (FSH) unresponsive to gonadotropin releasing hormone (GnRH), and absence of thyrotropin stimulating hormone (TSH) unresponsive to TRH. Basal serum prolactin (PRL) was low but secretion of ACTH was normal as evidenced by normal cortisol levels. Hypopituitarism in this isolate was not associated with a shortened life span or an increased incidence of diabetes. PROP-1 is a pituitary specific transcription factor that is required for the embryologic development of the pituitary cell types that ultimately produce GH, PRL, TSH and FSH/LH postnatally. Examination of genomic DNA from two of the patients revealed homozygosity for a one bp deletion in codon 50 of exon 2 of PROP-1. This mutation introduces a frame shift and results in a premature translational stop signal at codon 164. The truncated protein lacks the DNA-binding and transcriptional activation domains.

In conclusion, basic insights into the transcription factors contributing to pituitary development led to definition of hereditary multiple pituitary hormone deficiency (MPHD) dwarfism on the island of Krk. The hypopituitarism is due to a mutation in the PROP-1 gene. This genetic isolate provides a unique opportunity to characterize the long-term effects of hypopituitarism caused by PROP-1 deficiency.

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KEY WORDS

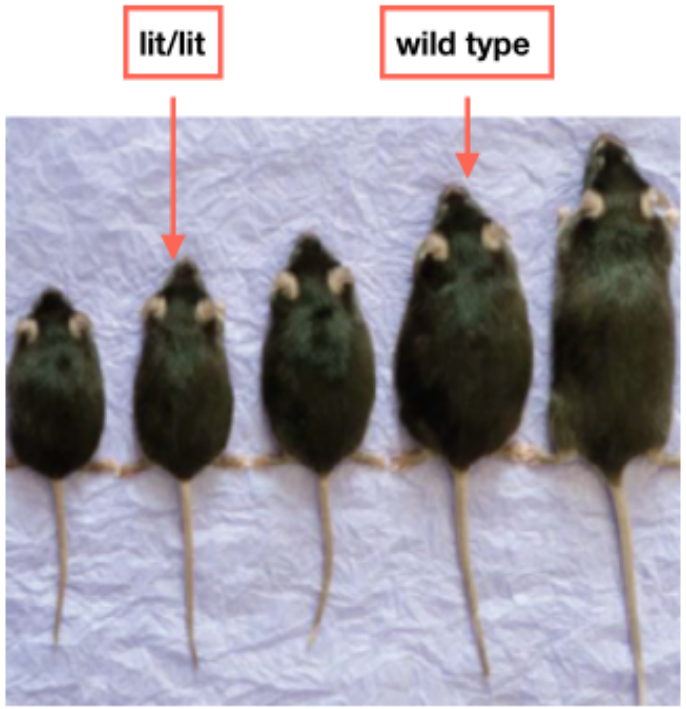
hereditary dwarfism, panhypopituitarism, PROP-1, island Krk

INTRODUCTION AND HISTORY

Hereditary dwarfism on the island of Krk in the North Eastern part of the Adriatic Sea (Fig. 1) was first recorded in the 19th century. The affected individuals originated from two closely located villages: Bascanska Draga and Jurandvor. They were called "Mali Ljudi" (short people) by the Croatian inhabitants. The surface area of Krk is 428 km^2 and the population is approximately 15,000. In the late 1980s the population of the village of Baščanska Draga was 509 and that of Jurandvor 175. The first recorded patient with dwarfism was born in 1864 in Bascanska Draga, the second 13 years later in the neighboring village of Jurandvor. By the end of the 19th century seven affected individuals had been born and currently there are

IGF 1 e longevità

Deficit isolato di GH: animali e uomo



Dimensioni 50 % in meno del wild type
Sopravvivenza 25 % in più le femmine - 23 % in più i maschi

Flurkey K, Papaconstantinou J, Miller RA, Harrison DE. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. Proc. Natl Acad Sci. USA. 2001; 98:6736–6741.

Familial Dwarfism due to a Novel Mutation of the Growth Hormone-Releasing Hormone Receptor Gene

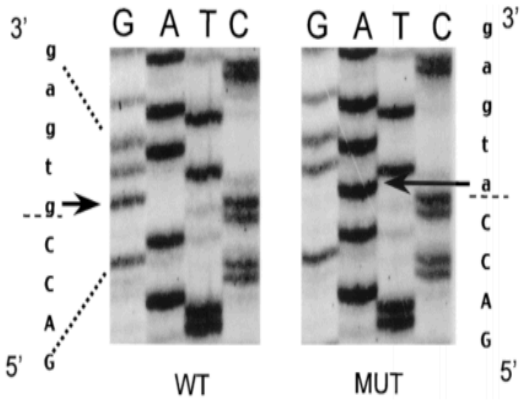
ABSTRACT

Isolated growth hormone (GH) deficiency (IGHD) is a rare cause of short stature. The same mutation of the gene encoding the growth hormone-releasing hormone receptor (GHRHR) has been identified as the basis for IGHD in three families from the Indian subcontinent. The prevalence and heterogeneity of defects in the GHRHR gene are not known.

Twenty-two dwarf members of a large, extended kindred containing at least 105 affected members with autosomal recessive short stature underwent extensive endocrine evaluation, which confirmed markedly reduced or undetectable serum concentrations of GH that did not increase in response to different stimuli.

DNA sequences of the 13 exons and intron-exon boundaries of the GHRHR gene were determined in an index patient. A novel homozygous 5′ splice site mutation (G→A at position +1) in IVS1 was found. Thirty of the affected subjects tested were homozygous for this mutation, and 64 clinically unaffected patients were either heterozygous for the mutation (n = 41, including 9 obligate carriers) or homozygous for the wild-type sequence (n = 23).

We describe a novel mutation in the GHRHR gene as cause of dwarfism in the largest kindred with familial IGHD described to date. (*J Clin Endocrinol Metab* **84:** 917–923, 1999)



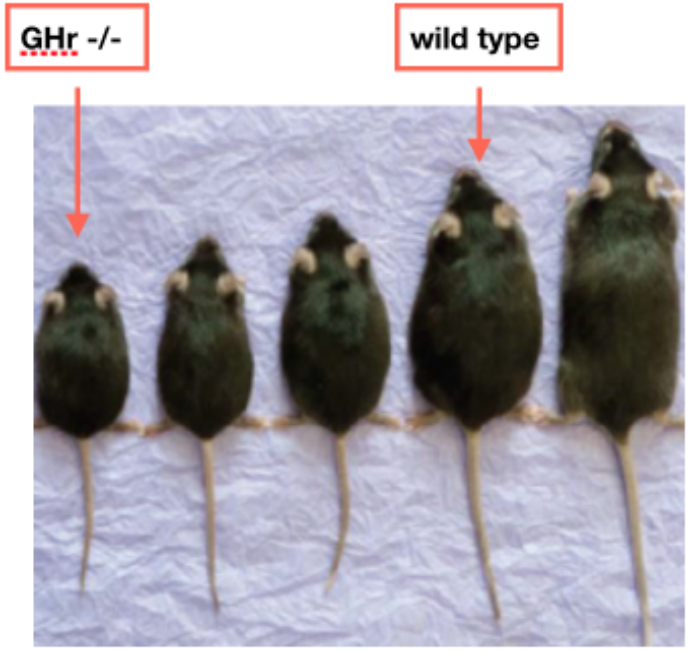
Reduced Longevity in Untreated Patients with Isolated Growth Hormone Deficiency

J Clin Endocrinol Metab 88: 3664–3667, 2003

		Life span (yr) mean (median, range)	
Affected males (IGHD type 1A)	n:5	57.4 (56, 41–77)	$P < 0.0001$
Unaffected healthy brothers	n:11	70.9 (75, 40–87)	ns
Unaffected healthy males (same population)	n:100	70.2 (74, 23–91)	
Affected females (IGHD type 1A)	n:6	47.4 (46, 29–63)	$P < 0.0001$
Unaffected healthy sisters	n:14	74.2 (80, 22–89)	ns
Unaffected healthy females (same population)	n:100	75.3 (79, 21–90)	

IGF 1 e longevità

Resistenza al GH: animali e uomo

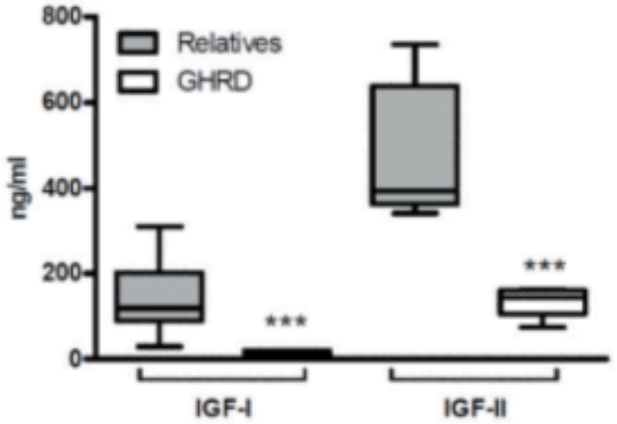


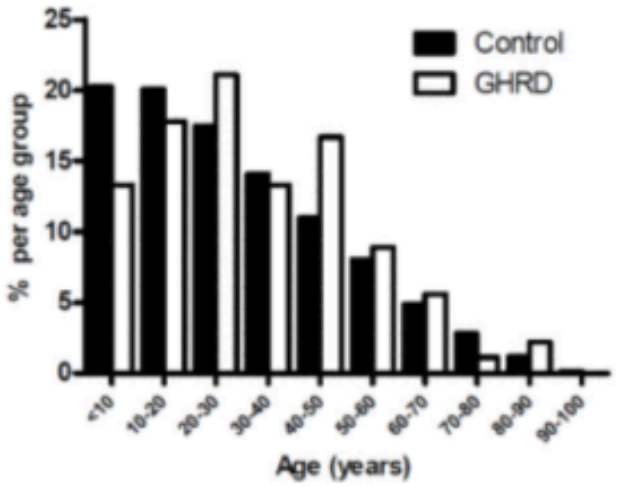
Dimensioni < 50 % del wild type
Sopravvivenza 21 % in più le femmine - 40 % in più i maschi

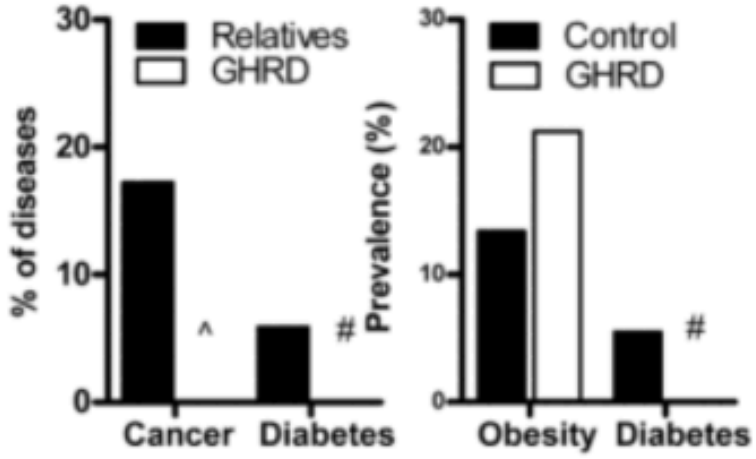
Coschigano KT, et al. Deletion, but not antagonism, of the mouse growth hormone receptor results in severely decreased body weights, insulin and IGF-1 levels and increased lifespan.
Endocrinology. 2003; 144:3799–3810.

Growth Hormone Receptor Deficiency is Associated With a Major Reduction in Pro-aging Signaling, Cancer and Diabetes in Humans

Sci Transl Med. 2011 February 16; 3







IGF 1 e longevità

Eccesso di GH: animali e uomo

Fenotipo gigante
Sopravvivenza 30 40 % in meno dei wild type
Magri (effetto lipolitico del GH)
Frequente glomerulosclerosi e epatomegalia
Iperinsulinemia e insulinoresistenza

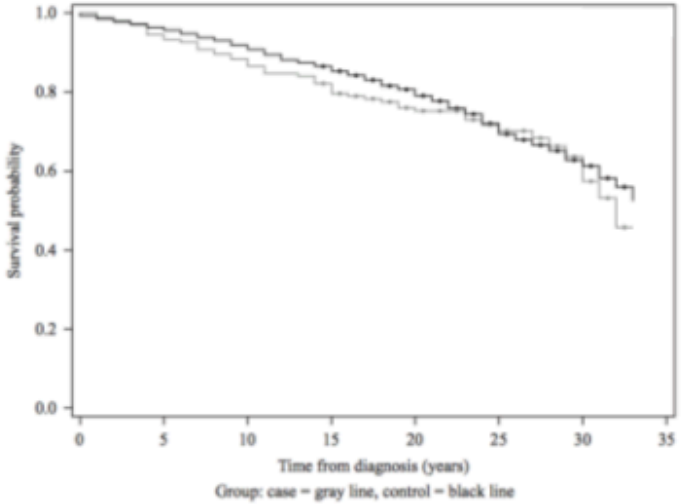
Endocrinology. 2009; 150:1353–1360.
Neuroendocrinology. 2003; 78:210–216.
Endocrinology. 1989; 124:40–48.

Mortality in acromegaly: a 20-year follow-up study

Endocrine-Related Cancer
(2016) **23**, 469–480

Patients and methods: We studied standardized mortality ratios (SMRs) relative to the general population and causes of death in acromegaly ($n = 333$) compared with age- and gender-matched controls ($n = 4995$).

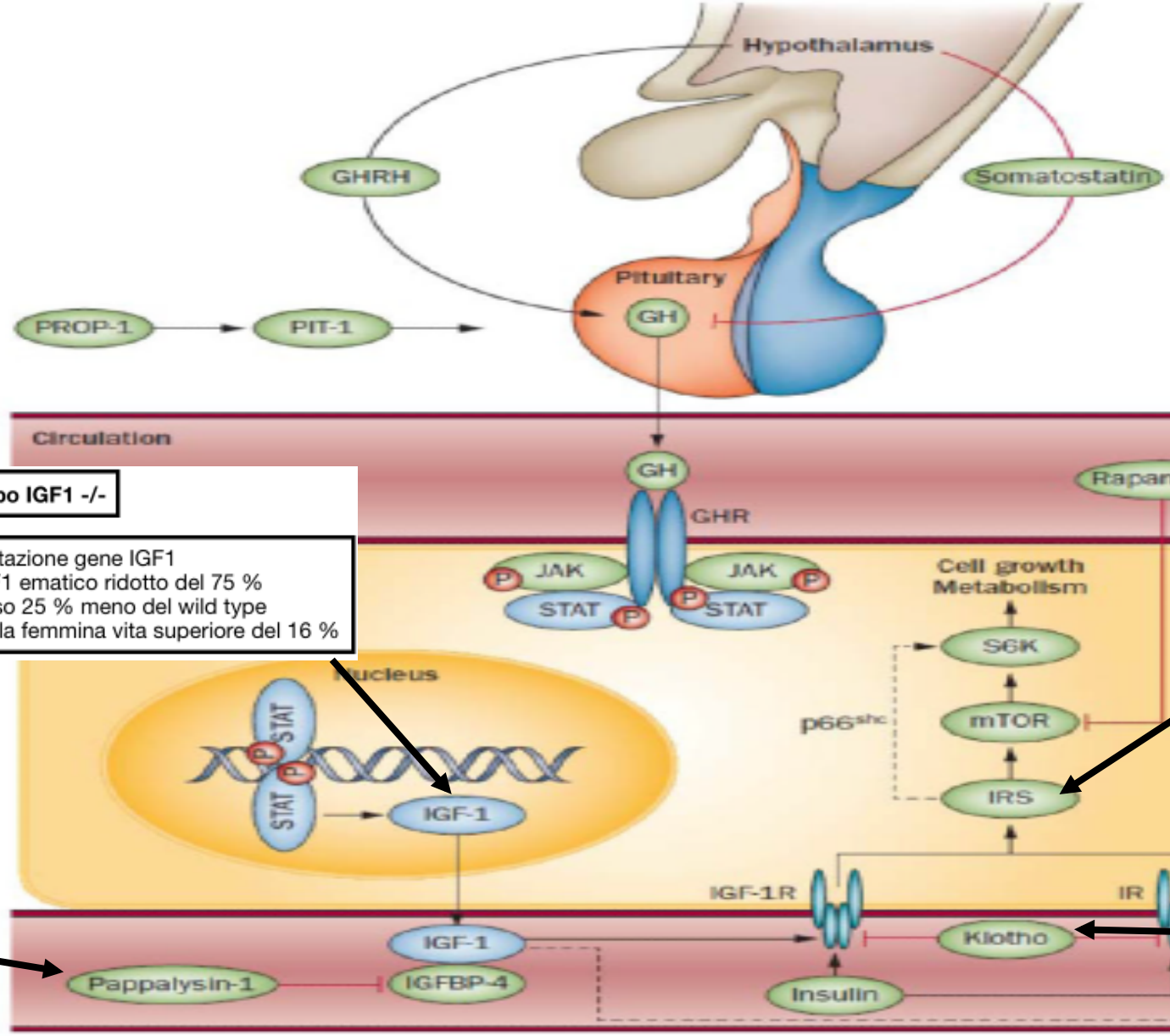
During 20 (0–33) years follow-up, 113 (34%) patients (n = 333, 52% women) and 1334 (27%) controls (n = 4995) died (P = 0.004). SMR (1.9, 95% CI: 1.53–2.34, P < 0.001) and all-cause mortality (OR 1.6, 95% CI: 1.2–2.2, P < 0.001) were increased in acromegaly



Overall distribution of causes of death (P < 0.001) differed between patients and controls but not cardiovascular (34% vs 33%) or cancer deaths (27% vs 27%).
In acromegaly, but not in controls, causes of deaths shifted from 44% cardiovascular and 28% cancer deaths during the 1rst decade, to 23% cardiovascular and 35% cancer deaths during the next two decades.
In acromegaly, cancer deaths were mostly attributed to pancreatic adenocarcinoma (n = 5), breast (n = 4), lung (n = 3) and colon (n = 3) carcinoma.

IGF 1 e longevità

Ridotto effetto dell' IGF 1: animali



Topo IGF1 -/-

Mutazione gene IGF1
IGF1 ematico ridotto del 75 %
Peso 25 % meno del wild type
Nella femmina vita superiore del 16 %

Topo IRS1 -/- e IRS2 -/-

Mutazione gene IRS1 o IRS 2

Peso 20 - 30 % meno del wild type

Vita media non differisce nell'IRS1 -/- ma più lunga del 15 % nell'IRS2 -/-

Topo Pappa -/-

Mutazione gene Pappalisina
Aumento legame IGF1 - IGF1BP4
Ridotta bio disponibilità IGF1
Peso 40 % meno del wild type
Vita media superiore del 38 %

Topo Klotho

Topi transgenici che esprimono Klotho

Ridotto legame di IGF1 a recettore di IGF1 e di Insulina

Dimensioni superiori al wild type

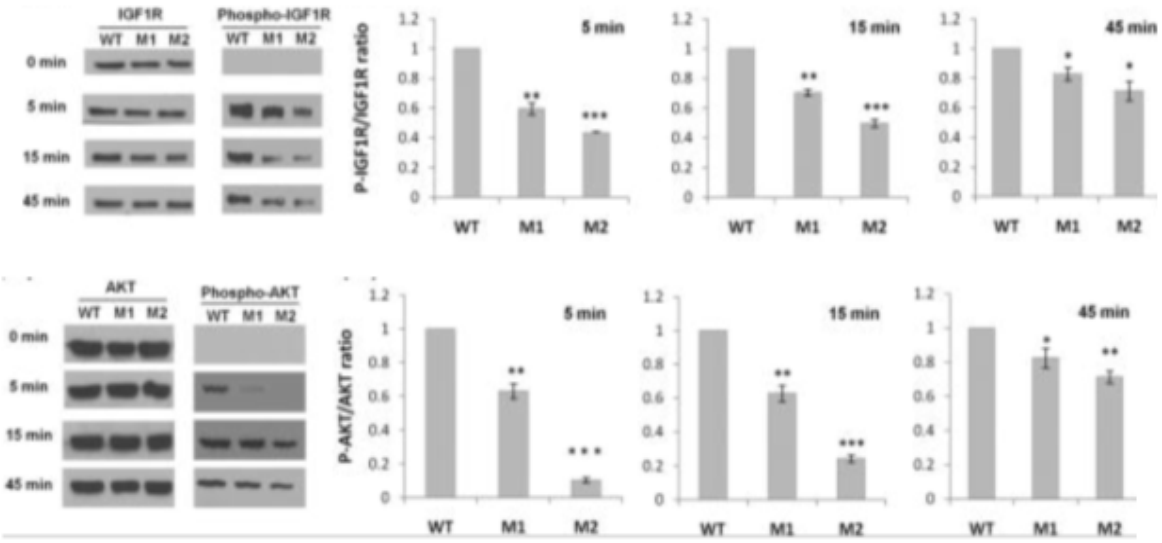
Vita media superiore del 20 -30 %

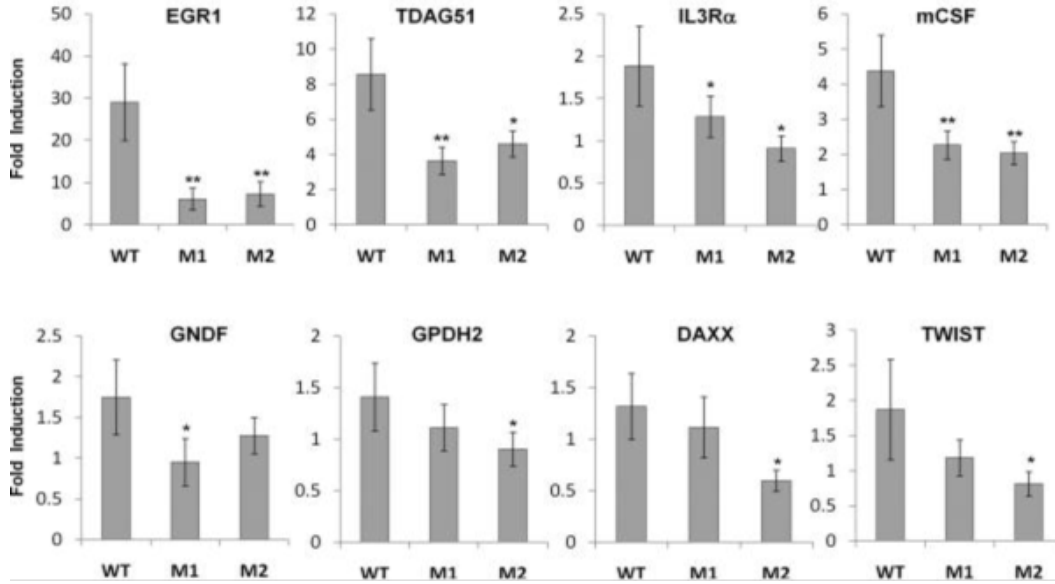
IGF 1 e longevità

Ridotto effetto dell' IGF 1: uomo

Impaired IGF1R signaling in cells expressing longevity- associated human IGF1R alleles
Aging Cell. 2011 June ; 10(3): 551–554

We previously identified two IGF1R mutations (Ala-37-Thr and Arg-407-His) that are enriched in Ashkenazi Jewish centenarians as compared to younger controls and are associated with reduced activity of the IGF1 receptor as measured in immortalized lymphocytes.
To determine whether these human longevity-associated IGF1R mutations affect IGF1 signaling, we engineered mouse embryonic fibroblasts (MEFs) expressing the different human IGF1R variants in a mouse Igf1r null background.
The results indicate that MEFs expressing the human longevity-associated IGF1R mutations attenuated IGF1 signaling, as demonstrated by significant reduction in phosphorylation of both IGF1R and AKT after IGF1 treatment, in comparisons to MEFs expressing the wild type IGF1R. The impaired IGF1 signaling caused by the IGF1R mutations resulted in reduced induction of the major IGF1-activated genes in MEFs, including EGR1, mCSF, IL3Rα, and TDAG51.
Furthermore, the IGF1R mutations caused a delay in cell cycle progression after IGF1 treatment, indicating a dysfunctional physiological response to a cell proliferation signal.
These results demonstrate that the human longevity- associated IGF1R variants are reduced-function mutations, implying that dampening of IGF1 signaling may be a longevity mechanism in humans.





IGF 1 e longevità

Ridotto effetto dell' IGF 1: uomo

Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity

Aging Cell (2014) **13**, pp769–771

Subject characteristics according to IGF-1 groups† (n = 184)

Characteristic	Low IGF-1 (n = 93)	High IGF-1 (n = 91)	P-value
IGF-1, ng mL^{-1}, median (IQR)	55 (36–72)	121 (112–158)	< 0.001
Age, years, median (IQR)	96.8 (95.9–98.1)	96.7 (95.6–97.9)	0.40
Sex, female%	73.1	78.0	0.44
Height‡, in (n = 135)	63.9 ± 3.3	63.2 ± 3.4	0.26
BMI§, kg m^{-2} (n = 126)	21.5 ± 3.6	21.6 ± 3.2	0.86
HDL, mg dL^{-1}, mean ± SD	53.1 ± 14.8	52.5 ± 17.3	0.81
Glucose, mg dL^{-1} (n = 179)	102.2 ± 33.1	113.4 ± 43.2	0.05
Insulin, μU mL^{-1}, median (IQR) (n = 81)	19.9 (10.7–35.7)	26.5 (11–44.2)	0.30
HOMA-IR, median (IQR) (n = 81)	4.9 (2.4–8.5)	7.1 (2.4–13.5)	0.20
Cancer¶, % (n = 151)	20.3 (15)	24.7 (19)	0.52
Diabetes mellitus, % (n = 142)	5.6 (4)	8.5 (6)	0.75
Cardiovascular disease,% (n=141)	22.5 (16)	27.1 (19)	0.53
Cognitive impairment**, % (n = 171)	52.4 (44)	49.4 (43)	0.70

†Groups dichotomized at the median IGF-1 level, 96 ng mL^{-1}.

‡Maximum adult height.

§BMI calculated using the maximum adult height.

¶Cancer diagnoses exclude nonmelanoma skin cancer.

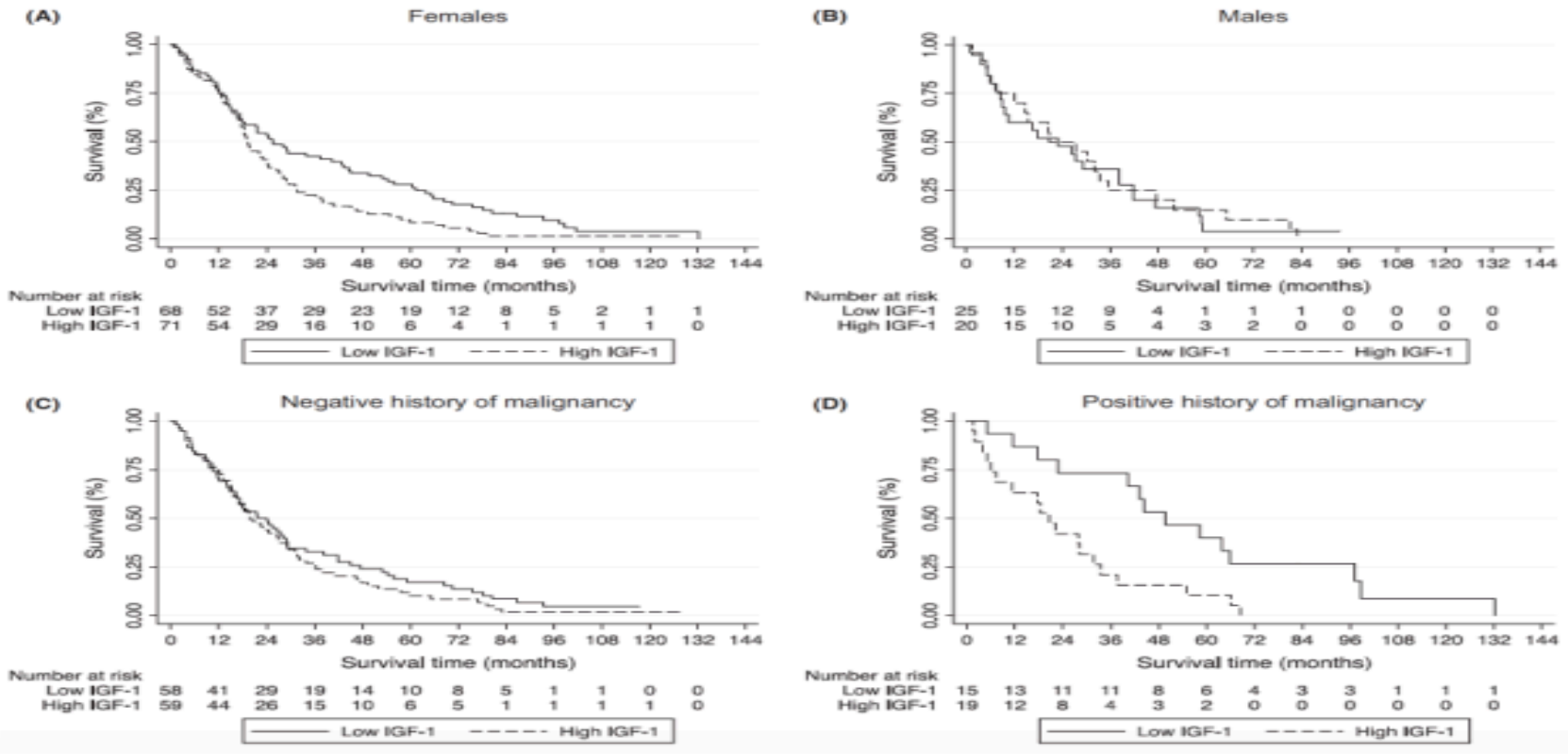
**Defined as Mini-Mental Examination (MMSE) score < 25 or Blind MMSE score < 16.

IGF 1 e longevità

Ridotto effetto dell' IGF 1: uomo

Low insulin-like growth factor-1 level predicts survival in humans with exceptional longevity

Aging Cell (2014) **13**, pp769–771



Kaplan–Meier curves for groups with IGF-1 levels below (low IGF-1) and above (high IGF-1) the median (A–D). P-values for comparison between IGF-1 groups.
(A) Females, $P < 0.01$. (B) Males, $P = 0.83$. (C) Negative history of malignancy, $P = 0.42$. (D) Positive history of malignancy, $P < 0.01$.

IGF 1 e longevità

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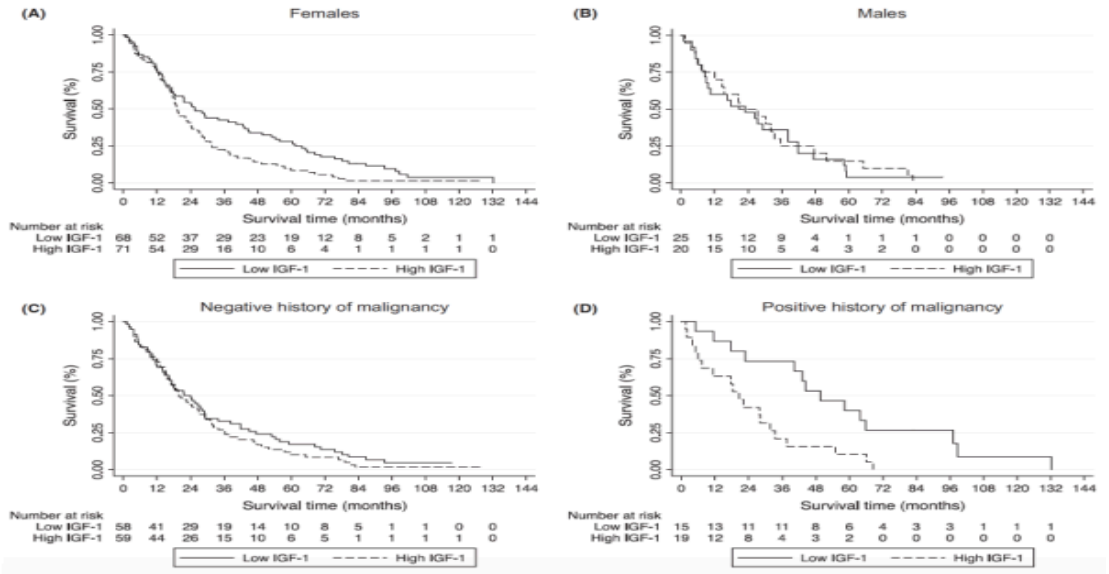

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(A) Females, P < 0.01. (B) Males, P = 0.83. (C) Negative history of malignancy, P = 0.42. (D) Positive history of malignancy, P < 0.01.

In women, each 1 ng/ mL increase in IGF-1 was associated with an average (95% CI) decrease of 0.1 (- 0.18 to - 0.02) months in survival.

This model significantly predicted survival time in females, P < 0.01, and IGF-1 explained approximately 6.2% of the variability in survival.

After stratification of all subjects by a history of cancer, IGF-1 was inversely associated with survival duration only in individuals with a positive history of malignancy, after adjustment for age, sex, HDL cholesterol, CVD and T2DM (P < 0.01).

In this group, each 1 ng /mL rise in IGF-1 level was related to a mean decline of 0.27 (- 0.45 to − 0,09 months in survival, P < 0.01

This model significantly predicted survival time (P = 0.01), with 23% of the variability in survival attributed to IGF–1.

IGF 1 e longevità

Ridotto effetto dell' IGF 1: uomo

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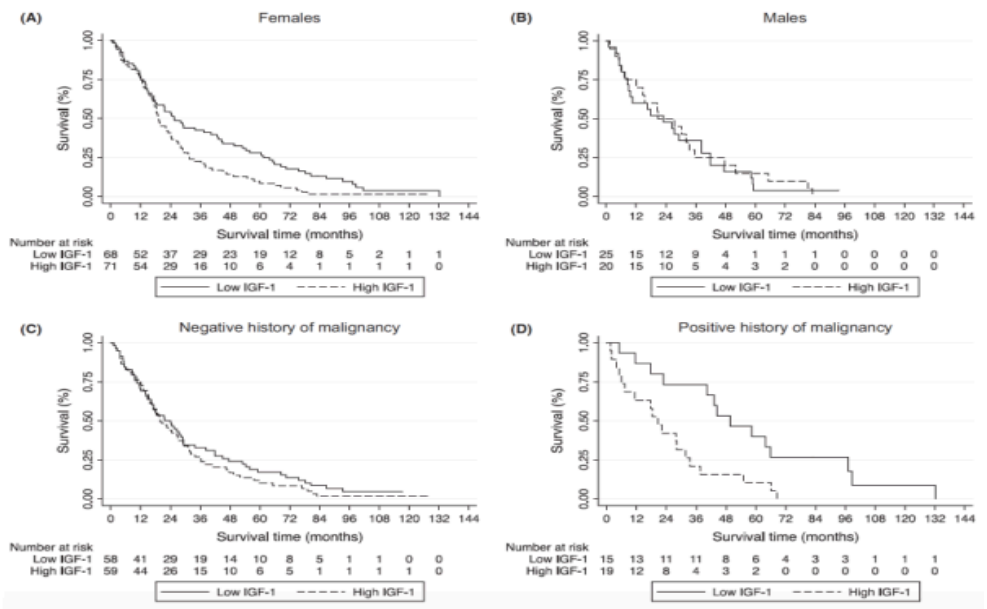


Kaplan–Meier curves for groups with IGF-1 levels below (low IGF-1) and above (high IGF-1) the median (A–D). P-values for comparison between IGF-1 groups.
(A) Females, P < 0.01. (B) Males, P = 0.83. (C) Negative history of malignancy, P = 0.42. (D) Positive history of malignancy, P < 0.01.

Thus, we conclude that attenuation of the GH/IGF-1 axis may play an important role in extending survival in humans who achieve exceptional longevity, although this effect may be gender and disease specific.

Furthermore, our results provide additional evidence against the rationale for treating older adults with GH replacement as an 'antiaging' strategy.

IGF 1 e longevità

Meccanismi che incrementano la longevità

Le Piccole Dimensioni ?

Modelli animali e anche umani (Laron) suggeriscono che le piccole dimensioni possono rappresentare un fattore protettivo nei confronti dell'invecchiamento.

Non è dimostrata però una correlazione tra dimensioni corporee e longevità

L' insulinosensibilità?

Dati controversi: in teoria la maggiore sensibilità insulinica protegge da malattie CV; tuttavia diversi modelli animali (Igf1r, Irs1 -/-, Irs2 -/-, Klotho) sono insulinoresistenti

L'effetto della sensibilità insulinica sulla longevità deve ancora essere definito

L' adiposità?

Topi con ridotto effetto GH/IGF1 e uomini Laron sono spesso obesi, per cui si potrebbe immaginare un ruolo protettivo del grasso (almeno quello sottocutaneo) sulle conseguenze tessutali dell'invecchiamento

Il realtà il fenotipo obeso o magro non è correlato con la longevità

IGF 1 e longevità

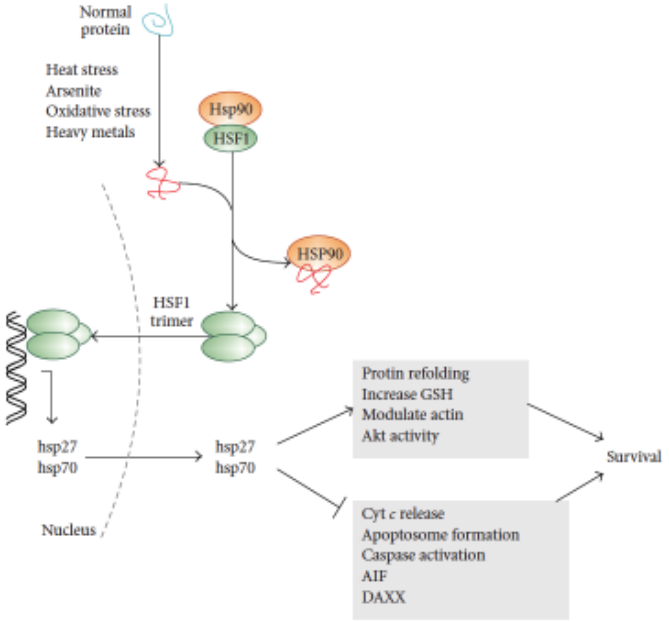
Meccanismi che incrementano la longevità

Ridotto signalling GH/ IGF1 e resistenza allo stress

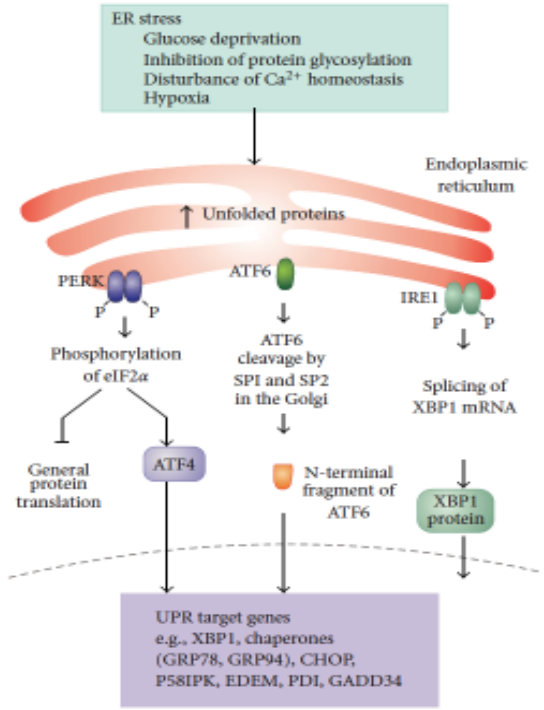
Ridotto signalling GH/ IGF1 e resistenza alle neoplasie

IGF 1 e longevità

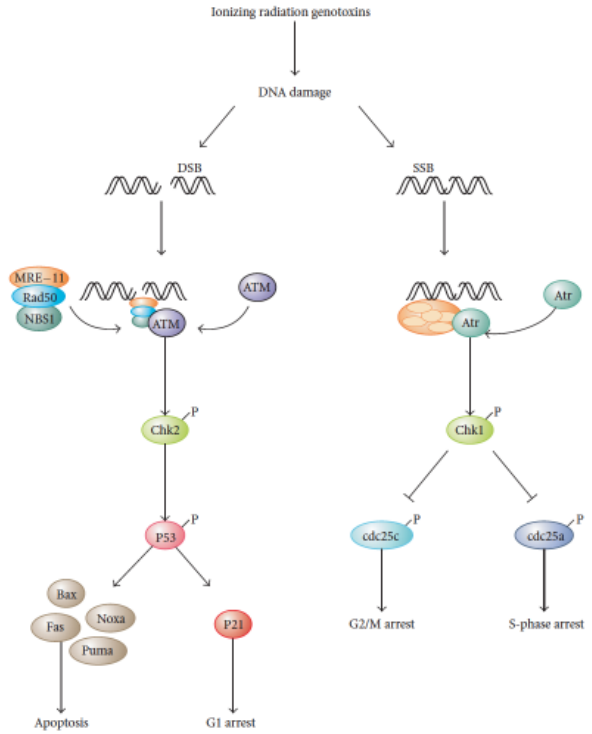
Meccanismi che incrementano la longevità



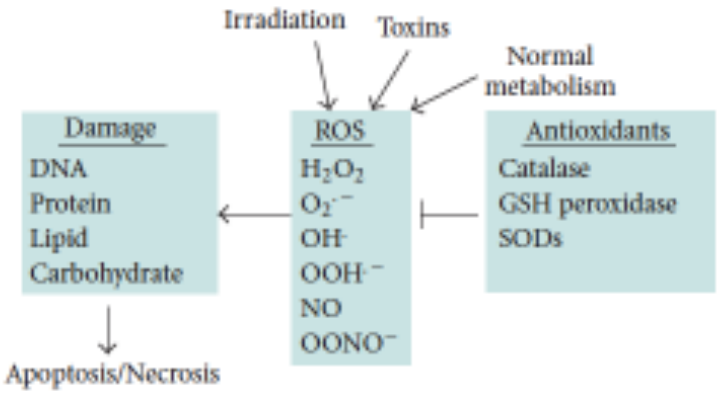
Induction of heat shock proteins inhibits apoptosis and promotes cell survival. Exposure of cells to elevated temperatures, oxidative stress, and heavy metals causes accumulation of unfolded proteins, which through activation of HSF1 leads to induction of Hsp27 and Hsp70. These Hsps inhibit apoptosis and promote survival.



ER stress and the unfolded protein response.
Stress to the ER stimulates the activation of the three endoplasmic reticulum (ER) stress receptors, PKR-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol-requiring enzyme 1(Ire1) that are involved in the unfolded protein response (UPR).



DNA damage responses and cell death.

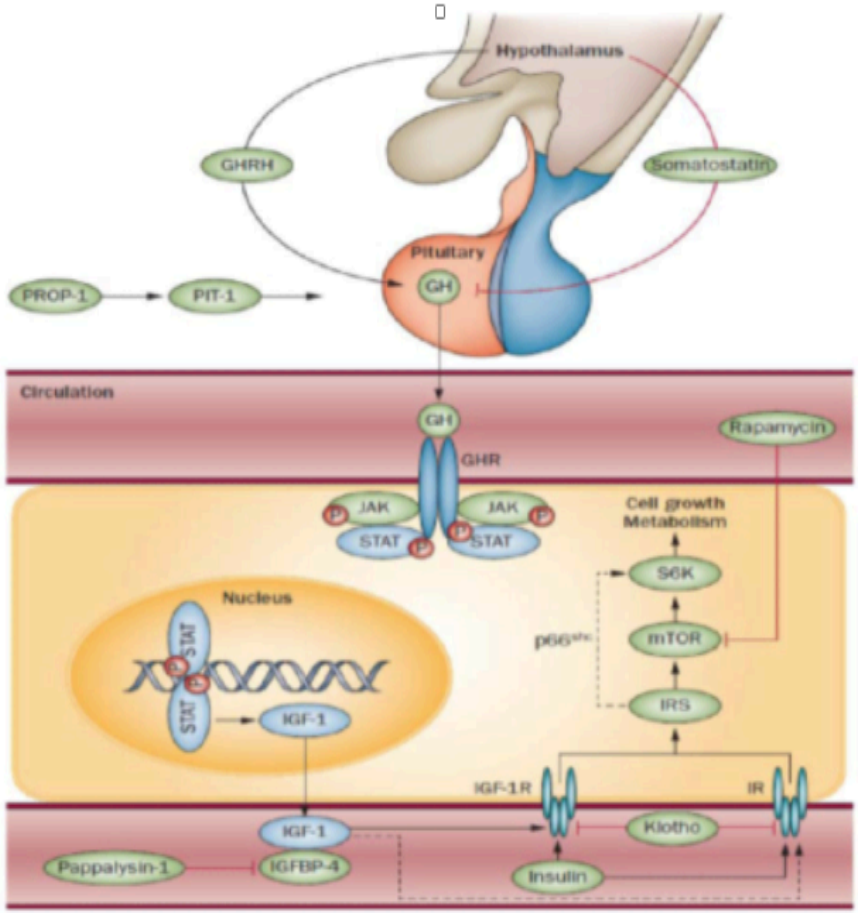


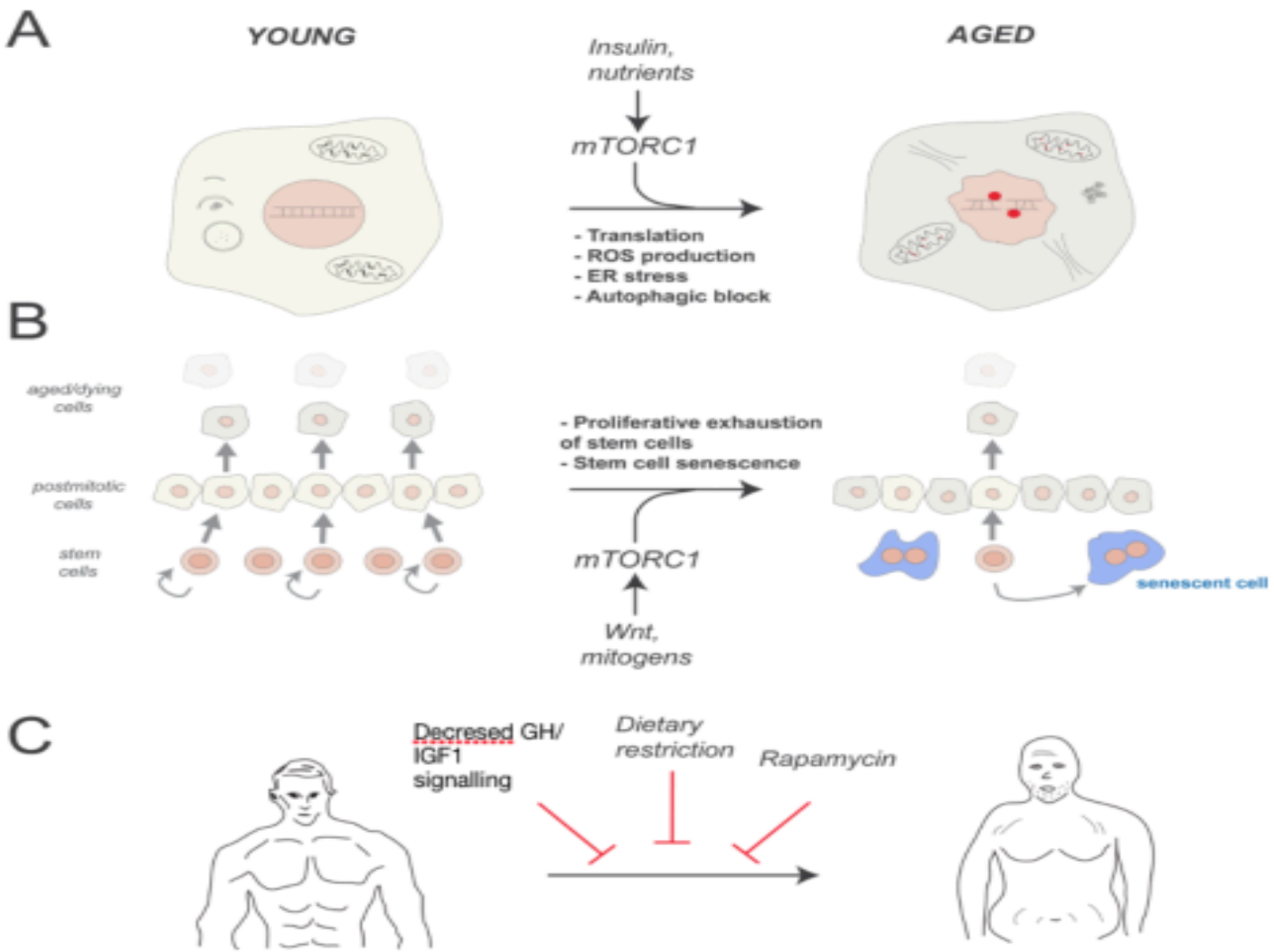
Oxidative stress and cell death. There is a plethora of stimuli that can trigger the generation of reactive oxygen species (ROS), among them irradiation, toxins, and also normal metabolic processes. A range of different ROS species have been identified, which are kept in check by antioxidant defenses. These include several detoxifying enzymes, for example, catalase, GSH peroxidase, and superoxide dismutase (SOD). If these antioxidants defense mechanisms are too weak, ROS-mediated damage to cellular macromolecules will eventually lead to cell death.

International Journal of Cell Biology
Volume 2010, Article ID 214074

IGF 1 e longevità

Meccanismi che incrementano la longevità





mTOR in ageing

A. mTORC1-regulated processes that promote cellular ageing. mTORC1-dependent translation may overcome the protein folding capacity of the cell, resulting in accumulation of unfolded proteins and ER stress. Stimulation of mitochondrial function may increase ROS production, resulting in oxidative damage to DNA, proteins and membranes. Inhibition of autophagy by mTORC1 reduces the turnover of cellular components and promotes the accumulation of their damaged forms (red).

B. mTORC1 promotes stem cell exhaustion and tissue ageing. In young tissues, stem cells divide asymmetrically to generate new stem cells as well as postmitotic cell that replace those that have undergone turnover (left). Continued exposure to mitogens that signal through mTORC1 causes stem cell exhaustion through hyperproliferation or senescence (right); thus, in aged tissues post-mitotic cells are no longer replaced and the overall performance of the tissue is degraded

C. Inhibiting mTORC1 activity by various means allows lifespan extension in multiple organisms, and may have beneficial effects on human ageing

Nat Rev Mol Cell Biol. 2011 January ; 12(1): 21–35

IGF 1 e longevità

Meccanismi che incrementano la longevità

ELSEVIER

Experimental Gerontology

Volume 41, Issue 10, October 2006, Pages 1014-1019

Stress resistance in long-lived mouse models

Shin Murakami

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https://doi.org/10.1016/j.exger.2006.06.061

Abstract

Cellular stress resistance has been observed in a variety of long-lived mouse systems. The Ames and Snell dwarf mice show altered hormonal profiles (low levels of growth hormone/IGF-1 and of other hormones). These altered hormonal profiles lead to physiological changes in cells, leading to increased resistance to multiple forms of stress including UV light, oxidative stress, heat, and the heavy metal cadmium. The cells also show resistance to carcinogen and senescence-like growth arrest induced by ambient oxygen. Thus, cellular stress resistance may confer resistance to various diseases associated with stress insults. Stress resistance has also been observed in various long-lived mice (hemizygous knockout of *igf-1r*, a mutation in $p66^{shc}$, and *klotho* overexpression) and *in vitro* CR (Carolie Restriction) system. Many of the long-lived mouse systems show reduction or inhibition of the insulin/IGF-1-FOXO pathway, thus suggesting that there may be an overlapping mechanism for increased life span. The insulin/IGF-1-FOXO pathway interlocks to several signal transduction pathways through AKT, FOXO, JNK, and other components. Taken together, stress resistance may be an essential function in cells that leads to increased longevity. I will summarize molecular basis of stress resistance and further discuss stress resistance in other systems.

TOPI Ames, Snell, Ghr -/-, lit/lit, IGF1r +/- e Klotho mostrano maggiore resistenza allo stress rispetto al wild type valutata attraverso la resistenza alle rotture del DNA.

Questa maggiore resistenza allo stress cellulare è ridotta dal trattamento con GH

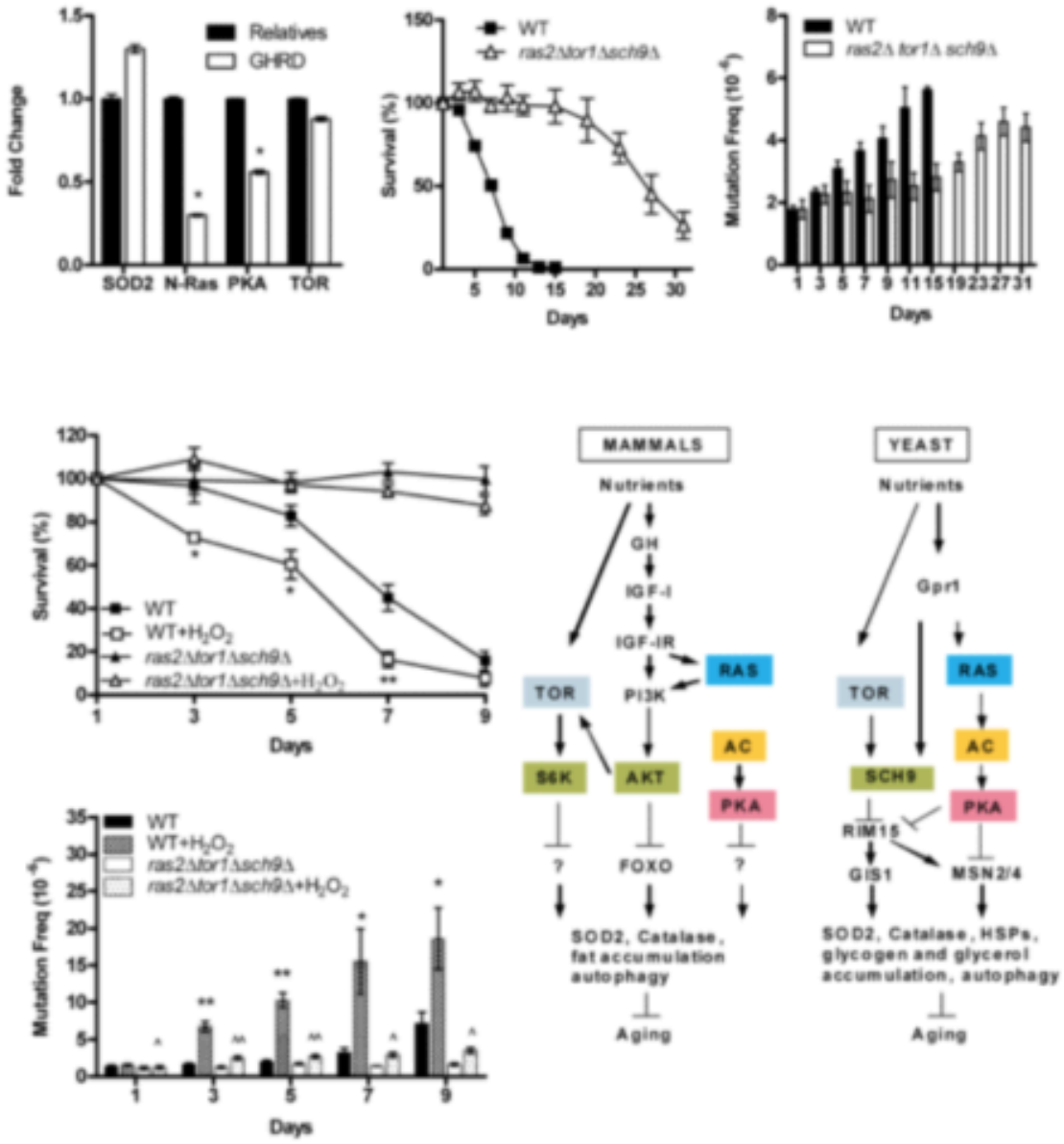
IGF 1 e longevità

Meccanismi che incrementano la longevità

Patients with Laron syndrome (Ecuadorian cohort) also show a reduction in stress-induced signalling.
This finding was investigated by incubating human epithelial cells with serum from these patients or their unaffected relatives.
The patient serum caused an increase in expression of SOD2 and a decrease in mTOR mRNA levels.
Following treatment with H2O2, cells treated with the patient serum displayed less DNA breakage.

Growth Hormone Receptor Deficiency is Associated With a Major Reduction in Pro-aging Signaling, Cancer and Diabetes in Humans

Sci Transl Med. 2011 February 16; 3(70)



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- Topi Ames, Snell, lit/lit, Ghr -/- e pappa -/- presentano una particolare resistenza all'insorgenza di tumori
  J. Gerontol. A. Biol. Sci. Med.Sci. 2004; 59:1244
  J. Gerontol. A. Biol. Sci. Med.Sci. 2003; 58:291
  Oncogene. 2005; 24:4736
  J. Gerontol. A. Biol. Sci. Med. Sci. 2009;64:522
  Aging Cell. 2007; 6:727
- I tumori sono praticamente inesistenti negli uomini Laron
  Sci. Transl. Med. 2011; 3:70
- Topi transgenici che sovraesprimono GH eterologo hanno un'incrementata incidenza di tumori
  Endocrinology. 1989; 124:40
- Uomini acromegalici hanno una maggiore incidenza di alcuni tipi di cancro
  Rev. Endocr. Metab. Disord. 2008;9:33
- L'inibizione di mTor aumenta la resistenza ai tumori in diverse specie
  Cell. 2006;124:471
  Nature. 2009; 460:392
  FEBS Lett. 2011; 585:1537